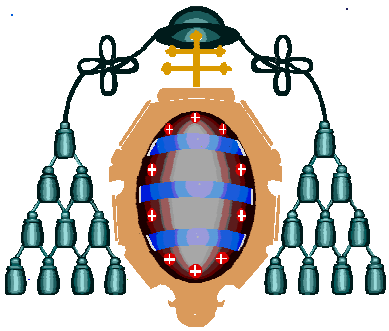


UNIVERSIDAD DE OVIEDO

Programa de Doctorado "Química Organometálica"

"Complejos areno-rutenio(II) como catalizadores selectivos para la formación de amidas primarias en agua y la isomerización redox de alcoholes alílicos"

Rocío García Álvarez

Tesis Doctoral

2013

RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español/Otro Idioma: "Complejos areno-rutenio(II) como catalizadores selectivos para la formación de amidas primarias en agua y la isomerización redox de alcoholes alílicos".	Inglés: "Arene-ruthenium(II) complexes as selective catalysts for the formation of primary amides in water, and for the redox isomerization of allylic alcohols".

2.- Autor	
Nombre: Rocío García Álvarez	
Programa de Doctorado: Química organometálica (Mención de Calidad)	
Órgano responsable: Química Orgánica e Inorgánica	

RESUMEN (en español)

En esta *Memoria* se aborda el desarrollo de nuevos catalizadores de rutenio(II) activos en diferentes transformaciones orgánicas de interés sintético.

Así, en el *Capítulo 1* se describe la síntesis y caracterización de una serie de complejos areno-rutenio(II) de fórmula general $[RuCl_2(\eta^6\text{-areno})(PR_3)]$ con ligandos fosfina (PR_3) capaces de establecer enlaces de hidrógeno con el agua, *i.e.* diferentes piridil-fosfinas, amino-aril-fosfinas y la tris(dimetilamino)fosfina. Dichos complejos fueron estudiados como catalizadores, potencialmente bifuncionales, en procesos de hidratación selectiva de nitrilos en amidas primarias, empleando un medio de reacción puramente acuoso.

En el *Capíltulo 2* se aborda la preparación de amidas primarias en agua a través de procesos de reordenamiento de aldoximas y de acoplamiento de aldehídos con derivados de la hidroxilamina. En ellos se ha empleado como catalizador el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$, que resultó ser el más activo en las reacciones de hidratación de nitrilos discutidas en el *Capitulo 1*.

En el *Capítulo 3* se presenta la síntesis y caracterización de una nueva familia de complejos areno-rutenio(II) con ligandos aniónicos de tipo guanidinato, así como el estudio de su actividad catalítica en la isomerización redox de alcoholes alílicos en compuestos carbonílicos saturados en ausencia de base.

Como *Anexo* a la *Memoria* se incluyen un artículo de revisión y un capítulo de libro, cuyo contenido está íntimamente relacionado con los aspectos abordados en los *Capítulos 1* y *2*.

RESUMEN (en Inglés)

This PhD Thesis focus on the development of novel ruthenium(II) complexes able to catalyze different organic transformations of synthetic relevance.

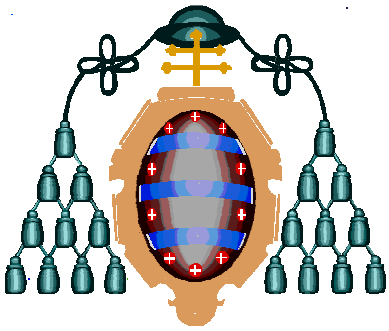
Thus, in the *First Chapter* we describe the synthesis and characterization of a series of arene-ruthenium(II) derivatives of general formula [$RuCl_2(\eta^6$-arene)(PR_3)], with phosphine ligands (PR_3) able to establish hydrogen-bonds with water molecules, *i.e.* different pyridyl-phosphines, amino-aryl-phosphines and tris(dimethylamino)phosphine. These complexes were studied as potential bifunctional catalysts for the selective hydration of nitriles into primary amides in a pure aqueous medium.

The *Second Chapter* deals with the preparation of primary amides in water by catalytic rearrangement of aldoximes, and by coupling of aldehydes with hydroxylamine derivatives. In both processes, complex [$RuCl_2(\eta^6$-C_6Me_6){$P(NMe_2)_3$}], which showed the best performances on the nitrile hydration studies discussed in the *First Chapter*, was used as the catalyst.

In the *Third Chapter*, the synthesis and characterization of a new family of arene-ruthenium(II) complexes containing anionic guanidinate ligands is presented. These species were found to catalyze efficiently the redox isomerization of allylic alcohols into saturated carbonyl compounds under base-free conditions.

Finally, an *Annex* containing a review article and a book chapter, both related to the catalytic processes addressed in the *First* and *Second Chapter* of this PhD Thesis, is also included.

SR/A. DIRECTOR/A DE DEPARTAMENTO DE QUIMICA ORGANICA E INORGANICA/
SR/A. PRESIDENTE/A DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN Química organometálica (Mención de Calidad)



UNIVERSIDAD DE OVIEDO

Programa de Doctorado "Química Organometálica"

"Complejos areno-rutenio(II) como catalizadores selectivos para la formación de amidas primarias en agua y la isomerización redox de alcoholes alílicos"

Rocío García Álvarez

Memoria para optar al grado de Doctor en Química

ÍNDICE

CAPÍTULO 3. COMPLEJOS ARENO-RUTENIO(II) CON LIGANDOS GUANIDINATO: SÍNTESIS, CARACTERIZACIÓN Y APLICACIÓN EN LA ISOMERIZACIÓN REDOX DE ALCOHOLES ALÍLICOS

LISTA DE ABREVIATURAS

ca		aproximadamente
acac		acetilacetonato
CG		Cromatografía de Gases
cod		1,5-ciclooctadieno
CV		voltametría cíclica
	E^o	potencial estándar
	$E^{o'}$	potencial formal
	V	voltio
Cy		ciclohexilo
Δ		calor
DMF		*N*,*N*-dimetilformamida
equiv.		Equivalente
FID		detector de ionización de llama
g		gramo
i.e.		id est, es decir
IR		Infrarrojo
	υ	Frecuencia de radiación
L		ligando
Li^nBu		butil-litio
M		molar

Me	metilo
MeOH	metanol
mg	miligramo
mL	mililitro
mmol	mmol
µL	microlitro
Ph	fenilo
PPh_3	trifenilfosfina
PPh_2py	2-difenilfosfinopiridina
Rdto.	rendimiento
RMN	Resonancia Magnética Nuclear
s	singulete
sa	singulete ancho
d	doblete
t	triplete
q	quintuplete
sept	septuplete
m	multiplete
ppm	partes por millón
Hz	hertzios
DEPT	“Distorsionless Enhancement by Polarization Transfer”
δ	desplazamiento químico

$\Delta\delta$	variación del desplazamiento químico
J	constante de acoplamiento
t.a.	temperatura ambiente
THF	tetrahidrofurano
TMS	tetrametilsilano
TOF	frecuencia de repetición
TON	número de repetición
TsOH	ácido *para*-toluensulfónico

Introducción general

Introducción general

La utilización de compuestos metálicos en síntesis orgánica es una de las piedras angulares de la Química Orgánica moderna.[1] Aunque la base fundamental de sus aplicaciones radica en las transformaciones estequiométricas, la capacidad de los complejos de metales de transición para catalizar reacciones orgánicas constituye una de las estrategias actuales más poderosas para el desarrollo de nuevas metodologías sintéticas.[2] De hecho, el uso de catalizadores metálicos está tan extendido que es difícil encontrar hoy en día alguna síntesis avanzada que no recurra a ellos en alguna de sus etapas.[1d] La amplia disponibilidad actual de procesos catalíticos eficientes y selectivos ha consolidado este campo de trabajo, haciendo que traspase la barrera que separa la pura investigación básica de las aplicaciones industriales.[3]

Desde un punto de vista meramente académico, la selectividad de los procesos, quimio-, regio- y estereoselectividad, han sido tradicionalmente las propiedades más deseadas a la hora de diseñar transformaciones catalíticas. No obstante, la selectividad, aunque puede ser determinante para la generación de un mínimo de subproductos, no elimina la necesidad de desarrollar procedimientos de separación y almacenamiento, o destrucción, de los residuos generados. Este supuesto conduce a la cuestión de cuánta cantidad de reactivos se transforma

---

[1] Ver, por ejemplo: (a) *Transitions Metals for Organic Synthesis* (eds. I. M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**; (b) W. Carruthers, I. Coldham, en *Modern Methods of Organic Synthesis*, Academic Press, Cambridge, **2004**; (c) G. S. Zweifel, M. H. Nantz, en *Modern Organic Synthesis: An Introduction*, W. H. Freeman & Co., New York, **2007**; (d) *Transition Metals in the Synthesis of Complex Organic Molecules* (eds. L. S. Hegedus, B. Soderberg), University Science Books, Sausalito, **2009**; (e) *Organotransition Metal Chemistry: From Bonding to Catalysis* (ed. J. F. Hartwig), University Science Books, Sausalito, **2010**.

[2] Ver, por ejemplo: (a) *Homogeneous Catalysis: Understanding the Art* (ed. P. W. N. M. van Leeuwen), Kluwer Academic Publishers, Amsterdam, **2004**; (b) D. Steinborn, en *Fundamentals of Organometallic Catalysis*, Wiley-VCH, Weinheim, **2012**.

[3] Ver, por ejemplo: (a) *Metal Catalysis in Industrial Organic Processes* (eds. G. P. Chiusoli, P. M. Maitlis), RSC Publishing, Cambridge, **2008**; (b) *Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective* (eds. M. L. Crawley, B. M. Trost), John Wiley & Sons, Hoboken, **2012**.

realmente en el producto deseado, surgiendo así el concepto de "economía atómica".[4] Es decir, se debe perseguir la optimización del coste global de un proceso simplificando el número de transformaciones para conseguir el producto deseado, y minimizando los subproductos de deshecho en cada una de las transformaciones involucradas (incorporación máxima en el producto deseado de todos los átomos que componen los reactivos). Es por ello que el desarrollo de procesos que operen tanto con selectividad como con economía atómica se ha convertido en un objetivo prioritario en la Química de nuestros días.

En esta misma línea de razonamiento ha surgido también en años recientes la llamada *Química Verde* que, a través de sus doce principios, promueve el desarrollo de procesos químicos de bajo impacto medioambiental.[5] La catálisis, la economía atómica y el uso de reactivos no tóxicos y renovables juegan un papel clave dentro de esta nueva filosofía de trabajo. Por tanto, la "*reacción química ideal*", además de transcurrir con la mayor eficiencia y selectividad posible, debería seguir criterios ambientales y sostenibles (Figura I.1).

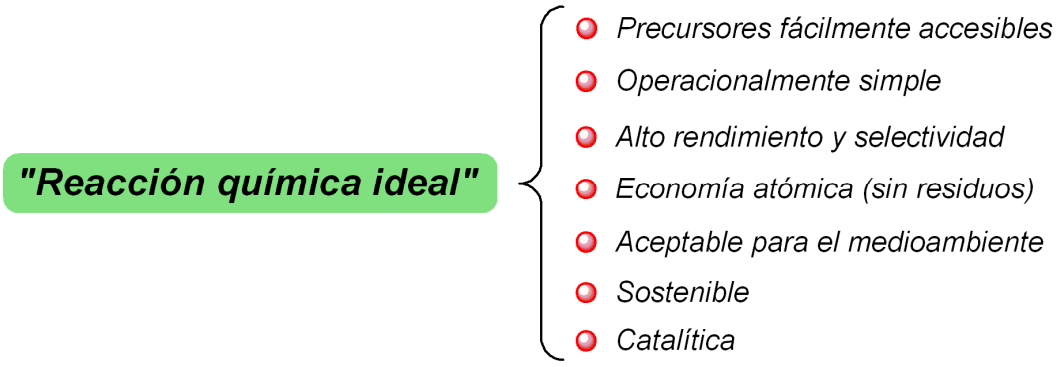


Figura I.1: Criterios deseables que debe cumplir una reacción química.

[4] (a) B. M. Trost, *Science* **1991**, *254*, 1471; (b) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; (c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695; (d) B. M. Trost, M. U. Fredericksen, M. T. Rudd, *Angew. Chem. Int. Ed.* **2005**, *44*, 6630; (e) R. A. Sheldon, *Green Chem.* **2007**, 1273; (f) R. A. Sheldon, *Chem. Commun.* **2008**, 3352.

[5] (a) P. T. Anastas, J. C. Warner, en *Green Chemistry Theory and Practice*, Oxford University Press, Oxford, **1998**; (b) A. S. Matlack, en *Introduction to Green Chemistry*, Marcel Dekker Inc., New York, **2001**; (c) *Handbook of Green Chemistry and Technology* (ed. J. H. Clark, D. J. Macquarrie), Blackwell Publishing, Abingdon, **2002**; (d) M. Poliakoff, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas, *Science*, **2002**, *297*, 807; (e) M. Lancaster, en *Green Chemistry: An Introductory Text*, RSC Publishing, Cambridge, **2010**.

De acuerdo con los principios de la *Química Verde*, la búsqueda de disolventes alternativos que permitan reducir o eliminar el uso de los disolventes orgánicos convencionales (generalmente volátiles, tóxicos e inflamables) se ha convertido también en un área de trabajo en plena expansión. En este sentido, el agua, el CO_2 supercrítico, los compuestos perfluorados, los líquidos iónicos y los compuestos orgánicos procedentes de fuentes renovables (biodisolventes) están siendo en la actualidad activamente investigados como alternativas a los disolventes orgánicos clásicos.[6] Aunque no exista un disolvente ideal para cualquier transformación, el agua es posiblemente la opción más atractiva ya que, además de ser no inflamable, es el disolvente más barato, inocuo y ecológico que se conoce.[7] Es por ello que durante los últimos años se ha dedicado una atención particular al desarrollo de transformaciones orgánicas que transcurran de manera eficiente y selectiva en medio acuoso,[8] incluyendo un buen número de procesos catalíticos promovidos por metales de transición.[9] Aunque los avances en este campo emanan fundamentalmente de los laboratorios de investigación, debemos reseñar que la industria química, y en particular el sector farmacéutico, no es

[6] Ver, por ejemplo: (a) W. M. Nelson, en *Green Solvents for Chemistry: Perspectives and Practice*, Oxford University Press, New York, **2003**; (b) R. A. Sheldon, *Green Chem.* **2005**, 7, 267; (c) F. M. Kerton, en *Alternative Solvents for Green Chemistry*, RSC Publishing, Cambridge, **2009**.

[7] Un análisis crítico sobre las ventajas y desventajas asociadas al uso de estos disolventes alternativos puede encontrarse en el siguiente artículo: J. H. Clark, S. T. Taverner, *Org. Process Res. Dev.* **2007**, *11*, 149.

[8] Ver, por ejemplo: (a) C.-J. Li, *Chem. Rev.* **1993**, *93*, 2023; (b) A. Lubineau, J. Auge, Y. Queneau, *Synthesis* **1994**, 741; (c) *Organic Synthesis in Water* (ed. P. A. Grieco), Blackie Academic & Professional, Londres, **1998**; (d) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751; (e) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095; (f) C. K. Z. Andrade, L. M. Alves, *Curr. Org. Chem.* **2005**, *9*, 195; (g) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68; (h) L. Chen, C.-J. Li, *Adv. Synth. Catal.* **2006**, *348*, 1459; (i) C. I. Herrerías, X. Yao, Z. Li, C.-J. Li, *Chem. Rev.* **2007**, *107*, 2546; (j) C.-J. Li, T. H. Chan, en *Comprehensive Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, **2007**; (k) *Organic Reactions in Water: Principles, Strategies and Applications* (ed. U. M. Lindström), Blackwell Publishing, Oxford, **2007**; (l) *Handbook of Green Chemistry (vol. 5)* (eds. P. T. Anastas, C.-J. Li), Wiley-VCH, Weinheim, 2010; (m) M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415; (n) *Water in Organic Synthesis* (ed. S. Kobayashi), Thieme, Stuttgart, **2012**.

[9] Ver, por ejemplo: (a) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications* (ed. B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **1998**; (b) *Aqueous Organometallic Catalysis* (ed. I. T. Horváth, F. Joó), Kluwer, Dordrecht, **2001**; (c) *Recoverable and Recyclable Catalysts* (ed. M. Benaglia), John Wiley & Sons, Chichester, **2009**; (d) *Metal-Catalyzed Reactions in Water* (ed. P. Dixneuf, V. Cadierno), Wiley-VCH, Weinheim, **2013**.

ajena a esta evolución.[10] Además, debemos destacar que en algunos casos, al emplear agua como disolvente se observan diferencias muy acusadas en la eficiencia y selectividad de los procesos con respecto a las que se obtienen en un medio orgánico clásico.[11]

Por otro lado, la utilización de complejos organometálicos de rutenio en síntesis orgánica ha experimentado un crecimiento espectacular en las tres últimas décadas (Figura I.2). Hasta los años 80, los únicos ejemplos de transformaciones orgánicas promovidas de forma eficiente por compuestos de rutenio se limitaban a algunas reacciones de oxidación, hidrogenación y transferencia de hidrógeno, pero la madurez alcanzada por la química de coordinación de este metal, que exhibe un amplio número de estados de oxidación y diversas geometrías en torno al centro metálico,[12] ha permitido disponer de una amplia gama de derivados útiles a la hora de diseñar nuevas metodologías sintéticas en Química Orgánica. Además, los complejos de rutenio presentan una serie de características generales que les convierten en candidatos idóneos para promover una gran variedad de transformaciones químicas. Entre ellas, podemos resaltar sus bajos potenciales de oxidación, su facilidad para transferir electrones y sus propiedades como ácido de Lewis, además de su tolerancia a un elevado número de grupos funcionales y la posibilidad de formar especies intermedias con una reactividad única. Todas estas propiedades, unidas a su bajo coste en comparación con otros metales del Grupo del Platino, han

[10] A modo de ejemplo, las compañías farmacéuticas multinacionales Pfizer Inc. Y GlaxoSmithKline han hecho públicas unas guías, empleadas en sus centros de investigación, para la selección de disolventes a la hora de desarrollar un proceso sintético. En dichas guías, basadas en criterios medioambientales, se preconiza el empleo del agua como disolvente: (a) K. Alfonsi, J. Coldberg, P. J. Dunn, T. Fevig, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry, M. Stefaniak, *Green Chem.* **2008**, *10*, 31; (b) R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854.

[11] Los trabajos pioneros de R. Breslow y P. A. Grieco, que pusieron de manifiesto el efecto positivo que ejerce el agua en la velocidad y selectividad *endo/exo* de reacciones de tipo Diels-Alder, son ejemplos ilustrativos de este fenómeno: (a) D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816; (b) P. A. Grieco, K. Yoshida, P. Garner, *J. Org. Chem.* **1983**, *48*, 3137.

[12] Ver, por ejemplo: (a) *Comprehensive Organometallic Chemistry I* (eds. G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, *vol. 4*, cap.32.1-32.9; (b) E. A. Sheddon, K. R. Seddon, en *The Chemistry of Ruthenium*, Elsevier, Amsterdam, **1984**; (c) *Comprehensive Organometallic Chemistry II* (eds. E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, *vol. 7*, cap. 5-16; (d) *Comprehensive Organometallic Chemistry III* (eds. R. H. Crabtree, D. M. P. Mingos), Elsevier, Oxford, **2007**, *vol. 6*, cap. 6.11-6.25.

afianzando al rutenio como uno de los metales más versátiles y útiles en catálisis homogénea.[13]

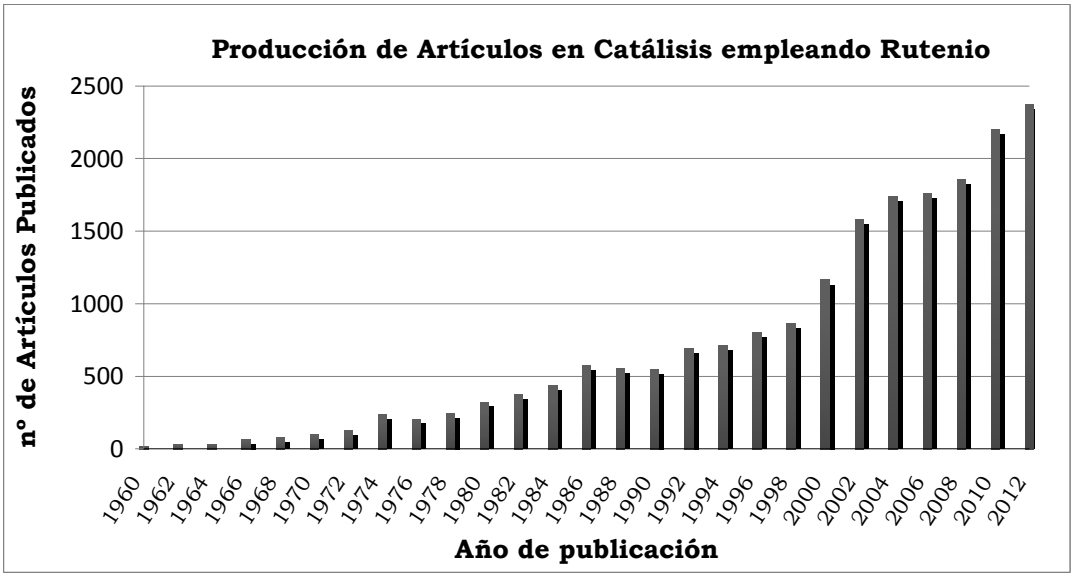


Figura I.2: Evolución del número de publicaciones donde se utiliza un complejo de rutenio como catalizador durante los últimos 50 años (datos obtenidos en SciFinder usando como palabra clave "ruthenium-catalyzed").

Cabe recordar en este punto que el papel clave que juega actualmente el rutenio en catálisis viene ratificado por la concesión de dos Premios Nobel de Química, a R. Noyori (2001) y a R. H. Grubbs (2005), por el desarrollo de transformaciones vitales en la síntesis orgánica moderna, *i.e.* las reacciones de hidrogenación asimétrica y la metátesis de olefinas, donde los catalizadores de rutenio juegan un papel muy importante.

En este contexto, durante los últimos años nuestro grupo de investigación ha centrado sus líneas de trabajo en el desarrollo de nuevos catalizadores, fundamentalmente basados en rutenio, capaces de promover transformaciones orgánicas que transcurran con alta economía atómica y, a ser posible, en medio acuoso.[14]

---

[13] Ver, por ejemplo: (a) *Ruthenium in Organic Synthesis* (ed. S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**; (b) *Ruthenium Catalysts and Fine Chemistry* (eds. C. Bruneau, P. H. Dixneuf), Springer, Berlin, **2004**; (c) *Ruthenium: Properties, Production and Applications* (ed. D. B. Watson), Nova Science Publishers, New York, **2011**; (d) *Ruthenium Oxidation Complexes: Their Uses as Homogeneous Organic Catalysts* (ed. W. P. Griffith), Springer, Dordrecht, **2011**.

[14] Ver, por ejemplo, los siguientes artículos de revisión y capítulos de libro publicados por el grupo: (a) V. Cadierno, P. Crochet, S. E. García-Garrido, J.

La presente *Tesis Doctoral* pretende avanzar en este campo diseñando nuevos catalizadores de rutenio y estudiando sus aplicaciones catalíticas en diferentes procesos de relevancia en síntesis orgánica. Así, en esta *Memoria* se describe:

- ✓ En el *Primer Capítulo*, el diseño de nuevos derivados de tipo rutenio(II)-areno, potencialmente bifuncionales, activos en la hidratación selectiva de nitrilos en amidas primarias, empleando directamente agua como disolvente.

- ✓ En el *Segundo Capítulo*, la aplicación de uno de los catalizadores sintetizados en el capítulo anterior en procesos de formación de amidas primarias en agua, a través de reacciones de reordenamiento de aldoximas, y de acoplamiento de aldehídos con derivados de la hidroxilamina.

- ✓ En el *Tercer Capítulo*, la síntesis y caracterización de una nueva familia de complejos rutenio(II)-areno con ligandos aniónicos de tipo guanidinato, y su actividad catalítica en la isomerización redox de alcoholes alílicos en compuestos carbonílicos saturados, trabajo que se ha llevado a cabo en colaboración con el grupo del Prof. Antonio Antiñolo de la Universidad de Castilla-La Mancha.

Gimeno, *Curr. Org. Chem.* **2006**, *10*, 165; (b) V. Cadierno, P. Crochet, en *Advances in Organometallic Chemistry Research* (ed. K. Yamamoto), Nova Science Publishers, New York, **2007**, pp. 37-65; (c) V. Cadierno, P. Crochet, *Curr. Org. Synth.* **2008**, *5*, 343; (d) V. Cadierno, P. Crochet, J. Gimeno, *Synlett* **2008**, 1105; (e) V. Cadierno, P. Crochet, S. E. García-Garrido, en *Green Chemistry Research Trends* (ed. J. T. Pearlman), Nova Science Publishers, New York, **2009**, pp. 97-130; (f) V. Cadierno, P. Crochet, S. E. García-Garrido, en *Aqueous Microwave Assisted Chemistry: Synthesis and Catalysis* (eds. V. Polshettiwar, R. S. Varma), RSC Publishing, Cambridge, **2010**, pp. 10-54; (g) V. Cadierno, P. Crochet, S. E. García-Garrido, J. Gimeno, *Dalton Trans.* **2010**, *39*, 4015; (h) V. Cadierno, S. E. García-Garrido, J. Gimeno, N. Nebra, *Inorg. Chim. Acta* **2010**, *363*, 1912; (i) V. Cadierno, J. García-Álvarez, en *Ruthenium: Properties, Production and Applications* (ed. D. B. Watson), Nova Science Publishers, New York, **2011**, pp. 189-220; (j) J. García-Álvarez, S. E. García-Garrido, P. Crochet, V. Cadierno, *Curr. Top. Catal.* **2012**, *10*, 35; (k) V. Cadierno, P. Crochet, en *Advances in Organic Synthesis (vol. 3)* (ed. Atta-ur-Rahman), Bentham Science Publishers, Sharjah, **2013**, pp. 36-80.

La *Memoria* se completa con un artículo de revisión y un capítulo de libro cuyo contenido está íntimamente relacionado con el trabajo desarrollado en los dos primeros capítulos de la Tesis.

Capítulo 1

Nuevos catalizadores de rutenio para la hidratación selectiva de nitrilos en medio acuoso

CAPÍTULO 1

1.1.- ANTECEDENTES Y OBJETIVOS

Antecedentes

Las amidas son uno de los grupos funcionales más importantes en la naturaleza (los aminoácidos que conforman los péptidos y proteínas se unen entre sí a través de enlaces amídicos), constituyen intermedios sintéticos muy versátiles en Química Orgánica, y muestran también una amplio rango de aplicaciones de interés industrial y farmacológico.[1] Por lo tanto, no es extrañar que las reacciones de formación de amidas se encuentren entre las operaciones sintéticas que se realizan con más frecuencia en los laboratorios e industrias químicas. A modo de ejemplo, un análisis llevado a cabo por las compañías farmacéuticas GlaxoSmithKline, AstraZeneca y Pfizer en el año 2006 puso de manifiesto que la generación de un grupo amida estaba involucrada en la preparación del 66% de los fármacos que estas compañías estaban desarrollando.[2]

Los métodos más comunes empleados para la formación de amidas involucran la activación de un ácido carboxílico y posterior tratamiento de la especie activada (el haluro, anhídrido o éster correspondiente) con una amina (Esquema 1.1).[1-3] La etapa de activación inicial del ácido carboxílico es necesaria ya que su reacción directa con una amina suele conducir a la formación de la sal de amonio correspondiente.[4]

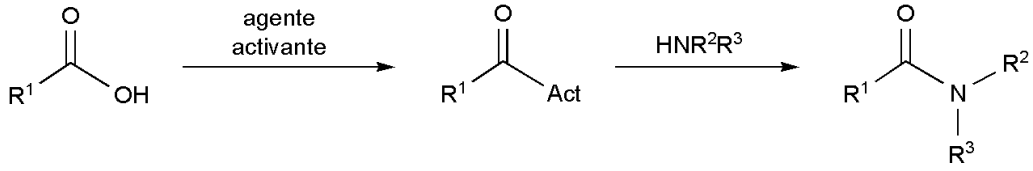
---

[1] Ver, por ejemplo: (a) *The Chemistry of Amides* (ed. J. Zabicky), Wiley-Interscience, New York, **1970**; (b) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science* (eds. A. Greenberg, C. M. Breneman, J. F. Liebman), John Wiley & Sons, New York, **2000**; (c) I. Johasson, en *Kirk-Othmer Encyclopedia of Chemical Tecnology (5th edn.)*, John Wiley & Sons, New York, **2004**, vol. 2, pp. 442-463; (d) *Polyesters and Polyamides* (eds. B. L. Deopura, B. Gupta, M. Josh, R. Alagisuri), CRC Press, Boca Raton, **2008**.

[2] J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337.

[3] Ver, por ejemplo: (a) *Methoden Org. Chem. (Houben Weyl)* (ed. D. Dopp, H. Dopp), Thieme Verlag, Stuttgart, **1985**, vol. E5(2), pp. 1024-1031; (b) P. D. Bailey, T. J. Mills, R. Pettecrew, R. A. Price, en *Comprehensive Organic Functional Group Transformations II* (ed. A. R. Katrizky, R. J. K. Taylor), Elsevier, Oxford, 2005, vol. 5, pp. 201-294; (c) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606.

[4] La formación de una amida por reacción directa de un ácido carboxílico y una amina tan sólo tiene lugar a temperaturas superiores a los 200 °C: B. S. Jursic, Z. Zdravkovdki, *Synth. Commun.* **1993**, *23*, 2761.



Esquema 1.1: Formación de amidas por activación de ácidos carboxílicos.

No obstante, estas metodologías clásicas presentan serios inconvenientes ya que requieren del uso de reactivos tóxicos, corrosivos y/o caros, son reacciones muy exotérmicas, presentan una baja tolerancia a la presencia de otros grupos funcionales y generan una enorme cantidad de residuos. De hecho, en el año 2005 la ACS-GCIPR (American Chemical Society - Green Chemistry Institute Pharmaceutical Roundtable) calificó la formación de amidas como una de las síntesis más problemáticas en la industria farmaceútica, catalogándola como un campo de investigación prioritario.[5]

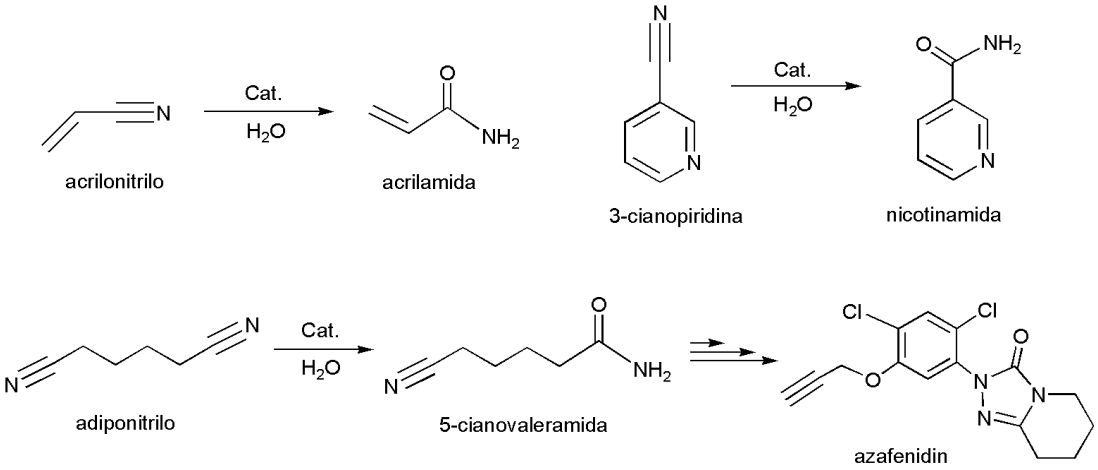
En la continua búsqueda de nuevas metodologías sintéticas más sencillas y eficientes, las transformaciones catalizadas por metales de transición han emergido en los últimos años como una de las alternativas más prometedoras para la síntesis de amidas en condiciones suaves y con alta economía atómica.[6] El uso de catalizadores metálicos ha permitido también abrir rutas sintéticas eficientes empleando sustratos de partida distintos a los ácidos carboxílicos y sus derivados.[7] En este contexto, la hidratación catalítica de nitrilos representa una vía muy simple y de alto interés industrial para la obtención de amidas primarias con economía atómica. De hecho, en la actualidad se producen industrialmente más de 2 x 10^5 toneladas anuales de acrilamida, que se emplea como monómero en la síntesis de poliacrilamida así como aditivo en las industrias textil y papelera, por hidratación catalítica del acrilonitrilo (ver Esquema 1.2),

[5] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411.

[6] Artículos sobre el concepto de economía atómica: (a) B. M. Trost, *Science* **1991**, *254*, 1471; (b) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; (c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695; (d) B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem. Int. Ed.* **2005**, *44*, 6630; (e) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273.

[7] Artículos de revisión generales cubriendo la síntesis catalítica de amidas: (a) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405; (b) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471; (c) R. García-Álvarez, P. Crochet, V. Cadierno, *Green Chem.* **2013**, *15*, 46.

representando la principal ruta de acceso para este derivado.[8] La hidratación de la 3-cianopiridina en nicotinamida, una de las formas en las que se presenta la vitamina B3, o la monohidratación selectiva del adiponitrilo en 5-cianovaleramida, producto intermedio en la síntesis del herbicida azafenidin producido por DuPont, son otros ejemplos ilustrativos del interés industrial que presenta este proceso.[9]



Esquema 1.2: Ejemplos de reacciones de hidratación de nitrilos con interés industrial.

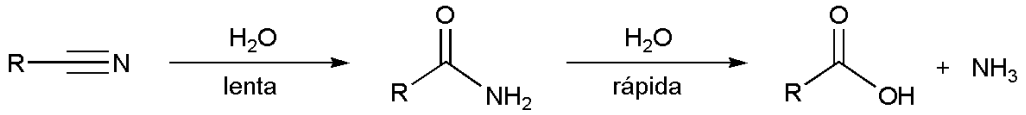
Los métodos clásicos empleados en Química Orgánica para llevar a cabo las reacciones de hidratación de nitrilos involucran el empleo de ácidos y bases fuertes, tales como H_2SO_4 o NaOH.[3a,b] No obstante, estas metodologías clásicas presentan dos grandes inconvenientes: *(i)* se requieren generalmente condiciones de reacción drásticas (altas temperaturas y pHs extremos), incompatibles con la presencia de un buen número de grupos funcionales en la molécula, y *(ii)* las reacciones presentan una baja selectividad.[3a,b] Esto último es debido, fundamentalmente, a la formación competitiva de los correspondientes, ácidos carboxílicos generados por hidrólisis de la amida (Esquema 1.3),[10]

[8] (a) H. Yamada, M. Kobayashi, *Biosci. Biotech. Biochem.* **1996**, *60*, 1391; (b) S. Sanchez, A. L. Demain, *Org. Process Res. Dev.* **2011**, *15*, 224.

[9] (a) S. van Pelt, F. van Rantwijk, R. A. Sheldon, en *Focus on Catalysis Applications* (suplemento a *Chimica Oggi / Chemistry Today*), Teknoscienze Srl, Milán, **2008**, vol. 26, pp. 2-4; (b) B. Li, J. Su, J. Tao, *Org. Process Res. Dev.* **2011**, *15*, 291.

[10] Conviene recordar en este punto que la transformación directa de nitrilos en ácidos carboxílicos también presenta un elevado interés sintético e industrial. A modo de ejemplo, los ácidos nicotínico, (*R*)-(-)-mandélico y el (*S*)-(+)-ibuprofeno se producen industrialmente a través de una reacción de hidrólisis del nitrilo

proceso que se encuentra especialmente favorecido desde un punto de vista cinético cuando las reacciones se llevan a cabo en medio básico.[11] Aunque cuando se trabaja en medio ácido es posible detener selectivamente el proceso en la primera etapa, *i.e.* la formación de la amida, en estos casos es necesario controlar cuidadosamente la temperatura y estequiometría empleadas en la reacción para evitar la formación de productos poliméricos laterales.[12] Por otro lado, cabe destacar también que, desde un punto de vista industrial, la etapa final de neutralización, requerida tanto en medio básico como en medio ácido, conduce a la formación de una gran cantidad de sales lo que dificulta en muchos casos la purificación del producto final, además de llevar asociado un problema relacionado con el tratamiento de dichos residuos.



Esquema 1.3: Reacciones de hidratación e hidrólisis de nitrilos.

La utilización de medios de reacción extremadamente ácidos o básicos puede evitarse empleando enzimas (conocidas bajo el nombre genérico de "nitrilo hidratasas"),[8,9,13] así como catalizadores metálicos heterogéneos[14] y homogéneos,[15] lo que conduce a procesos más selectivos

---

correspondiente. Ver referencias 3a,b y: K. Weissermel, H.-J. Arpe, en *Industrial Organic Chemistry (4th edn.)*, Wiley-VCH, Weinheim, **2003**.

[11] Como ejemplo ilustrativo, las constantes de velocidad para las reacciones de hidratación del acetonitrilo e hidrólisis de la acetamida, medidas a pH 12 y a 25 ºC, son 1.6 x 10^{-6} y 7.4 x 10^{-5} M^{-1} s^{-1}, respectivamente. Estos valores ponen de manifiesto que, en medio básico, la hidrólisis final de la amida es un proceso más rápido que la etapa inicial de hidratación del nitrilo: J. Chin, *Acc. Chem. Res.* **1991**, *24*, 145.

[12] Ver, por ejemplo: (a) J. T. Edward, S. C. R. Meacock, *J. Chem. Soc.* **1957**, 2000; (b) P. J. Steynberg, Z. Denga, R. Steyn, B. C. Bezuidenhout, N. L. Stark, *Int. Pat. Appl.* WO 0026178, **2000**.

[13] Revisiones cubriendo el uso de enzimas en la hidratación catalítica de nitrilos: (a) M. Kobayashi, S. Shimizu, *Curr. Opin. Chem. Biol.* **2000**, *4*, 95; (b) I. Endo, M. Nojori, M. Nakasako, S. Nagashima, M. Yohda, M. Odaka, *J. Inorg. Biochem.* **2001**, 83, 247; (c) V. Mylerová, L. Martínková, *Curr. Org. Chem.* **2003**, *7*, 1279; (d) J. A. Kovacs, *Chem. Rev.* **2004**, *104*, 825; (e) G. De Santis, R. Di Cosimo, en *Biocatalysis for the Pharmaceutical Industry: Discovery, Development and Manufacturing* (eds. J. Tao, G.-Q. Lin, A. Liese), Wiley-VCH, Weinheim, **2009**, pp.153-181; (f) S. Prasad, T. C. Bhalla, *Biotechnol. Adv.* **2010**, *28*, 725.

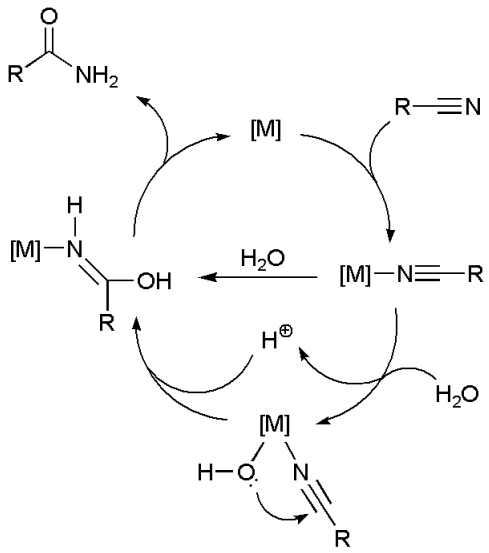
[14] Ejemplos representativos de catalizadores heterogéneos pueden encontrarse en: (a) H. Hayashi, K. Nishi, Y. Watanabe, T. Okazaki, *J. Catal.* **1981**, *69*, 44; (b) C. G. Rao, *Synth. Commun.* **1982**, *12*, 177; (c) K.-T. Liu, M.-H. Shih, H.-W. Huang, C.-J. Hu, *Synthesis* **1988**, 715; (d) P. Breuilles, R. Leclerc, D. Uguen, *Tetrahedron Lett.*

hacia la formación de las amidas. Las enzimas han encontrado, durante los últimos años, diversas aplicaciones a nivel industrial. De hecho, los ejemplos recogidos en el Esquema 1.2 se llevan a cabo en la industria empleando catalizadores enzimáticos. No obstante, la alta especificidad que presentan las enzimas (cada sustrato a transformar requiere de una enzima específica) y su alto coste hace que los catalizadores metálicos, más generales y experimentalmente más fáciles de manipular, representen una alternativa mucho más simple y atractiva.

Las reacciones de hidratación de nitrilos catalizadas por metales de transición involucran la activación inicial del nitrilo por coordinación al centro metálico. De esta forma se favorece la posterior adición nucleofílica de la molécula de agua, o el grupo OH^- si se trabaja en medio básico, sobre el triple enlace C≡N (Esquema 1.4).[15] El proceso de adición de agua puede producirse de forma tanto inter- como intramolecular, postulándose generalmente en el segundo caso un hidroxo-complejo como intermedio de reacción.

1994, *35*, 1401; (e) N. Toshima, Y. Wang, *Langmuir* **1994**, *10*, 4574; (f) C. P. Wilgus, S. Downing, E. Molitor, S. Bains, R. M. Pagni, G. W. Kabalka, *Tetrahedron Lett.* **1995**, *36*, 3469; (g) S. Sebti, A. Rhihil, A. Saber, N. Hanafi, *Tetrahedron Lett.* **1996**, 37, 6555; (h) Y. Wang, H. Liu, N. Toshima, *J. Phys. Chem.* **1996**, *100*, 19533; (i) B. M. Khadilkar, V. R. Madyar, *Synth. Commun.* **2002**, *32*, 1731; (j) A. Solhy, A. Smahi, H. El Badaoui, B. Elaabar, A. Amoukal, A. Tikad, S. Sebti, D. J. Macquarrie, *Tetrahedron Lett.* **2003**, *44*, 4031; (k) F. Bazi, H. El Badaoui, S. Tamani, S. Sokori, A. Solhy, D. J. Macquarri, S. Sebti, *Appl. Catal. A: Gen.* **2006**, *301*, 211; (l) T. Mitsudome, Y. Mikami, H. Mori, S. Arita, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Chem. Commun.* **2009**, 3258; (m) A. Y. Kim, H. S. Bae, S. Park, S. Park, K. H. Park, *Catal. Lett.* **2011**, *141*, 685; (n) Z. Gordi, H. Eshghi, *J. Korean Chem. Soc.* **2011**, *55*, 715; (o) M. Tamura, H. Wakasugi, K.-I. Shimizu, A. Satsuma, *Chem. Eur. J.* **2011**, *17*, 11428; (p) Y. Gangarajula, B. Gopal, *Chem. Lett.* **2012**, *41*, 101; (q) Y.-M. Liu, L. He, M.-M. Wang, Y. Cao, H-Y. He, K.-N. Fan, *ChemSusChem* **2012**, *5*, 1392; (r) K.-I. Shimizu, N. Imaiida, K. Sawabe, A. Satsuma, *Appl. Catal. A: Gen.* **2012**, *421-422*, 114; (s) T. Subramanian, K. Pitchumani, *Catal. Commun.* **2012**, *29*, 109; (t) K.-I. Shimizu, T. Kubo, A. Satsuma, T. Kamachi, K. Yoshizawa, *ACS Catal.* **2012**, *2*, 2467; (u) T. Hirano, K. Uehara, K. Kamata, N. Mizuno, *J. Am. Chem. Soc.* **2012**, *134*, 6425; (v) M. B. Gawande, P. S. Branco, I. D. Nogueira, A. A. Ghumman, N. Bundaleski, A. Santos, O. M. N. D. Teodoro, R. Luque, *Green Chem.* **2013**, *15*, 682; (x) M. Tamura, A. Satsuma, K.-I. Shimizu, *Catal. Sci. Technol.* **2013**, en imprenta (DOI: 10.1039/C3CY00033H).

[15] Revisiones sobre el uso de catalizadores metálicos homogéneos en reacciones de hidratación de nitrilos: (a) A. W. Parkins, *Platinum Metals Rev.* **1996**, *40*, 169; (b) V. Y. Kukushkin, A. J. L. Pombeiro, *Chem. Rev.* **2002**, *102*, 1771; (c) N. A. Bokach, V. Y. Kukushkin, *Russ. Chem. Rev.* **2005**, *74*, 153; (d) V. Y. Kukushkin, A. J. L. Pombeiro, *Inorg. Chim. Acta* **2005**, *358*, 1; (e) T. J. Ahmed, S. M. M. Knapp, D. R. Tyler, *Coord. Chem. Rev.* **2011**, *255*, 949.



Esquema 1.4: Ciclos catalíticos simplificados para las reacciones de hidratación de nitrilos.

Estudios recientes han puesto también de manifiesto que el ataque nucleofílico de la molécula de agua al nitrilo coordinado puede verse favorecido por la presencia en la esfera de coordinación del metal de ligandos auxiliares capaces de establecer enlaces de hidrógeno con el agua, activándola y facilitando su aproximación al nitrilo (Figura 1.1).[15] Este efecto supone un ejemplo de la llamada "*catálisis bifuncional*", donde el ión metálico actúa como ácido de Lewis y el ligando *"cooperativo"* como base de Lewis, concepto muy explotado en el campo de la catálisis homogénea durante los últimos años.[16]

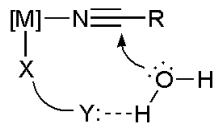


Figura 1.1: Efecto cooperativo del ligando en los procesos de hidratación de nitrilos.

[16] Los procesos de transferencia de hidrógeno a cetonas a través de mecanismos de esfera externa, descritos por R. Noyori y colaboradores, así como las reacciones de hidratación selectiva de alquinos para dar aldehídos (adición *anti*-Markovnikov), desarrolladas por el grupo de D. B. Grotjahn, son sin lugar a dudas los ejemplos más ilustrativos de este concepto. Ver, por ejemplo: (a) R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931; (b) R. Noyori, T. Ohkuma, *Angew. Chem. Int. Ed.* **2001**, *40*, 40; (c) D. B. Grotjahn, *Chem. Eur. J.* **2005**, *11*, 7146; (d) A. S. Borovik, *Acc. Chem. Res.* **2005**, *38*, 54; (e) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393; (f) T. Ikariya, A. J. Blacker, *Acc. Chem. Res.* **2007**, *40*, 1300; (g) D. B. Grotjahn, *Dalton Trans.* **2008**, 6497; (h) D. B. Grotjahn, *Pure Appl. Chem.* **2010**, *82*, 635; (h) D. B. Grotjahn, *Top. Catal.* **2010**, *53*, 1009.

Centrándonos en los catalizadores homogéneos, en la actualidad se conoce una gran variedad de complejos metálicos, fundamentalmente de los grupos 8-12, capaces de promover la hidratación selectiva de nitrilos en amidas.[15] Entre ellos merece ser destacado, por su elevada actividad catalítica en condiciones de reacción suaves (70-100 ºC), el hidruro-complejo de platino(II) [PtH(PMe_2OH){$(PMe_2O)_2H$}] (**1.1**), descrito por A. W. Parkins y colaboradores en el año 1995.[17] Con este derivado han llegado a alcanzarse valores de TOF (*turnover frequency*) y TON (*turnover number*) de hasta 1500 h^{-1} y 77000, respectivamente,[18] que se encuentran entre los más altos descritos hasta la fecha para las reacciones de hidratación de nitrilos empleando catalizadores metálicos. La exquisita tolerancia a otros grupos funcionales que muestra el complejo **1.1** ha sido explotada con éxito en la síntesis multi-etapa de un buen número de productos naturales[19] y compuestos con actividad biológica[20] de estructura elaborada.

---

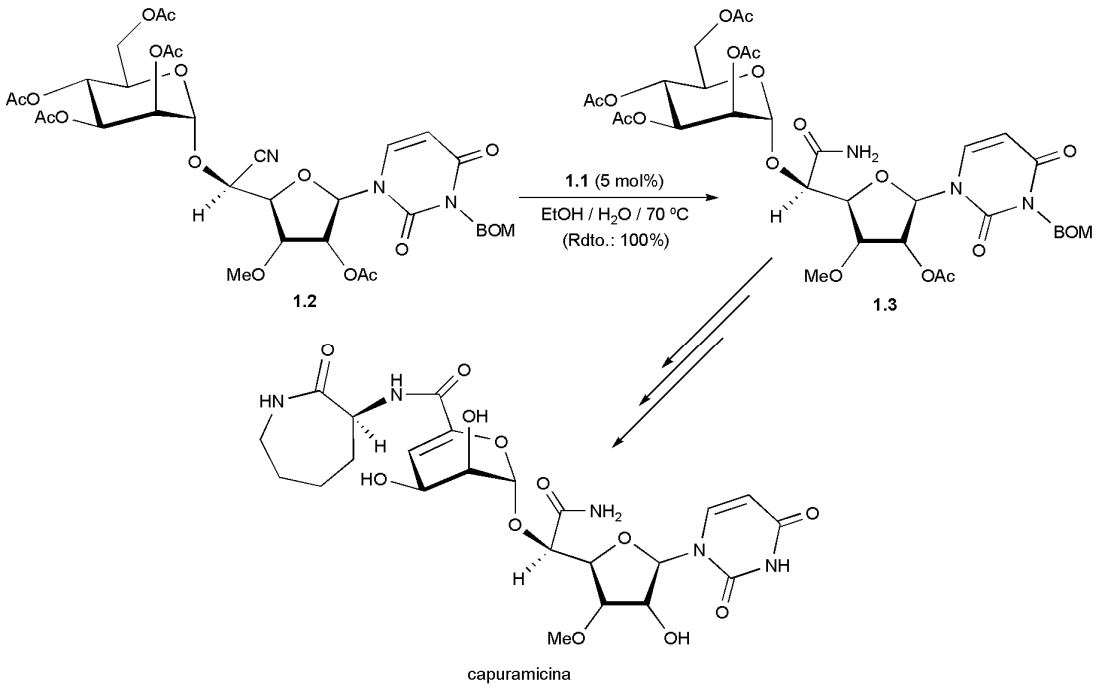
[17] (a) T. Ghaffar, A. W. Parkins, *Tetrahedron Lett.* **1995**, *36*, 8657; (b) T. Ghaffar, A. W. Parkins, *J. Mol. Catal. A: Chem.* **2000**, *160*, 249.

[18] La velocidad de un catalizador se expresa habitualmente a través de la llamada *frecuencia de repetición de ciclo* (*turnover frequency* o TOF), que se define como la cantidad de moles de producto formados por unidad de tiempo dividida por la cantidad de moles de catalizador. Por otro lado, la productividad de un catalizador se expresa a través del llamado *número de repetición de ciclo* (*turnover number* o TON), que se define como el número de moles de producto obtenido por mol de catalizador.

[19] Ver, por ejemplo: (a) J. C. Rech, P. E. Floreancig, *Org. Lett.* **2005**, *7*, 5175; (b) S. B. Herzon, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 5342; (c) X. Jiang, J. García-Fortanet, J. K. De Brabander, *J. Am. Chem. Soc.* **2005**, *127*, 11254; (d) T. J. Greshock, R. L. Funk, *Org. Lett.* **2006**, *8*, 2643; (e) X. Jiang, N. Williams, J. K. De Brabander, *Org. Lett.* **2007**, *9*, 227; (f) T. Kan, Y. Kawamoto, T. Asakawa, T. Furuta, T. Fukuyama, *Org. Lett.* **2008**, *10*, 169; (g) L. E. Brown, Y. R. Landaverry, J. R. Davies, K. A. Milinkevich, S. Ast, J. S. Carlson, A. G. Oliver, J. P. Konopelski, *J. Org. Chem.* **2009**, *74*, 5405; (h) R. A. Jones, M. J. Krische, *Org. Lett.* **2009**, *11*, 1849; (i) M. Kurosu, K. Li, D. C. Crick, *Org. Lett.* **2009**, *11*, 2393; (j) F. J. Cortez, R. Sarpong, *Org. Lett.* **2010**, *12*, 1428; (k) C.-K. Mai, M. F. Sammons, T. Sammakia, *Angew. Chem. Int. Ed.* **2010**, *49*, 2397; (l) M. K. M. Tun, D. J. Wüstmann, S. B. Herzon, *Chem. Sci.* **2011**, *2*, 2251; (m) B. M. Trost, J. Xie, J. D. Sieber, *J. Am. Chem. Soc.* **2011**, *133*, 20611; (n) L. Yao, B. Pitta, P. C. Ravikumar, M. Purzycki, F. F. Fleming, *J. Org. Chem.* **2012**, *77*, 3651.

[20] Ver, por ejemplo: (a) J. Akisanya, A. W. Parkins, J. W. Steed, *Org. Process. Res. Dev.* **1998**, *2*, 274; (b) A. Papakyprianou, A. W. Parkins, P. D. Prince, J. W. Steed, *Org. Prep. Proced. Int.* **2002**, *34*, 436; (c) M. North, A. W. Parkins, A. N. Shariff, *Tetrahedron Lett.* **2004**, *45*, 7625; (d) X.-B. Jiang, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Org. Chem.* **2004**, *69*, 2327; (e) J. R. Falck, S. Gao, R. N. Prasad, S. R. Koduru, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1768; (f) T. A. Brugel, R. W. Smith, M. Balestra, C. Becker, T. Daniels, G. M. Koether, S. R. Throner, L. M. Panko, D. G. Brown, R. Liu, J. Gordon, M. F. Peters, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5405; (g) T. A. Brugel, R. W. Smith, M. Balestra, C. Becker, T. Daniels, T. N. Hoerter, G. M. Koether, S. R. Throner, L. M. Panko, J. J. Folmer, J. Cacciola, A. M. Hunter, R. Liu, P. D. Edwards, D. G. Brown, J. Gordon, N. C. Ledonne, M. Pietras, P. Schroeder, L. A. Sygowski, L. T. Hirata, A. Zacco, M. F. Peters, *Bioorg. Med.*

A modo de ejemplo, en el Esquema 1.5 se muestra la transformación del nitrilo **1.2** en la amida primaria **1.3**, etapa involucrada en la síntesis total de la capuramicina, un producto natural que exhibe actividad antituberculosa.[19i]

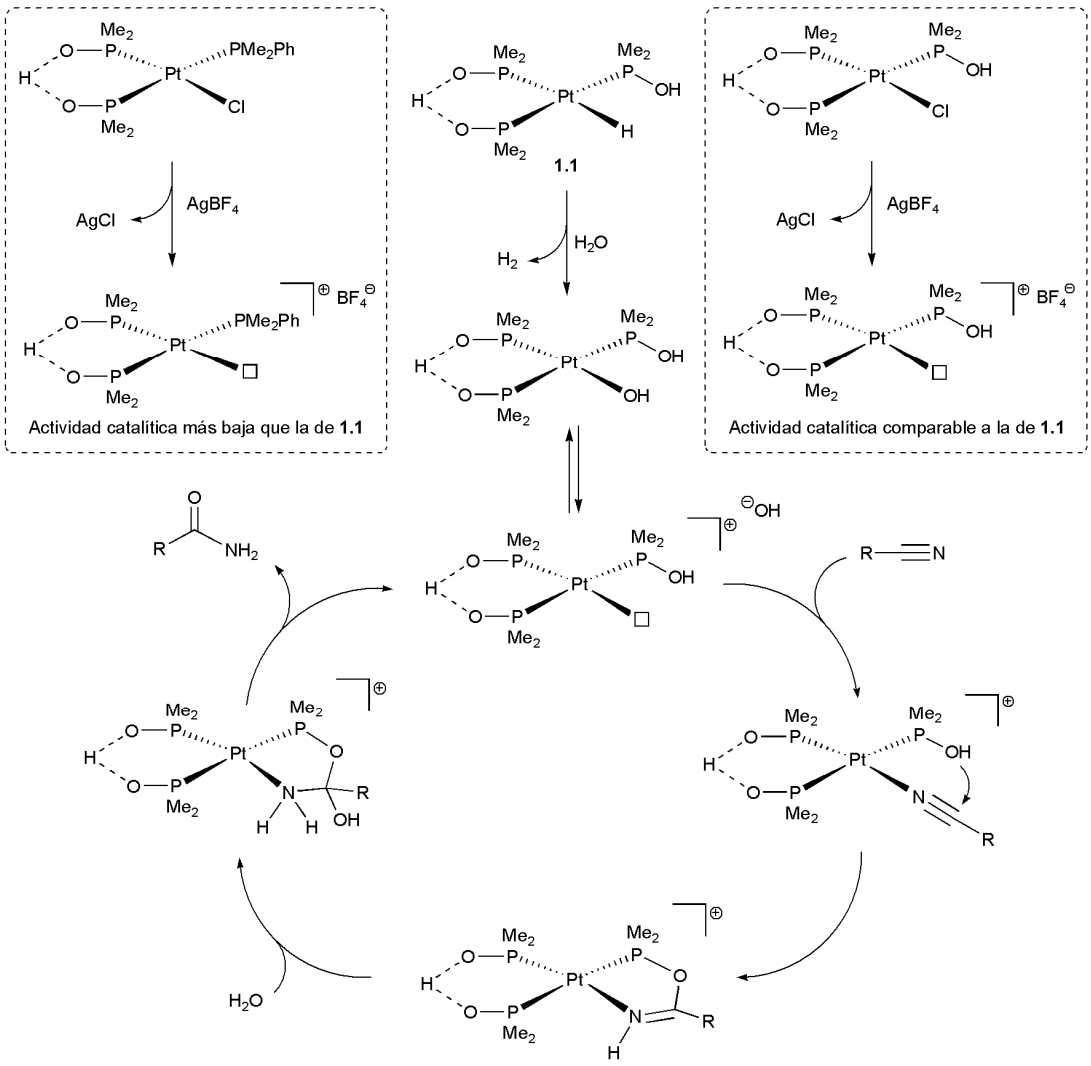


Esquema 1.5: Etapa de hidratación del nitrilo **1.2** en la amida **1.3** en la síntesis total de la capuramicina.

La efectividad del catalizador de Parkins [PtH(PMe$_2$OH){(PMe$_2$O)$_2$H}] (**1.1**) se explica por la presencia del ligando fosfinito PMe$_2$OH en su estructura que, como puede verse en el Esquema 1.6, participa activamente en el proceso de hidratación.[17]

Otro sistema catalítico que merece ser destacado por su remarcable actividad es la combinación [{Rh(μ-OMe)(cod)}$_2$]/PCy$_3$ (cod = 1,5-ciclooctadieno) descrita por S. Saito y colaboradores,[21] ya que es capaz de promover la hidratación selectiva de una gran variedad de nitrilos a temperatura ambiente (TOF ≤ 8 h^{-1}). Al igual que con el derivado **1.1**, el proceso transcurre en ausencia de base, empleando un alcohol como disolvente, y en presencia de pequeñas cantidades de agua.

Chem. Lett. **2010**, *20*, 5847; (h) R. S. Andrews, J. J. Becker, M. R. Gagné, *Angew. Chem. Int. Ed.* **2012**, *51*, 4140.
[21] A. Goto, K. Endo, S. Saito, *Angew. Chem. Int. Ed.* **2008**, *47*, 3607.



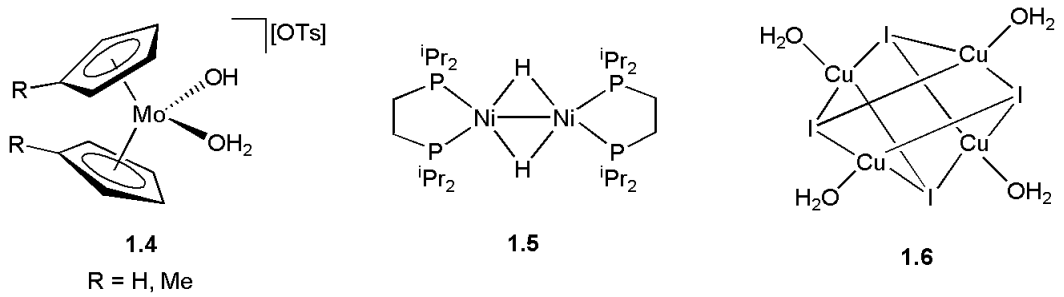
Esquema 1.6: Mecanismo de acción propuesto para el catalizador de Parkins **1.1**.

También se han descrito diferentes catalizadores capaces de operar directamente en agua sin el requerimiento de un co-disolvente orgánico. Este aspecto, además de ser interesante en el contexto de la *Química Verde*, es particularmente adecuado al tratarse de una transformación catalítica en la que el agua participa como reactivo. Entre otros ejemplos podemos citar los derivados molibdoceno $[(\eta^5\text{-}C_5H_4R)_2Mo(OH)(H_2O)][OTs]$ (OTs = *p*-toluensulfonato) (**1.4**),[22] la especie dímera de niquel(I) $[\{Ni(dippe)(\mu\text{-}H)\}_2]$ (**1.5**)[23] o el acuo-complejo de cobre(I) $[Cu_4(\mu_3\text{-}I)_4(H_2O)_4]$

[22] (a) K. L. Breno, M. D. Pluth, D. R. Tyler, *Organometallics* **2003**, *22*, 1203; (b) K. L. Breno, M. D. Pluth, C. W. Landorf, D. R. Tyler, *Organometallics* **2004**, *23*, 1738; (c) T. J. Ahmed, L. V. Zakharov, D. R. Tyler, *Organometallics* **2007**, *26*, 5179; (d) T. J. Ahmed, D. R. Tyler, *Organometallics* **2008**, *27*, 2608.

[23] (a) M. G. Crestani, A. Arévalo, J. J. García, *Adv. Synth. Catal.* **2006**, *348*, 732; (b) C. Crisóstomo, M. G. Crestani, J. J. García, *J. Mol. Catal. A: Chem.* **2007**, *266*,

(**1.6**)[24] representados en la Figura 1.2. No obstante, la actividad de estos derivados es muy inferior a la presentada por el catalizador de Parkins [PtH(PMe_2OH){$(PMe_2O)_2H$}] (**1.1**) (TOF ≤ 10 h^{-1}).



1.4
R = H, Me

1.5

1.6

Figura 1.2: Ejemplos de catalizadores metálicos activos en agua.

Como se ha comentado en la *Introducción General* de esta *Memoria*, el rutenio se ha afianzado en las últimas décadas como uno de los metales más versátiles y más utilizados en catálisis homogénea,[25] conociéndose en la actualidad un buen número de sistemas catalíticos para la hidratación de nitrilos basados en este metal. En las siguientes líneas se presenta una revisión bibliográfica breve de los avances alcanzados en este campo.

El primer ejemplo de la utilización de un complejo de rutenio para promover la hidratación de nitrilos fue descrito por H. Taube y colaboradores en el año 1974.[26] Empleando cantidades estequiométricas del derivado $[RuCl(NH_3)_5][Cl]_2$, dichos autores fueron capaces de convertir una familia variada de nitrilos aromáticos y alifáticos en las amidas primarias correspondientes, con buenos rendimientos (64-99%), tras 6-8 h de calentamiento en diclorometano húmedo. Unos años más tarde, S.-I. Murahashi y colaboradores describieron la hidratación selectiva de un buen número de nitrilos empleando cantidades catalíticas (3 mol%) del

---

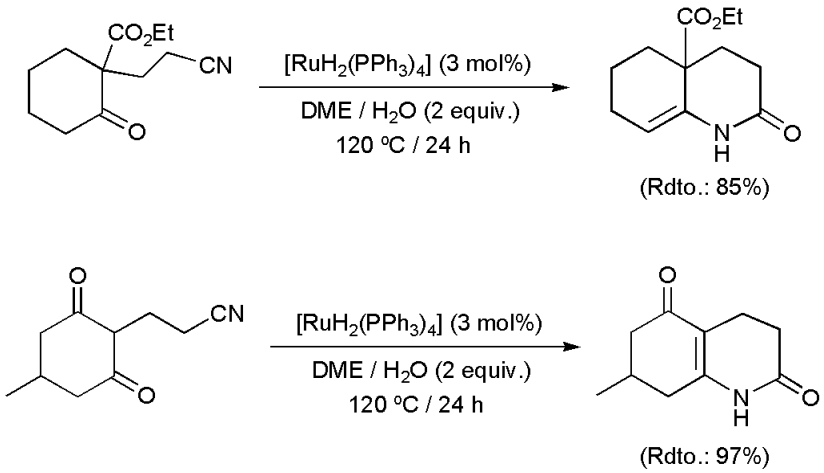
139; (c) M. G. Crestani, J. J. García, *J. Mol. Catal. A: Chem.* **2009**, *299*, 26; (d) C. Crisóstomo, M. G. Crestani, J. J. García, *Inorg. Chim. Acta* **2010**, *363*, 1092.

[24] Z. Li, L. Wang, X. Zhou, *Adv. Synth. Catal.* **2012**, *354*, 584.

[25] Ver, por ejemplo: (a) *Ruthenium in Organic Synthesis* (ed. S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**; (b) *Ruthenium Catalysts and Fine Chemistry* (eds. C. Bruneau, P. H. Dixneuf), Springer, Berlin, **2004**; (c) *Ruthenium: Properties, Production and Applications* (ed. D. B. Watson), Nova Science Publishers, New York, **2011**; (d) *Ruthenium Oxidation Complexes: Their Uses as Homogeneous Organic Catalysts* (ed. W. P. Griffith), Springer, Dordrecht, **2011**.

[26] S. E. Diamond, B. Grant, G. M. Tom, H. Taube, *Tetrahedron Lett.* **1974**, *15*, 4025.

complejo dihidruro de rutenio(II) $[RuH_2(PPh_3)_4]$.[27] Así, llevando a cabo las reacciones en 1,2-dimetoxietano (DME) a 120 ºC durante 24 h, y en presencia de 2 equivalentes de agua, fueron capaces de generar las amidas deseadas con rendimientos superiores al 92% (TOF ≤ 2 h^{-1}). Bajo las mismas condiciones de reacción, el complejo $[RuH_2(PPh_3)_4]$ también fue capaz de transformar una serie de *δ*-cetonitrilos en las correspondientes lactamas a través de un proceso *tandem* hidratación/condensación, que no contaba con precedentes bibliográficos previos (ejemplos representativos se muestran en el Esquema 1.7).[27,28]



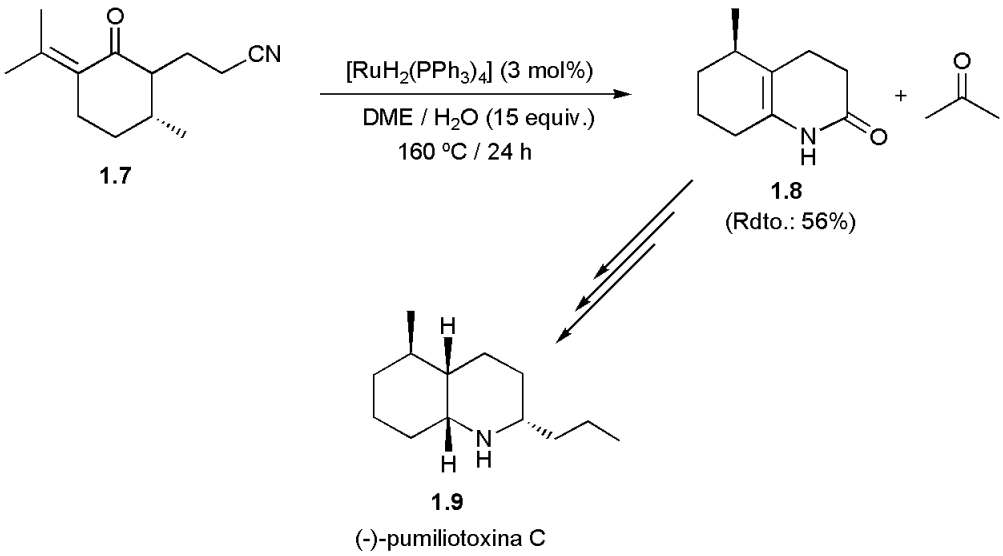
Esquema 1.7: Síntesis catalítica de lactamas empleando $[RuH_2(PPh_3)_4]$.

El potencial sintético de este proceso *tandem* queda claramente reflejado en la síntesis total de la (-)-pumiliotoxina C (**1.9**), un alcaloide de origen natural producido por ciertas ranas de América Central.[27] Como se muestra en el Esquema 1.8, la etapa clave en la síntesis del alcaloide **1.9** es la reacción del *δ*-cetonitrilo **1.7** con agua catalizada por el complejo $[RuH_2(PPh_3)_4]$, que conduce a la lactama ópticamente activa **1.8** a través de una secuencia de reacciones retroaldólica, de hidratación de la unidad CN y de condensación intramolecular de la amida resultante.

---

[27] (a) S.-I. Murahashi, S. Sasao, E. Saito, T. Naota, *J. Org. Chem.* **1992**, *57*, 2521; (b) S.-I. Murahashi, S. Sasao, E. Saito, T. Naota, *Tetrahedron* **1993**, *49*, 8805; (c) S.-I. Murahashi, T. Naota, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1805; (d) S.-I. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, *23*, 225.

[28] El complejo $[RuH_2(PPh_3)_4]$ también ha mostrado ser activo en procesos de amidación hidrolítica de nitrilos con aminas ($R^1C{\equiv}N + HNR^1R^2 + H_2O \rightarrow R^1C(=O)NR^2R^3 + NH_3$). Ver, por ejemplo: (a) S.-I. Murahashi, T. Naota, E. Saito, *J. Am. Chem. Soc.* **1986**, *108*, 7846; (b) A. J. M. van Dijk, T. Heyligen, R. Duchateau, J. Meuldijk, C. E. Koning, *Chem. Eur. J.* **2007**, *13*, 7664; (c) A. J. M. van Dijk, R. Duchateau, E. J. M. Hensen, J. Meuldijk, C. E. Koning, *Chem. Eur. J.* **2007**, *13*, 7673.



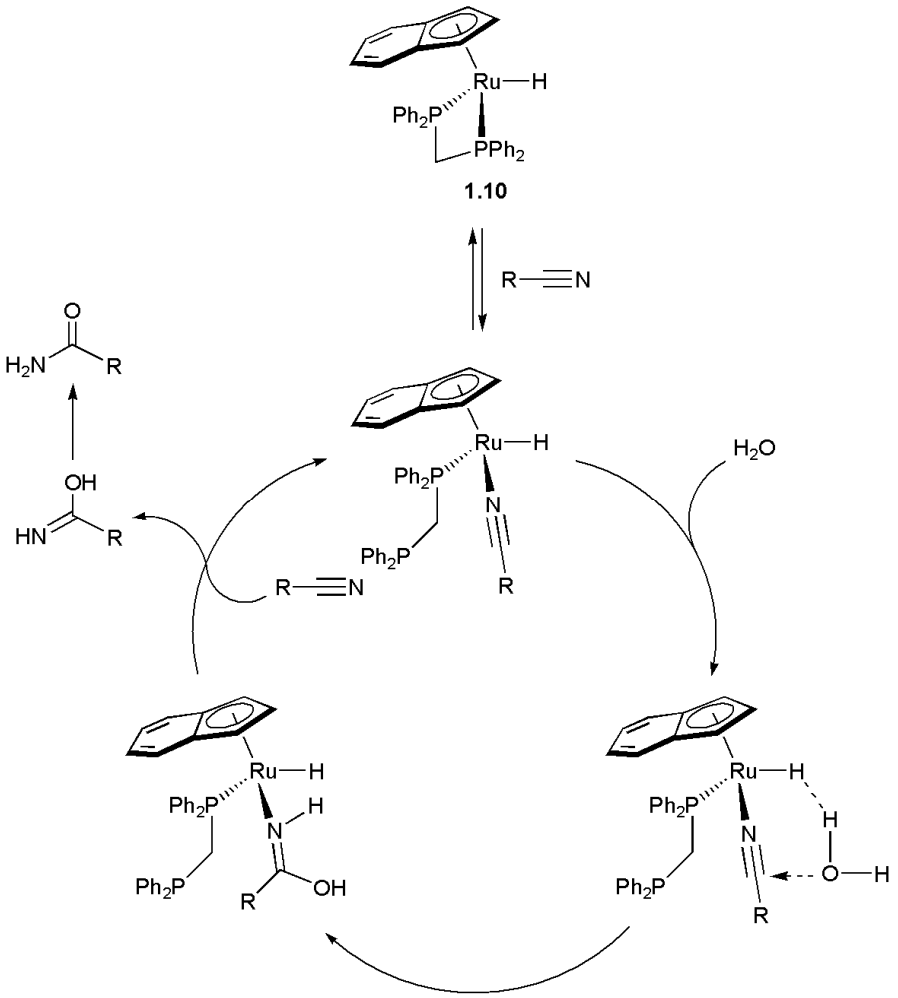
Esquema 1.8: Implicación del complejo $[RuH_2(PPh_3)_4]$ en la síntesis total del alcaloide **1.9**.

El complejo $[RuH(\eta^5\text{-}C_9H_7)(dppm)]$ (**1.10**; C_9H_7 = indenilo; dppm = bis(difenilfosfino)metano) es otro ejemplo relevante de un hidruro-derivado de rutenio(II) activo en la hidratación selectiva de nitrilos en amidas. Con este sistema, que es capaz de operar directamente en agua a 120 ºC, se han llegado a alcanzar valores de TON de 800 y 865 en la hidratación del benzonitrilo y del acetonitrilo, respectivamente.[29] El ligando hidruro juega un papel clave en la eficiencia del proceso, ya que el complejo cloruro análogo $[RuCl(\eta^5\text{-}C_9H_7)(dppm)]$ resultó ser totalmente inactivo en las mismas condiciones de reacción. Este hecho pudo ser explicado mediante cálculos teóricos DFT (Teoría del Funcional de la Densidad), que pusieron de manifiesto el efecto cooperativo que ejerce el ligando hidruro, capaz de activar la molécula de agua a través de un "enlace de dihidrógeno" Ru-H···H-OH (Esquema 1.9). De esta forma se facilita el ataque nucleófilico del agua sobre el nitrilo coordinado al rutenio, coordinación que implica la ruptura de uno de los enlaces fósforo-rutenio del catalizador.

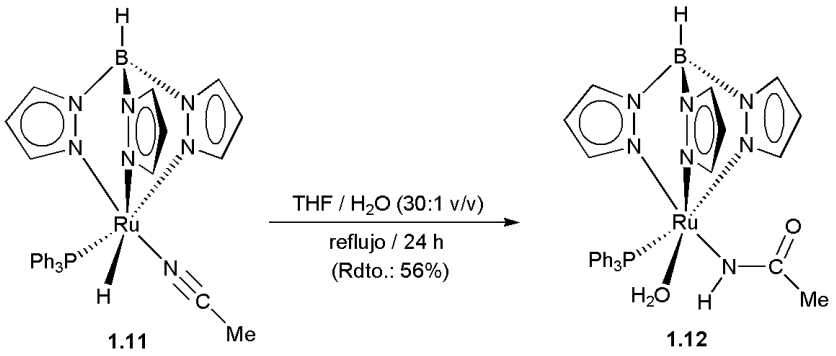
El mismo efecto cooperativo del ligando hidruro también ha sido evidenciado mediante cálculos DFT en la reacción del complejo tris(pirazolil)borato $[RuH(Tp)(PPh_3)(NCMe)]$ (**1.11**) con agua, que conduce a

[29] (a) W. K. Fung, X. Huang, M. L. Man, S. M. Ng, M. Y. Hung, Z. Lin, C. P. Lau, *J. Am. Chem. Soc.* **2003**, *125*, 11539; (b) C. P. Lau, S. M. Ng, G. Jia, Z. Lin, *Coord. Chem. Rev.* **2007**, *251*, 2223.

la formación del derivado acetamido [Ru(Tp)(PPh_3)(H_2O){NHC(=O)Me}] (**1.12**) (Esquema 1.10).[30]



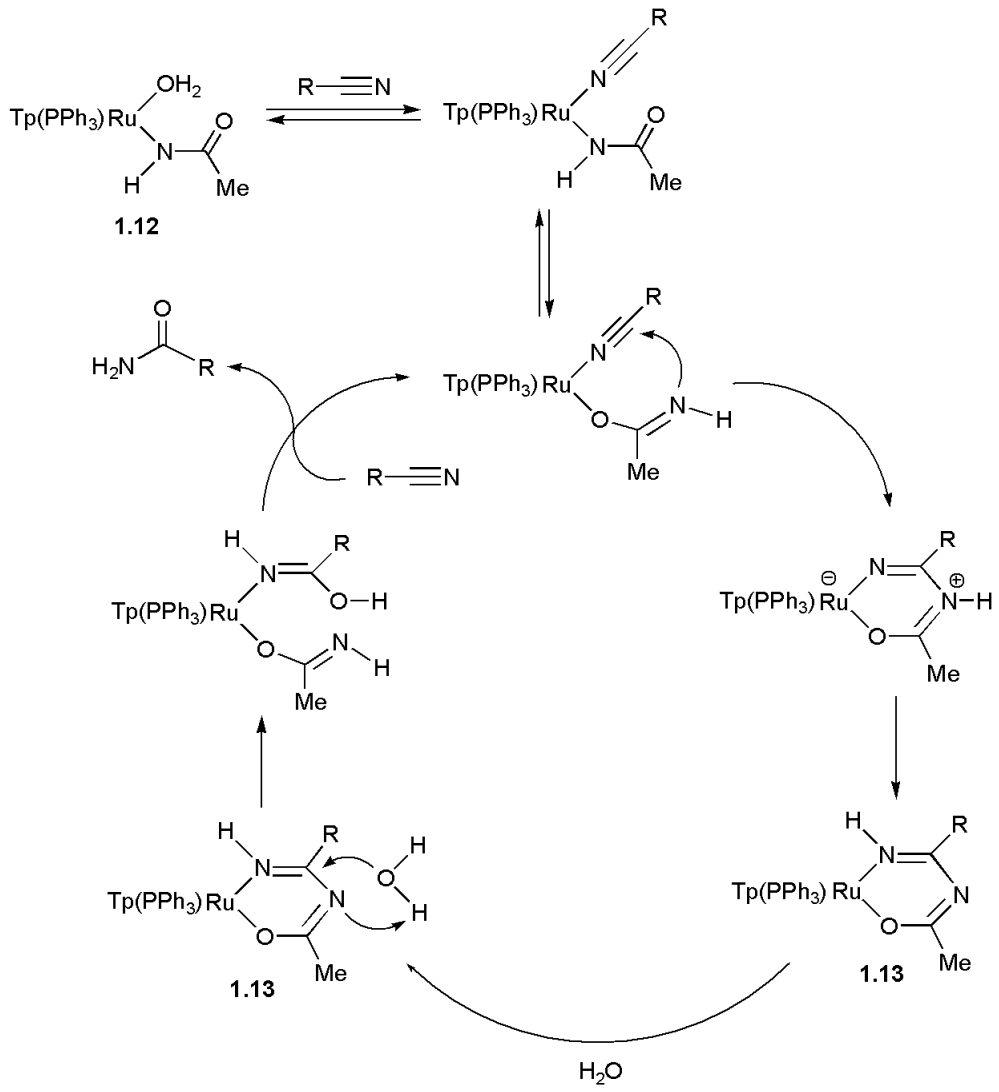
Esquema 1.9: Efecto cooperativo del ligando hidruro en el complejo [RuH(η^5-C_9H_7)(dppm)] (**1.10**).



Esquema 1.10: Reactividad del complejo [RuH(Tp)(PPh_3)(NCMe)] (**1.11**) frente al agua.

[30] C. W. Leung, W. Zheng, D. Wang, S. M. Ng, C. H. Yeung, Z. Zhou, Z. Lin, C. P. Lau, *Organometallics* **2007**, *26*, 1924.

Dicho complejo acetamido [Ru(Tp)(PPh_3)(H_2O){NHC(=O)Me}] (**1.12**) es capaz de promover la hidratación de diferentes nitrilos en mezclas 1,4-dioxano/agua a 150 °C, llegando a alcanzarse con él valores máximos de TON y TOF de 200 y 8 h^{-1}, respectivamente.[31] La monitorización de las reacciones catalíticas mediante la técnica de Resonancia Magnética Nuclear (RMN), en combinación con cálculos DFT, ha permitido proponer el ciclo catalítico que se recoge en el Esquema 1.11. En dicho ciclo, el ataque nucleofílico del agua se produce sobre un intermedio de tipo *N*-imidoilimidato (**1.13**), que pudo ser aislado y caracterizado, y que es generado por acoplamiento del nitrilo con el grupo acetamido.



Esquema 1.11: Mecanismo propuesto para la hidratación de nitrilos catalizada por el complejo acetamido de rutenio **1.12**.

[31] C. W. Leung, W. Zheng, Z. Zhou, Z. Lin, C. P. Lau, *Organometallics* **2008**, *27*, 4957.

El cluster tetranuclear **1.14**[32] y el derivado mononuclear **1.15**[33] son ejemplos adicionales de complejos rutenio-hidruro capaces de promover la hidratación de enlaces C≡N (Figura 1.3). El primero de ellos (1 mol%) resultó ser efectivo en la hidratación de una gran variedad de nitrilos aromáticos, heteroaromáticos, *α,β*-insaturados y alifáticos empleando ^{i}PrOH, THF o DME como disolvente, 10-20 equivalentes de agua, y temperaturas de trabajo comprendidas entre los 80 y 100 ºC (TOF ≤ 16 h^{-1}). Por su parte, el complejo **1.15** fue ensayado exclusivamente en la transformación del benzonitrilo en benzamida, mostrando una actividad catalítica comparativamente mucho más baja en condiciones de reacción similares (TOF < 1 h^{-1}).

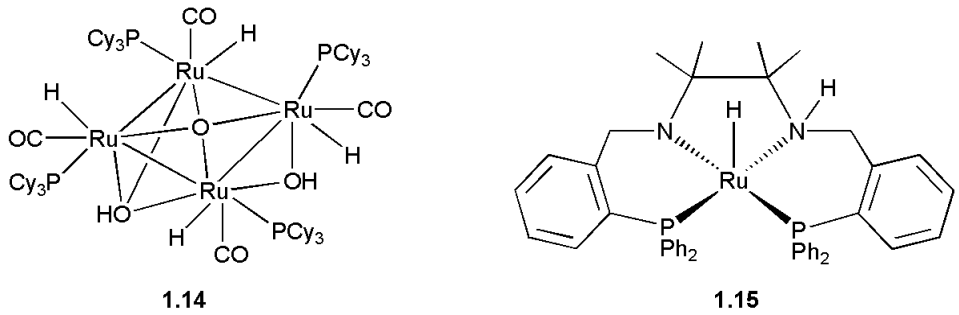
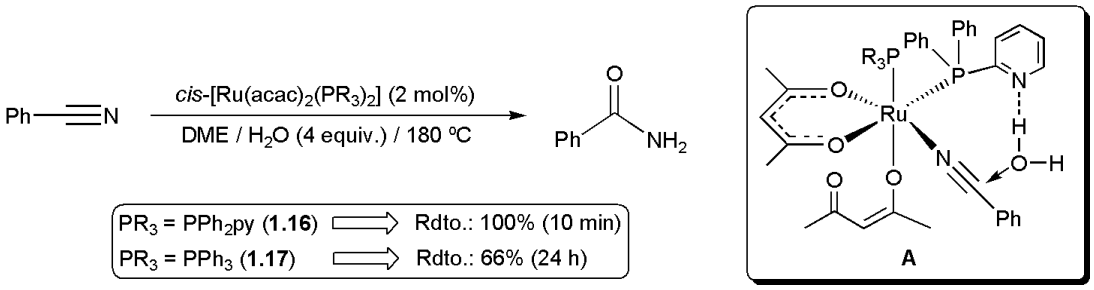


Figura 1.3: Estructura de los complejos hidruro de rutenio **1.14** y **1.15**.

El papel clave que juegan los ligandos auxiliares en las reacciones de hidratación de nitrilos queda claramente reflejado en los trabajos de T. Oshiki y colaboradores. Estos autores han descrito que el complejo *cis*-$[Ru(acac)_2(PPh_2py)_2]$ (**1.16**; acac = acetilacetonato; PPh_2py = 2-(difenilfosfino)piridina), a diferencia de su análogo *cis*-$[Ru(acac)_2(PPh_3)_2]$ (**1.17**), es capaz de hidratar de manera muy eficiente (valores de TOF de hasta 20900 h^{-1}) una gran variedad de nitrilos a 180 ºC empleando DME como disolvente y 4 equivalentes de agua.[34] A modo de ejemplo, en el Esquema 1.12 se muestra la diferente actividad catalítica que presentan estos derivados en el proceso de hidratación de benzonitrilo para generar benzamida. Así, a pesar de que ambos catalizadores presentan la misma

[32] C. S. Yi, T. N. Zeczycki, S. V. Lindeman, *Organometallics* **2008**, *27*, 2030.
[33] T. Li, I. Bergner, F. N. Haque, M. Zimmer-De Iuliis, D. Song, R. H. Morris, *Organometallics* **2007**, *26*, 5940.
[34] (a) M. Utsunomiya, K. Takahashi, T. Oshiki, K. Takai, *Jpn. Kokai Tokkyo Koho* JP 2004269522, **2004**; (b) T. Oshiki, H. Yamashita, K. Sawada, M. Utsunomiya, K. Takahashi, K. Takai, *Organometallics* **2005**, *24*, 6287; (c) T. Oshiki, K. Takai, *Jpn. Kokai Tokkyo Koho* JP 2008088153, **2008**; (d) T. Oshiki, I. Hyodo, A. Ishizuka, *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 41.

estructura, además de propiedades electrónicas y estéricas muy parecidas, el complejo *cis*-[Ru(acac)$_2$(PPh$_2$Py)$_2$] (**1.16**) es mucho más activo que el derivado *cis*-[Ru(acac)$_2$(PPh$_3$)$_2$] (**1.17**) debido a la capacidad del ligando 2-difenilfosfinopiridina para generar enlaces de hidrógeno con el agua. De esta forma, la formación del intermedio **A**, no accesible cuando se emplea PPh$_3$ como ligando, activa la molécula de agua facilitando el proceso de adición.



Esquema 1.12: Efecto cooperativo del ligando 2-difenilfosfinopiridina (PPh$_2$Py).

Con el objetivo de profundizar en este efecto cooperativo, los mismos autores estudiaron también la actividad catalítica del complejo [Ru(η^3-2-metilalil)$_2$(cod)] en presencia de diferentes piridil-fosfinas (Figura 1.4).[35] Aunque la actividad catalítica mostrada por estos sistemas fue tan sólo moderada (TOF ≤ 5 h^{-1}), se observó que ésta era comparativamente superior al emplear la 2-difenilfosfino-4-piridil(dimetil)amina como ligando, argumentándose que el aumento en la densidad electrónica del anillo piridínico favorece la formación del enlace de hidrógeno con el agua.

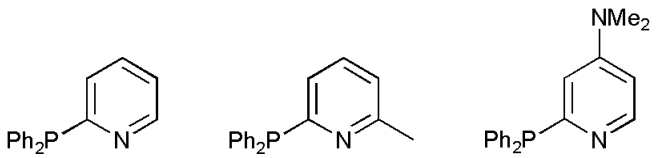


Figura 1.4: Piridil-fosfinas empleadas por T. Oshiki y colaboradores.

Tomando como base algunos de estos resultados, T. Šmejkal y B. Breit sintetizaron los complejos acetilacetonato de rutenio(II) *cis*-[Ru(acac)$_2$(PR$_3$)$_2$] (PR$_3$ = 6-difenilfosfino-*N*-pivaloil-2-aminopiridina (**1.18**), 3-difenilfosfinoisoquinolona (**1.19**)) (Figura 1.5), que mostraron ser catalizadores activos y selectivos en la hidratación del sustrato modelo 4-

[35] M. Muranaka, I. Hyodo, W. Okumura, T. Oshiki, *Catal. Today* **2011**, *164*, 552.

metilbenzonitrilo.[36] No obstante, bajo las mismas condiciones de reacción, su efectividad fue comparativamente muy inferior (TOF ≤ 20 h^{-1}) a la del complejo *cis*-[Ru(acac)$_2$(PPh$_2$py)$_2$] (**1.16**). Tal y como apuntan los autores en su trabajo, una de las posibles causas para explicar la baja actividad catalítica de los complejos **1.18** y **1.19** podría estar relacionada con la quelatación de los ligandos fosfina al rutenio, *vía N*-coordinación de los restos piridina e isoquinolona. De esta forma se bloquearía parcialmente la esfera de coordinación del metal, dificultando la coordinación del nitrilo.

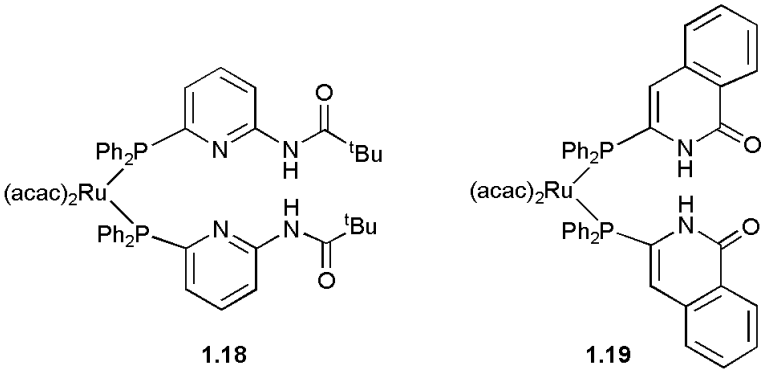


Figura 1.5: Estructura de los complejos *cis*-[Ru(acac)$_2$(PR$_3$)$_2$] **1.18** y **1.19**.

El posible efecto cooperativo de los ligandos fosfina hidrosolubles PTA (1,3,5-triaza-7-fosfatriciclo[3.3.1.1^{3,7}]decano o 1,3,5-triaza-fosfaadamantano), PTA-Bn (cloruro de 1-bencil-3,5-diaza-1-azonia-7-fosfatriciclo[3.3.1.1^{3,7}]decano) y DAPTA (3,7-diacetil-1,3,7-triaza-5-fosfabiciclo[3.3.1]nonano), capaces de interaccionar con el agua a través de enlaces de hidrógeno, ha sido evocado en nuestro grupo de investigación para explicar la mayor actividad catalítica de los complejos [RuCl$_2$(η^6-areno)(PTA)] (**1.20a-d**), [RuCl$_2$(η^6-areno)(PTA-Bn)] (**1.21a-d**) y [RuCl$_2$(η^6-areno)(DAPTA)] (**1.22a-d**) en comparación con sus análogos [RuCl$_2$(η^6-areno)(TPPMS)] (**1.23a-d**), que contienen como ligando auxiliar la trifenilfosfina monosulfonada TPPMS (sal sódica de la (3-sulfonatofenil)difenilfosfina), incapaz de formar enlaces de hidrógeno con el agua (Figura 1.7).[37] Dentro de cada una de estas familias de complejos, se observaron igualmente diferencias apreciables en la actividad catalítica en función del ligando areno unido al rutenio. Así, el orden de velocidad observado en todos los casos, *i.e.* C$_6$Me$_6$ (**d**) > 1,3,5-C$_6$H$_3$Me$_3$ (**c**) > *p*-cimeno

[36] T. Šmejkal, B. Breit, *Organometallics* **2007**, *26*, 2461.
[37] V. Cadierno, J. Francos, J. Gimeno, *Chem. Eur. J.* **2008**, *14*, 6601.

(**b**) > C_6H_6 (**a**), puso de manifiesto que cuanto más voluminoso y rico en densidad electrónica es el ligando areno, mayor es la eficiencia del proceso. De entre todos los complejos sintetizados, el derivado [$RuCl_2(\eta^6$-$C_6Me_6)$(PTA-Bn)] (**1.21d**) resultó ser el más activo, siendo capaz de hidratar de manera eficiente y selectiva una gran variedad de nitrilos (aromáticos, heteroaromáticos, alifáticos y *a,ß*-insaturados), empleando directamente agua como disolvente, en condiciones de pH neutro, y a una temperatura de trabajo de 100 ºC (TOF ≤ 127 h^{-1} y TON ≤ 100). El complejo **1.21d** mostró además una gran tolerancia hacia la presencia de diferentes grupos funcionales en los sustratos, incluyendo ésteres y alquinos que son susceptibles de sufrir fácilmente procesos de hidrólisis o hidratación, respectivamente.

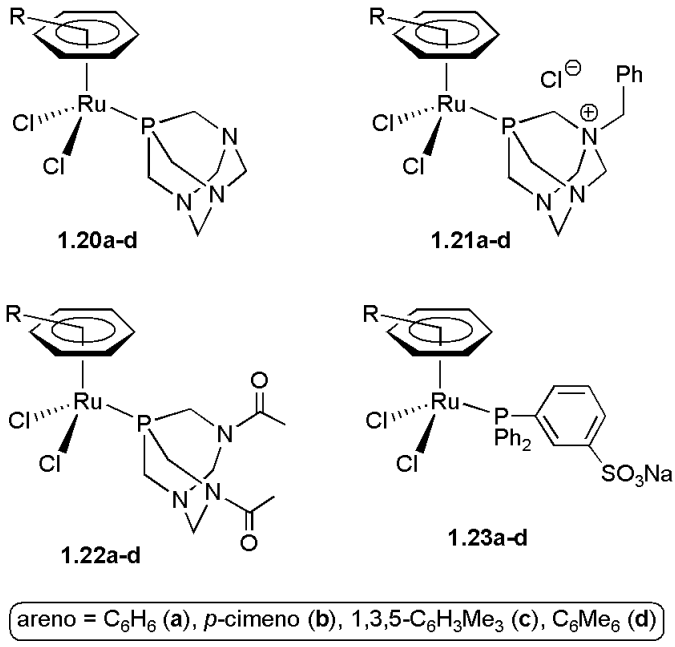


Figura 1.6: Estructura de los complejos rutenio(II)-areno **1.20**-**1.23a-d**.

Un estudio de similares características con los complejos bis(alilo) de rutenio(IV) **1.24-1.29** (Figura 1.7), desarrollado también por nuestro grupo de investigación, volvió a evidenciar el papel clave que juegan los ligandos fosfina capaces de establecer enlaces de hidrógeno con el agua en la efectividad del proceso.[38] Así, al igual que en el caso anterior, los complejos mononucleares **1.24-1.27** y el dinuclear **1.29** resultaron ser mucho más activos que **1.28**. Llevando a cabo las reacciones en agua a 100 ºC, con los

[38] V. Cadierno, J. Díez, J. Francos, J. Gimeno, *Chem. Eur. J.* **2010**, *16*, 9808.

derivados **1.27** y **1.29** consiguieron alcanzarse valores de TON y TOF muy similares a los obtenidos con [$RuCl_2(\eta^6\text{-}C_6Me_6)$(PTA-Bn)] (**1.21d**). Tomando como base estos resultados de nuestro grupo, B. J. Frost y colaboradores describieron posteriormente los sistemas catalíticos [$RuCl_2(PTA)_4$][39] y [$RuCl_2(\eta^6$-tolueno)(PTA-CPh_2NHPh)].[40] Estos complejos fueron capaces de hidratar selectivamente, y de manera muy eficiente (TOF ≤ 285 h^{-1} y TON ≤ 97000), una gran variedad de nitrilos en agua a 100 ºC. Además, el derivado [$RuCl_2(PTA)_4$] pudo ser reciclado hasta 7 veces sin pérdida significativa de su actividad catalítica.

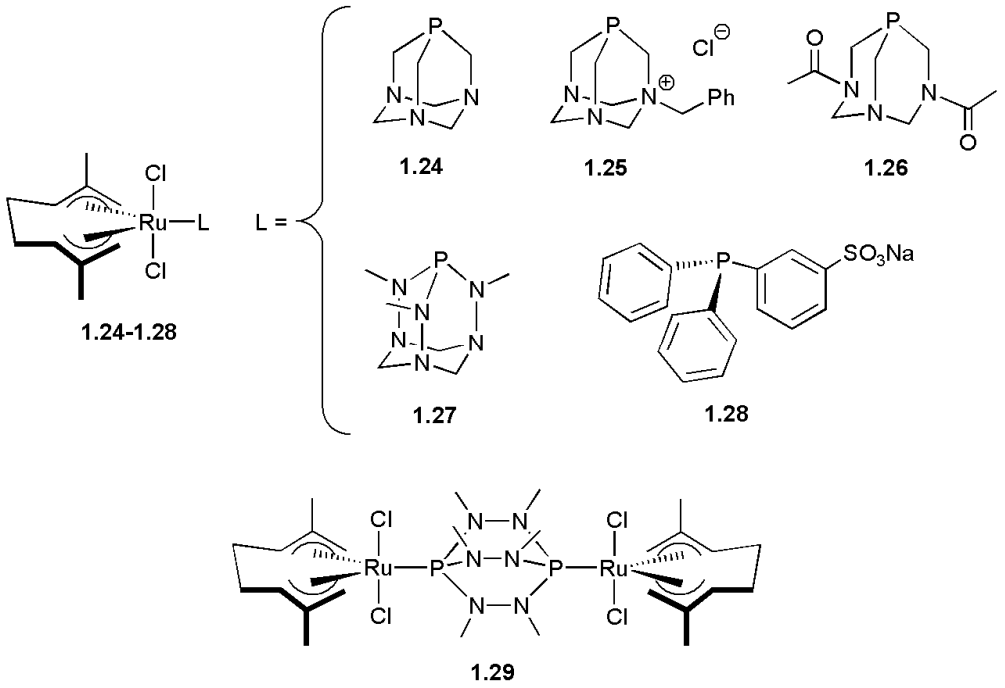
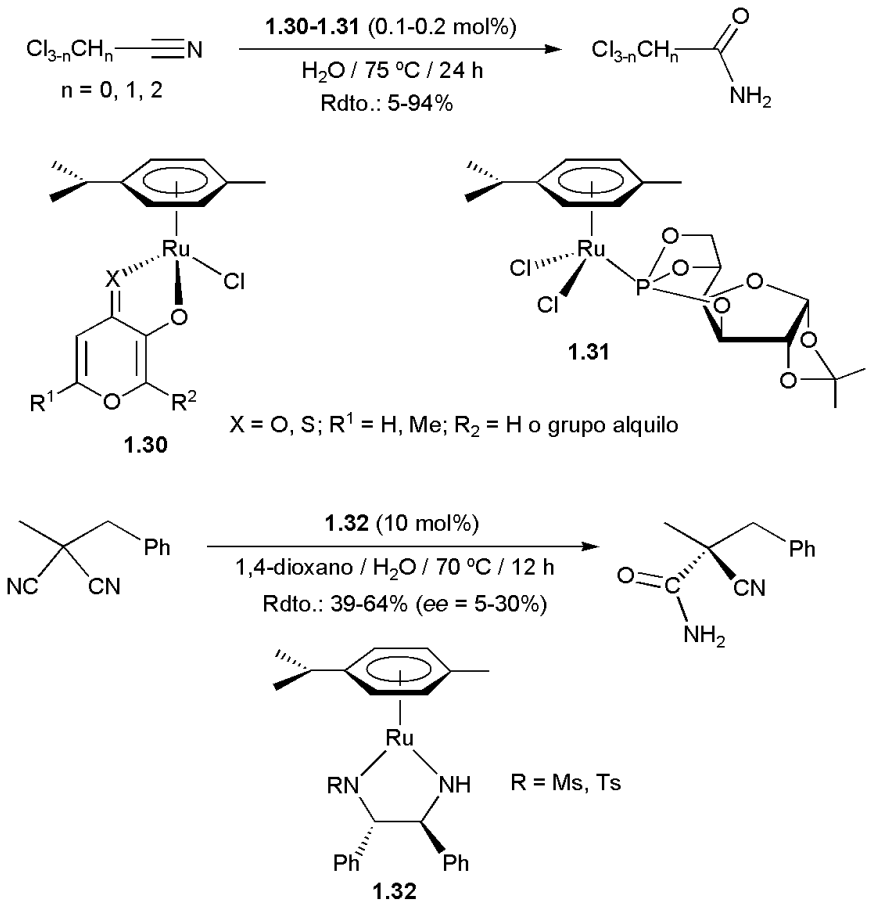


Figura 1.7: Estructura de los complejos bis(alilo)-rutenio(IV) **1.24**-**1.29**.

Los complejos [$Ru(H_2O)(NCMe)_4(P^iPr_3)][BF_4]_2$[41] y [$RuCl_2(\eta^6$-areno)($PR_3$)] (areno = C_6H_6, *p*-cimeno; PR_3 = P^iPr_3, $P(OEt)_3$, $PPh(OEt)_2$, $PPh_2(OEt)$, PPh_3)[42] son otros ejemplos de catalizadores homogéneos de rutenio activos en un medio puramente acuoso, si bien su actividad es tan sólo moderada (TOF ≤ 5 h^{-1} y TON ≤ 96). Además, la baja solubilidad de los segundos en agua hace que sea necesario introducir surfactantes en el medio de reacción para que las reacciones catalíticas tengan lugar. Por otro

[39] W.-C. Lee, B. J. Frost, *Green Chem.* **2012**, *14*, 62.
[40] W.-C. Lee, J. M. Sears, R. A. Enow, K. Eads, D. A. Krogstad, B. J. Frost, *Inorg. Chem.* **2013**, *52*, 1737.
[41] M. Martín, H. Horváth, E. Sola, Á. Kathó, F. Joó, *Organometallics* **2009**, *28*, 561.
[42] A. Cavarzan, A. Scarso, G. Strukul, *Green Chem.* **2010**, *12*, 790.

lado, los derivados rutenio(II)-areno **1.30**,[43] **1.31**[44] y **1.32**[45] también han sido ensayados en la hidratación de triples enlaces C≡N (Esquema 1.13).[46] En particular, los complejos **1.30** y **1.31** resultaron ser activos en la hidratación de cloroacetonitrilos, llegando a generar las correspondientes cloroacetamidas con rendimientos de hasta el 94%, empleando cargas de catalizador bajas y directamente agua como disolvente (TOF ≤ 39 h^{-1} y TON ≤ 562). Por su parte, los derivados quirales **1.32** fueron aplicados en la hidratación asimétrica del *a*-bencil-*a*-metilmalononitrilo, conduciendo a la amida deseada con rendimientos y excesos enantioméricos tan sólo moderados.



Esquema 1.13: Aplicaciones de los complejos rutenio(II)-areno **1.30**-**1.32**.

[43] S. M. Ashraf, I. Berger, A. A. Nazarov, C. G. Hartinger, M. P. Koroteev, E. E. Nifant´ev, B. K. Keppler, *Chem. Biodiversity* **2008**, *5*, 1640.
[44] S. M. Ashraf, W. Kandioller, M. G. Mendoza-Ferri, A. A. Nazarov, C. G. Hartinger, B. K. Keppler, *Chem. Biodiversity* **2008**, *5*, 2060.
[45] S. Kamezaki, S. Akiyama, Y. Kayaki, S. Kuwata, T. Ikariya, *Tetrahedron: Asymmetry* **2010**, *21*, 1169.
[46] P. H. Dixneuf y col. han demostrado que el dímero [{RuCl(μ-Cl)(η^6-*p*-cimeno)}$_2$] es capaz de hidratar con éxito el benzoxazolilacetonitrilo en benzoxazolilacetamida: H. B. Ammar, X. Miao, C. Fischmeister, L. Toupet, P. H. Dixneuf, *Organometallics* **2010**, *29*, 4234.

Muy recientemente, en un intento de emular los centros activos de las "nitrilo hidratasas" de hierro, C. A. Grapperhaus y colaboradores han descrito la hidratación catalítica de benzonitrilo empleando los complejos de rutenio(II) **1.33** (Figura 1.8).[47] Estos derivados fueron capaces de operar en agua a pH neutro con cargas de metal muy bajas (≈ 10^{-3} mol%), generando selectivamente la benzamida deseada (valores de TON y TOF de hasta 242 y 13 h^{-1}, respectivamente, a 124 ºC).

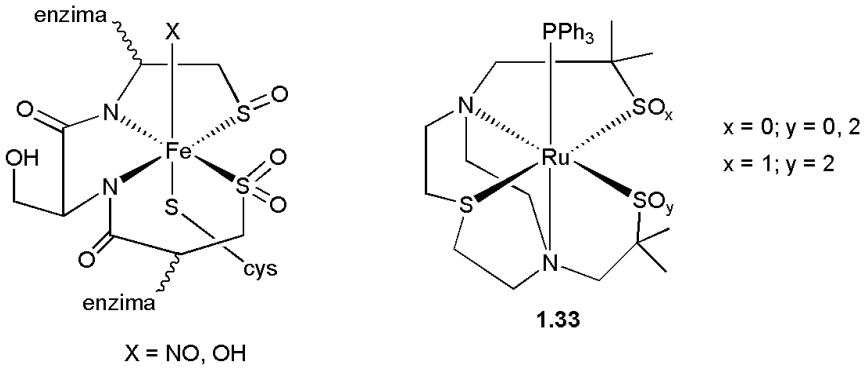


Figura 1.8: Estructura de los centros activos de las "nitrilo hidratasas" de hierro y de los complejos **1.33**.

En otro orden de cosas, a pesar de la alta actividad y generalidad mostrada por los complejos de rutenio(II) **1.20-1.23a-d** (Figura 1.6) y rutenio(IV) **1.24-1.29** (Figura 1.7) desarrollados por nuestro grupo de investigación, éstos presentan dos puntos débiles: *(i)* precisan del uso de disolventes orgánicos durante el proceso de aislamiento de la amida final (purificación cromatográfica), y *(ii)* su reciclaje no es sencillo ya que se encuentra condicionado a la capacidad de la amida para cristalizar selectivamente en el medio de reacción. Esta baja reciclabilidad conduce a que los valores de TON sean relativamente bajos (TON ≤ 100). Conviene recordar en este punto que la reciclabilidad del catalizador es uno de los grandes retos a los que se enfrenta la catálisis homogénea, problema que en muchos casos puede llegar a solventarse por inmovilización del mismo en diversos soportes insolubles, tales como sólidos inorgánicos, polímeros o dendrímeros.[48] En este contexto, las nanopartículas (NPs) han emergido muy recientemente como alternativas muy atractivas y competitivas a estos

[47] D. Kumar, C. A. Masitas, T. N. Nguyen, C. A. Grapperhaus, *Chem. Commun.* **2013**, *49*, 294.
[48] *Recoverable and Recyclable Catalysts* (ed. M. Benaglia), John Wiley & Sons, Chichester, **2009**.

soportes clásicos.[49] De hecho, los catalizadores organometálicos soportados sobre nanopartículas actúan de manera muy similar a como si se encontrasen en estado libre (condiciones homogéneas), considerándose como un sistema *"cuasi"* soluble debido a la gran dispersión que presentan las NPs en el medio de reacción. Este hecho, unido a la alta área superficial de las NPs, permite una accesibilidad muy alta de los sustratos a los centros activos de los complejos soportados.

Un caso particular y muy interesante de NPs son las nanopartículas magnéticas (MNPs), tales como las nanoferritas (Fe_3O_4), que debido a su naturaleza paramagnética pueden ser separadas fácilmente del medio de reacción mediante la ayuda de un imán externo. Este tipo de separación es, operativamente hablando, mucho más cómodo que los procesos clásicos de separación por centrifugación, filtración o separación por membrana.[50] En este contexto, tomando como modelo el sistema **1.34** descrito por V. Polshettiwar y R. S. Varma,[51] nuestro grupo de investigación desarrolló en colaboración con uno de estos autores el catalizador rutenio(II)-areno soportado en nanopartículas magnéticas de tipo Fe_3O_4@SiO_2 **1.35** (Figura 1.9).[52] Ambos nano-catalizadores han mostrado buenas actividades (valores de TOF ≤ 63 h^{-1}) y excelentes selectividades en la hidratación de un amplio rango de nitrilos (aromáticos, heteroaromáticos, alifáticos y *α,β*-insaturados) en agua bajo irradiación microondas (130-150 °C). Una vez finalizadas las reacciones (0.5-7 h de irradiación), los nano-catalizadores **1.34-1.35** pudieron ser fácilmente separados del medio de reacción con la ayuda de un imán externo y

[49] Ver, por ejemplo: (a) A. Corma, H. García, *Top. Catal.* **2008**, *48*, 8; (b) B. M. Weckhuysen, *Nature Chem.* **2009**, *1*, 690; (c) G. J. Hutchings, *J. Mater. Chem.* **2009**, *19*, 1222; (d) S. Wittmann, A. Shätz, R. N. Grass, W. J. Stark, O. Reiser, *Angew. Chem. Int. Ed.* **2010**, *49*, 1867 y referencias allí citadas.

[50] Ver, por ejemplo: (a) A. Hu, G. T. Yee, W. Lin, *J. Am. Chem. Soc.* **2005**, *127*, 12486; (b) N. T. S. Phan, C. S. Gill, J. V. Nguyen, Z. J. Zhang, C. W. Jones, *Angew. Chem. Int. Ed.* **2006**, *45*, 2209; (c) R. Abu-Reziq, H. Alper, D. Wang, M. L. Post, *J. Am. Chem. Soc.* **2006**, *128*, 5279; (d) C. Ó. Daláigh, S. A. Corr, Y. Gun´ko, S. J. Connon, *Angew. Chem. Int. Ed.* **2007**, *46,* 4329; (e) A.-H. Lu, E. L. Salabas, F. Schüth, *Angew. Chem. Int. Ed.* **2007**, *46*, 1222; (f) T. Hara, T. Kaneta, K. Mori, T. Mitsudome, T. Mizugaki, K. Ebitani, K. Kaneda, *Green Chem.* **2007**, *9*, 1246; (g) F. Shi, M. K. Tse, S. Zhou, M.-M. Pohl, J. Radnik, S. Hubner, K. Jahnisch, A. Bruckner, M. Beller, *J. Am. Chem. Soc.* **2009**, *131*, 1775; (h) V. Polshettiwar, R. S. Varma, *Green Chem.* **2010**, *12*, 743; (i) S. Shylesh, V. Schünemann, W. R. Thiel, *Angew. Chem. Int. Ed.* **2010**, *49*, 3428.

[51] V. Polshettiwar, R. S. Varma, *Chem. Eur. J.* **2009**, *15*, 1582.

[52] S. E. García-Garrido, J. Francos, V. Cadierno, J.-M. Basset, V. Polshettiwar, *ChemSusChem* **2011**, *4*, 104.

reciclados tres (**1.34**) o seis (**1.35**) veces. Además, después de la separación, por enfriamiento de la disolución acuosa se forman cristales de la correspondiente amida con buena pureza y alto rendimiento (70-95%), evitando así procesos de purificación que involucren el empleo de disolventes orgánicos.[53]

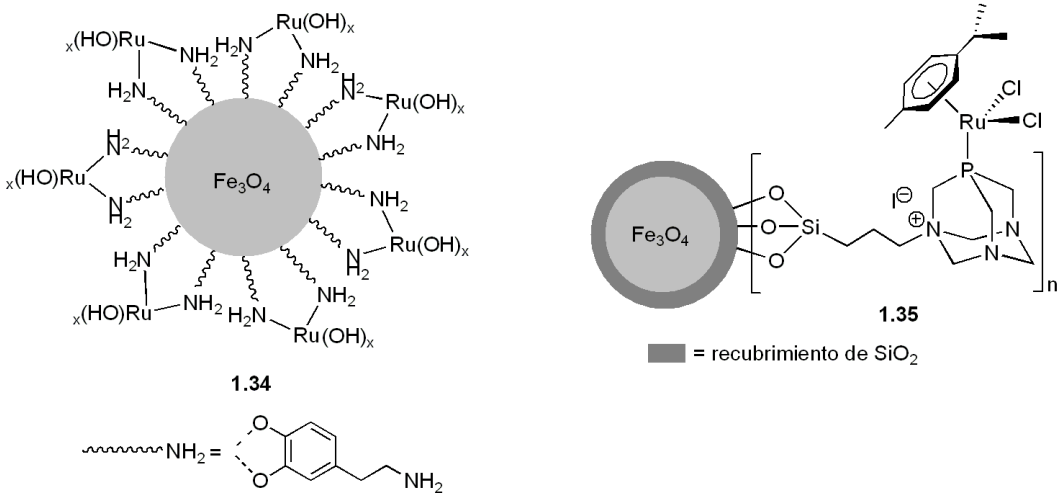


Figura 1.9: Estructura de los nano-catalizadores magnéticos **1.34** y **1.35**.

Ru/C,[54] Ru/Al_2O_3,[55] $Ru(OH)_x/Al_2O_3$,[56] la hidroxiapatita modificada $(RuCl)_2Ca_8(PO_4)_6(OH)_2$[57] y la resina Nafion-Ru[58] son otros ejemplos de sistemas catalíticos heterogéneos basados en rutenio activos en la hidratación de nitrilos. Todos ellos operan directamente en agua, a temperaturas que oscilan entre los 130 y los 175 ºC, y pueden ser reciclados al final de la reacción por filtración. Cabe destacar que, en el caso del hidróxido de rutenio soportado en alúmina ($Ru(OH)_x/Al_2O_3$), ha podido desarrollarse también un proceso en el que no se emplea en ningún

---

[53] Estudios recientes han demostrado también la utilidad de nanopartículas de hidróxido de rutenio ($Ru(OH)_x$) inmovilizadas sobre $Fe_3O_4@SiO_2$ para la hidratación selectiva de nitrilos en agua. Al igual que **1.34** y **1.35**, la separación del catalizador con un imán externo permitió su reciclaje (3 ciclos catalíticos consecutivos sin pérdida de actividad) y el aislamiento de las amidas sin ayuda de disolventes orgánicos: (a) R. B. N. Baig, R. S. Varma, *Chem. Commun.* **2012**, *48*, 6220; (b) R. B. N. Baig, R. S. Varma, *Green Chem.* **2013**, *15*, 398.

[54] T. Kurata, A. Tamaru, Y. Murata, S. Nagashima, T. Okano, K. Ohfuchi, *Jpn. Kokai Tokkyo Koho* JP 48054021, **1971**.

[55] T. Mizuno, *Jpn. Kokai Tokkyo Koho* JP 2005170821, **2005**.

[56] (a) K. Yamaguchi, M. Matsushita, N. Mizuno, *Angew. Chem. Int. Ed.* **2004**, *43*, 1576; (b) K. Yamaguchi, N. Mizuno, *Synlett* **2010**, 2365.

[57] K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani, K. Kaneda, *Chem. Commun.* **2001**, 461.

[58] G. K. S. Prakash, S. B. Munoz, A. Papp, K. Masood, I. Bychiskaya, T. Mathew, G. A. Olah, *Asian J. Org. Chem.* **2012**, *1*, 146.

momento disolvente orgánico alguno, ya que el catalizador sólido se separa fácilmente de la mezcla de reacción por filtración en caliente, y las amidas finales cristalizan en forma pura por enfriamiento del filtrado a 0 °C.

Objetivos

Los antecedentes que acabamos de comentar ponen de manifiesto el interés en el desarrollo de catalizadores metálicos activos y selectivos en las reacciones de hidratación de nitrilos en amidas, así como el papel clave que juegan los ligandos auxiliares en la efectividad del proceso. Los resultados previos obtenidos por nuestro grupo, así como los trabajos publicados por otros autores, indican que sistemas sencillos de tipo rutenio(II)-areno [$RuCl_2(\eta^6$-areno)(L)] presentan una elevada actividad catalítica en estos procesos de hidratación, y que dicha actividad se ve potenciada cuando los ligandos L son capaces de actuar como bases de Lewis activando las moléculas de agua. Con el objetivo final de desarrollar catalizadores "bifuncionales" de tipo [$RuCl_2(\eta^6$-areno)(L)] más eficientes, decidimos evaluar el posible efecto cooperativo de una serie de ligandos *P*-dadores funcionalizados capaces de establecer enlaces de hidrógeno con el agua.

Así, en este *Capítulo 1* se describe:

1.- La síntesis y caracterización de una familia de complejos rutenio(II)-areno de fórmula general [$RuCl_2(\eta^6$-areno)(L)] por reacción de las especies dímeras [{$RuCl(\mu$-Cl)(η^6-areno)}$_2$] (areno = C_6H_6, *p*-cimeno, 1,3,5-$C_6H_3Me_3$, C_6Me_6) con las fosfinas PPh_2py, PPh_2(py-4-NMe_2), PPh_2(py-6-*terc*-amil), 2-$Ph_2PC_6H_4CH_2NHR$ (R = ^{i}Pr, ^{t}Bu), 3-$Ph_2PC_6H_4CH_2NHR$ (R = ^{i}Pr, ^{t}Bu), 4-$Ph_2PC_6H_4CH_2NHR$ (R = ^{i}Pr, ^{t}Bu) y $P(NMe_2)_3$.

2.- La evaluación de la actividad catalítica de estos nuevos complejos en procesos de hidratación de nitrilos en un medio puramente acuoso.

CAPÍTULO 1

1.2.- DISCUSIÓN DE RESULTADOS

Como se acaba de comentar en la *Introducción* del presente *Capítulo*, el objetivo de nuestro trabajo ha sido la preparación de nuevos complejos rutenio(II)-areno [$RuCl_2(\eta^6$-areno$)(PR_3)$] con ligandos *P*-dadores capaces de establecer enlaces de hidrógeno con el agua, y el estudio de su capacidad para actuar como catalizadores bifuncionales en la reacción de hidratación selectiva de nitrilos en amidas primarias. Tomando como base los resultados previos descritos por T. Oshiki[34,35] y nuestro propio grupo de investigación,[37,38] elegimos como ligandos potencialmente cooperativos las piridil-fosfinas PPh_2py (**1.26**), PPh_2(py-4-NMe_2) (**1.27**) y PPh_2(py-6-*terc*-amil) (**1.28**), las amino-aril-fosfinas 2-$Ph_2PC_6H_4CH_2NHR$ (**1.29a-b**), 3-$Ph_2PC_6H_4CH_2NHR$ (**1.30a-b**) y 4-$Ph_2PC_6H_4CH_2NHR$ (**1.31a-b**), y la amino-fosfina $P(NMe_2)_3$ (**1.32**) (Figura 1.10).

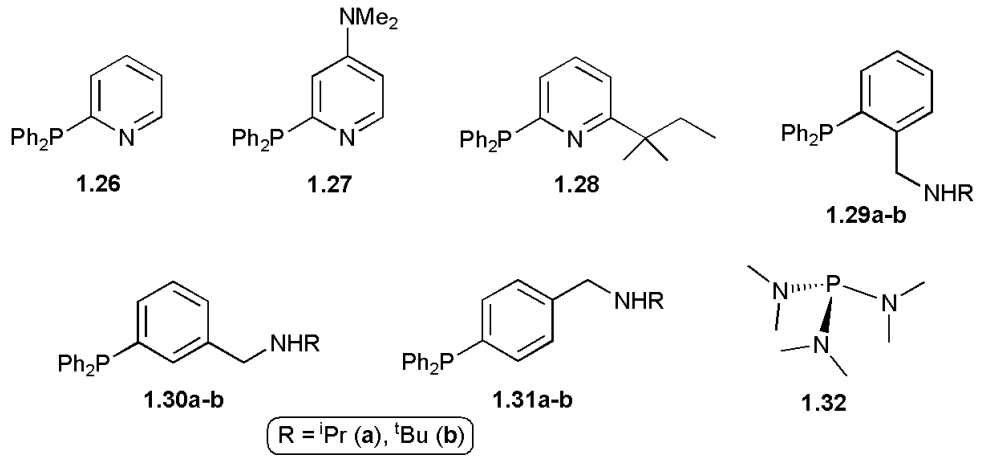
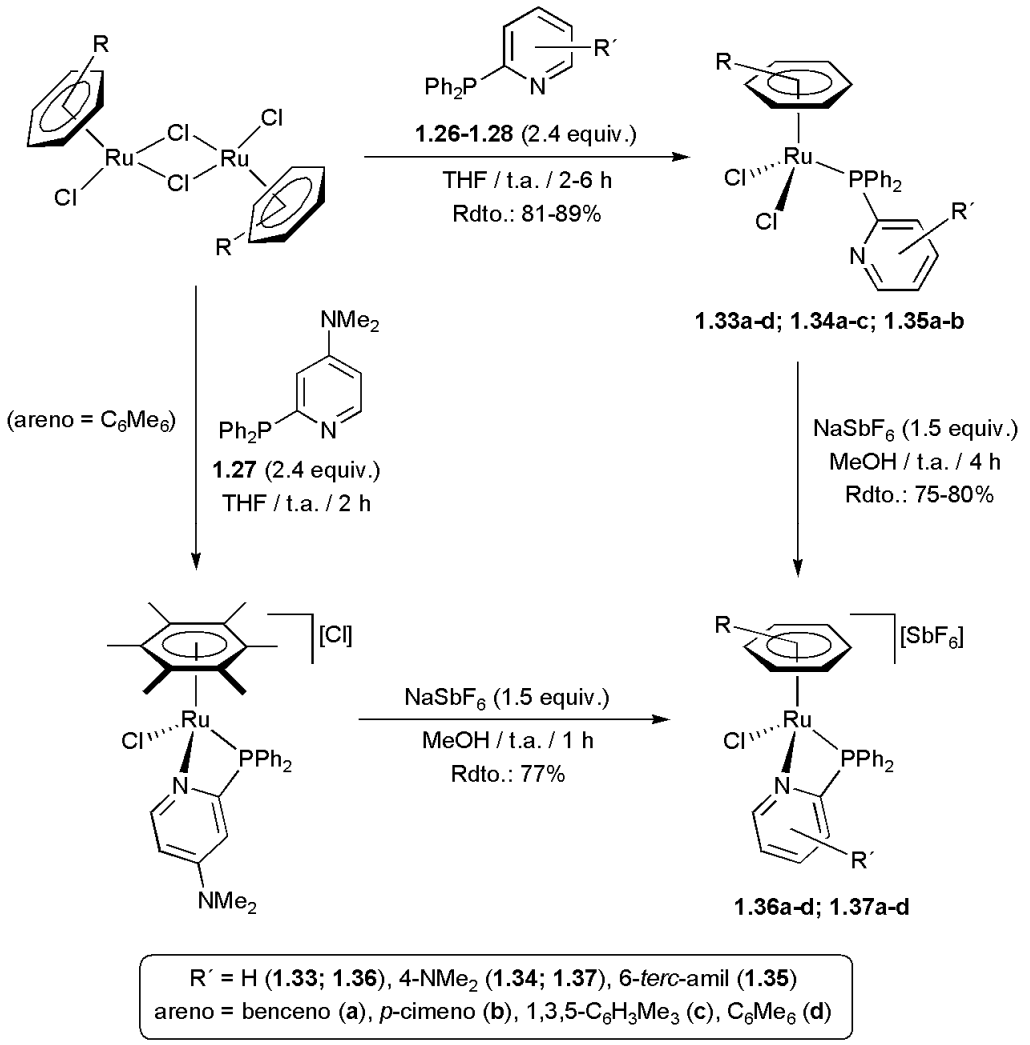


Figura 1.10: Estructura de los ligandos fosfina empleados en este trabajo.

1.2.1.- Síntesis, caracterización y evaluación de la actividad catalítica de complejos rutenio(II)-areno derivados de las piridil-fosfinas PPh_2py (1.26), PPh_2(py-4-NMe_2) (1.27) y PPh_2(py-6-*terc*-amil) (1.28).

La coordinación de los ligandos piridil-fosfina **1.26-1.28** a fragmentos rutenio(II)-areno se llevó a cabo haciendo reaccionar, en tetrahidrofurano y a temperatura ambiente, las especies dímeras [{RuCl(μ-

Cl)(η^6-areno)}$_2$] (areno = C_6H_6, *p*-cimeno, 1,3,5-$C_6H_3Me_3$, C_6Me_6) con un ligero exceso (2.4 equivalentes) de dichos ligandos. Los resultados obtenidos se encuentran recogidos en el Esquema 1.14.



Esquema 1.14: Reactividad de las especies dímeras [{RuCl(μ-Cl)(η^6-areno)}$_2$] frente a las piridil-fosfinas **1.26-1.28**.

Como era de esperar, las reacciones condujeron a la formación de especies mononucleares de tipo [$RuCl_2$(η^6-areno)(PR_3)] (complejos **1.33a-d**, **1.34a-c** y **1.35a-b**) en altos rendimientos (81-89%), resultado de la coordinación selectiva del átomo de fósforo de los ligandos piridil-fosfina **1.26-1.28** al centro metálico. No obstante, debemos hacer notar que: *(i)* Todos los intentos llevados a cabo para obtener el complejo neutro [$RuCl_2$(η^6-C_6Me_6){κ^1-(*P*)-PPh_2(py-4-NMe_2)}], por reacción de [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$] con el ligando PPh_2(py-4-NMe_2) (**1.27**), resultaron infructuosos, generándose en su lugar de manera rápida y selectiva la especie catiónica

[RuCl(η^6-C_6Me_6){κ^2-(*P,N*)-PPh_2(py-4-NMe_2)}][Cl] por quelatación directa del ligando. Este complejo fue aislado como la correspondiente sal de hexafluoroantimoniato **1.37d**, tras el intercambio del anión cloruro con $NaSbF_6$ en metanol. *(ii)* Debido posiblemente a la repulsión estérica entre el grupo *terc*-amilo voluminoso y los sustituyentes del ligando areno, no se observó reacción alguna entre los dímeros [{RuCl(μ-Cl)(η^6-areno)}$_2$] (areno = 1,3,5-$C_6H_3Me_3$, C_6Me_6) y el ligando PPh_2(py-6-*terc*-amil) (**1.28**), incluso a alta temperatura.

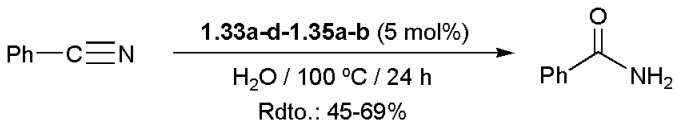
Como era de esperar también, el tratamiento de los complejos neutros **1.33a-d** y **1.34a-c** con $NaSbF_6$ en metanol nos permitió sintetizar los correspondientes derivados catiónicos **1.36a-d** y **1.37a-c**, respectivamente, donde los ligandos piridil-fosfina **1.26-1.27** adoptan un modo de coordinación quelato κ^2-(*P,N*). Sin embargo, debido nuevamente a los impedimentos estéricos asociados al grupo *terc*-amilo, los complejos [$RuCl_2$(η^6-areno){κ^1-(*P*)-PPh_2(py-6-*terc*-amil)}] (areno = C_6H_6 (**1.35a**), *p*-cimeno (**1.35b**)) se mantuvieron inalterados en presencia de $NaSbF_6$, incluso tras tiempos largos de reflujo en metanol. Esto indica que el equilibrio [$RuCl_2$(η^6-areno){κ^1-(*P*)-PPh_2(py-6-*terc*-amil)}] $\rightleftharpoons$ [RuCl(η^6-areno){κ^2-(*P,N*)-PPh_2(py-6-*tert*-amil)}][Cl] se encuentra totalmente desplazado hacia la izquierda en disolución.

Todos los complejos sintetizados fueron caracterizados mediante las técnicas analíticas y espectroscópicas habituales (IR y RMN de $^{31}P\{^1H\}$, ^1H y $^{13}C\{^1H\}$).[59] Además, la estructuras de los derivados [$RuCl_2$(η^6-C_6H_6){κ^1-(*P*)-PPh_2(py-6-*terc*-amil)}] (**1.35a**) y [RuCl(η^6-1,3,5-$C_6H_3Me_3$){κ^2-(*P,N*)-PPh_2(py-4-NMe_2)}][SbF_6] (**1.37c**) pudieron ser confirmadas también de manera inequívoca mediante la técnica de difracción de rayos X de monocristal. Todos los datos obtenidos se encuentran recogidos y discutidos en la correspondiente publicación adjunta, por lo que no serán aquí comentados.

---

[59] Los complejos [$RuCl_2$(η^6-areno){κ^1-(*P*)-PPh_2py}] (areno = C_6H_6 (**1.33a**), *p*-cimeno (**1.33b**), C_6Me_6 (**1.33d**)) y [RuCl(η^6-areno){κ^2-(*P,N*)-PPh_2py}][SbF_6] (areno = C_6H_6 (**1.36a**), *p*-cimeno (**1.36b**), C_6Me_6 (**1.36d**)) han sido publicados con anterioridad en la bibliografía: (a) I. Moldes, E. de la Encarnación, J. Ros, A. Álvarez-Larena, J. F. Piniella, *J. Organomet. Chem.* **1998**, *566*, 165; (b) D. Drommi, C. G. Arena, F. Nicolò, G. Bruno, F. Faraone, *J. Organomet. Chem.* **1995**, *485*, 115; (c) P. Govindaswamy, Y. A. Mozharivskyj, M. R. Kollipara, *Polyhedron* **2004**, *23*, 3115; (d) R. Lalrempuia, P. J. Carroll, M. R. Kollipara, *J. Chem. Sci.* **2004**, *116*, 21.

La capacidad de los complejos neutros [$RuCl_2(\eta^6$-areno){κ^1-(*P*)-PPh_2py}] (**1.33a-d**), [$RuCl_2(\eta^6$-areno){κ^1-(*P*)-PPh_2(py-4-NMe_2)}] (**1.34a-c**) y [$RuCl_2(\eta^6$-areno){κ^1-(*P*)-PPh_2(py-6-*terc*-amil)}] (**1.35a-b**), candidatos potenciales para operar a través de un mecanismo bifuncional, para promover la hidratación catalítica de nitrilos fue evaluada empleando benzonitrilo como sustrato modelo. De forma general, las reacciones se llevaron a cabo bajo atmósfera de nitrógeno, en un tubo sellado, añadiendo el complejo correspondiente (5 mol%) sobre una disolución del benzonitrilo en agua (0.33 M), y calentando la mezcla resultante a 100 ºC durante 24 h (Esquema 1.15).[60]



Esquema 1.15: Hidratación catalítica de benzonitrilo en benzamida empleando los complejos **1.33a-d-1.35a-b** como catalizadores.

Todos los complejos sintetizados mostraron ser catalizadores activos y selectivos en la hidratación del benzonitrilo, generando como único producto de reacción la benzamida deseada, aunque con un rendimiento tan sólo moderado (en ningún caso fue detectada por CG la presencia de ácido benzoico en el crudo de estas reacciones).[61] El mejor resultado se obtuvo con el complejo [$RuCl_2(\eta^6$-C_6Me_6){κ^1-(*P*)-PPh_2py}] (**1.33d**), con el que se alcanzó una conversión del 69% (TOF = 0.3 h^{-1}). Cabe destacar que, al contrario de las observaciones realizadas por T. Oshiki y colaboradores,[35] la presencia del sustituyente dimetilamino en el anillo piridínico no ejerció ningún efecto beneficioso en nuestros sistemas. Así, no se encontraron diferencias de actividad apreciables entre los complejos [$RuCl_2(\eta^6$-areno){κ^1-(*P*)-PPh_2py}] (**1.33a-c**) y [$RuCl_2(\eta^6$-areno){κ^1-(*P*)-PPh_2(py-4-NMe_2)}] (**1.34a-c**). Por otro lado, la efectividad mostrada por esta serie de complejos resultó ser muy similar a la de sus análogos [$RuCl_2(\eta^6$-areno)(PPh_3)] (areno = C_6H_6,

[60] Estas condiciones de reacción resultaron óptimas en los estudios previos llevados a cabo por el grupo con los catalizadores **1.20-1.23a-d** y **1.24-1.29** (Figuras 1.7 y 1.8): Ver referencias 37 y 38.

[61] A pesar de que todos estos complejos son muy poco solubles en agua, este hecho no explica las modestas actividades catalíticas observadas, ya que las mismas reacciones llevadas a cabo en presencia de los surfactantes dodecilsulfato de sodio (SDS) o bromuro de cetiltrimetilamonio (CTABr) no condujeron a rendimientos superiores en la benzamida deseada.

p-cimeno, 1,3,5-$C_6H_3Me_3$, C_6Me_6), que contienen un ligando fosforado, *i.e.* la trifenilfosfina, incapaz de interaccionar con las moléculas de agua a través de enlaces de hidrógeno. Este hecho pone claramente de manifiesto que el efecto cooperativo de las piridil-fosfinas **1.26-1.28** es despreciable en nuestros compuestos.

La quelatación de los ligandos piridil-fosfina durante las reacciones catalíticas, proceso que se encuentra favorecido por la alta polaridad del medio, parece ser la responsable de la baja actividad catalítica observada para los complejos [$RuCl_2(\eta^6$-areno){κ^1-(*P*)-PPh_2py}] (**1.33a-d**) y [$RuCl_2(\eta^6$-areno){κ^1-(*P*)-PPh_2(py-4-NMe_2)}] (**1.34a-c**). De hecho, los espectros de RMN de $^{31}P\{^1H\}$ de los crudos de reacción mostraron la presencia mayoritaria de las especies catiónicas [$RuCl(\eta^6$-areno){κ^2-(*P,N*)-PPh_2py}][Cl] y [$RuCl(\eta^6$-areno){κ^2-(*P,N*)-PPh_2(py-4-NMe_2)}][Cl] en disolución. Estos derivados son comparativamente mucho menos activos que los complejos neutros **1.33a-d** y **1.34a-c**, hecho que pudo ser confirmado al llevar a cabo la hidratación del benzonitrilo con las sales de hexafluoroantimoniato [$RuCl(\eta^6$-areno){κ^2-(*P,N*)-PPh_2py}][SbF_6] (**1.36a-d**) y [$RuCl(\eta^6$-areno){κ^2-(*P,N*)-PPh_2(py-4-NMe_2)}][SbF_6] (**1.37a-c**) sintetizadas previamente (conversiones inferiores al 37% tras 24 h de calentamiento).[62] En el caso de los complejos [$RuCl_2(\eta^6$-areno){κ^1-(*P*)-PPh_2(py-6-*terc*-amil)}] (**1.35a-b**) que, como se ha comentado anteriormente, no sufren procesos de quelatación del ligando piridil-fosfina, su baja actividad catalítica podría venir motivada por la alta congestión estérica alrededor del centro metálico que confiere el grupo *terc*-amilo. Dicha congestión estérica desfavorecería la aproximación del benzonitrilo al átomo de rutenio.

Merece la pena comentar también que, empleando los complejos [$RuCl_2(\eta^6$-*p*-cimeno){κ^1-(*P*)-PPh_2py}] (**1.33b**) y [$RuCl(\eta^6$-*p*-cimeno){κ^2-(*P,N*)-PPh_2py}][SbF_6] (**1.36b**) como catalizadores, llevamos a cabo la reacción de hidratación del benzonitrilo (Esquema 1.15) en presencia de *p*-cimeno libre

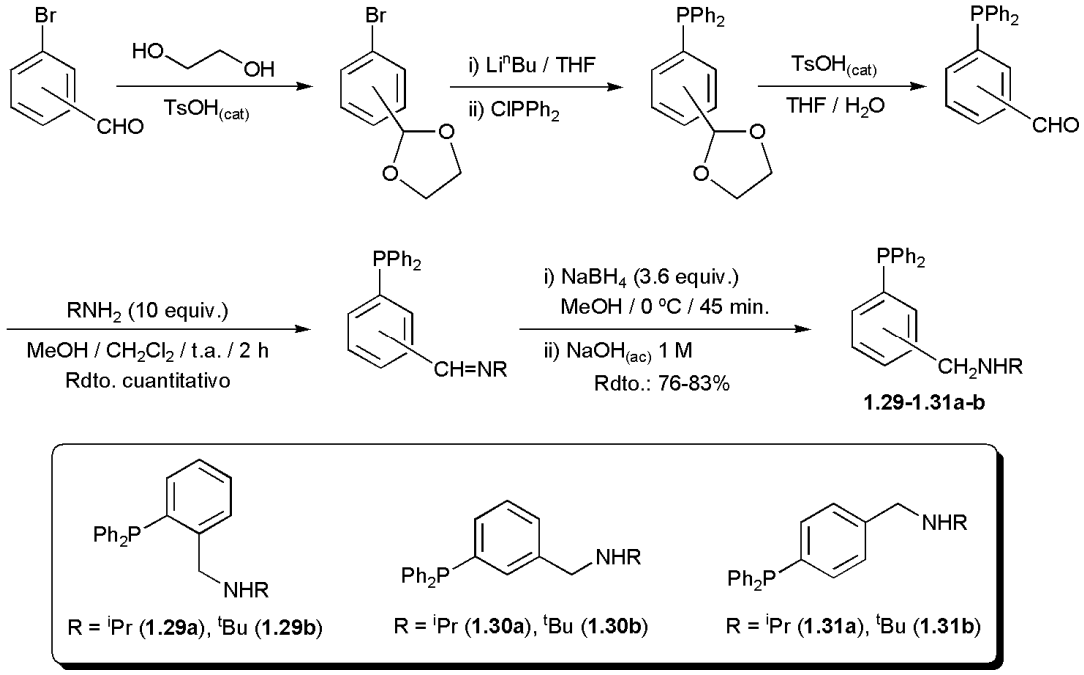
[62] A pesar de que las piridil-fosfinas tienen la reputación de comportarse como ligandos hemilábiles, todos los intentos llevados a cabo para generar los compuestos [$RuCl(\eta^6$-*p*-cimeno)(N≡CPh){κ^1-(*P*)-PPh_2py}][SbF_6] y [$RuCl(\eta^6$-*p*-cimeno)(N≡CPh){κ^1-(*P*)-PPh_2(py-4-NMe_2)}][SbF_6] por tratamiento de los complejos **1.33b** y **1.34b**, respectivamente, con benzonitrilo resultaron infructuosos. Este hecho pone de manifiesto la alta estabilidad de los anillos quelato generados tras la coordinación κ^2-(*P,N*) de las priril-fosfinas PPh_2py (**1.26**) y PPh_2(py-4-NMe_2) (**1.27**) a las unidades Ru(II)-areno.

(250 mol%). Los resultados obtenidos en estas condiciones fueron comparativamente inferiores a los obtenidos en ausencia del areno. Este hecho parece indicar que, durante las reacciones catalíticas, la coordinación del nitrilo al centro metálico se produce por disociación del ligando η^6-areno. Por otro lado, también observamos que, cuando se añade al medio de reacción un poco de PPh_2py libre, la actividad catalítica aumenta ligeramente. Así, por ejemplo, adicionando un 10 mol% de PPh_2py llegaron a alcanzarse con ambos complejos conversiones cuantitativas del benzonitrilo en benzamida tras 24 h de calentamiento. Esta mejoría está asociada a la formación *in situ* de la especie dicatiónica octaédrica $[Ru\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}_3][Cl]_2$, complejo que pudo ser sintetizado independientemente por reacción de $[RuCl_2(\eta^6\text{-}p\text{-cimeno})\{\kappa^1\text{-}(P)\text{-}PPh_2py\}]$ (**1.33b**) con 2.2 equivalentes de PPh_2py, y que mostró una actividad catalítica ligeramente superior a la de $[RuCl_2(\eta^6\text{-}p\text{-cimeno})\{\kappa^1\text{-}(P)\text{-}PPh_2py\}]$ (**1.33b**) y $[RuCl(\eta^6\text{-}p\text{-cimeno})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ (**1.36b**) (TOF = 0.8 h^{-1}).

1.2.2.- Síntesis, caracterización y evaluación de la actividad catalítica de complejos rutenio(II)-areno derivados de las amino-aril-fosfinas 2-$Ph_2PC_6H_4CH_2NHR$ (R = ^{i}Pr (1.29a), ^{t}Bu (1.29b)), 3-$Ph_2PC_6H_4CH_2NHR$ (R = ^{i}Pr (1.30a), ^{t}Bu (1.30b)) y 4-$Ph_2PC_6H_4CH_2NHR$ (R = ^{i}Pr (1.31a), ^{t}Bu (1.31b)).

La segunda familia de ligandos estudiada es la constituida por las amino-aril-fosfinas **1.29-1.31a-b** (Figura 1.10). En principio, la presencia en su estructura de restos amino, capaces de interaccionar con el agua a través de enlaces de hidrógeno, habilita a las mismas para ejercer un efecto cooperativo durante las reacciones catalíticas. Además, la posición exacta de este sustituyente en el anillo aromático del ligando debería afectar también drásticamente a la eficiencia de los catalizadores resultantes, ya que condicionaría su posible quelatación, y el acercamiento eficaz de la molécula de agua activada al nitrilo coordinado al centro metálico. De esta manera, con este estudio sistemático del patrón de sustitución del ligando podríamos obtener información directa sobre la operatividad de un mecanismo de catálisis bifuncional.

Los ligandos **1.29-1.31a-b** fueron preparados siguiendo metodologías sintéticas clásicas,[63] basadas en la condensación de las correspondientes (formilfenil)difenilfosfinas (generadas a partir de bromo-benzaldehídos comerciales)[64] con *iso*-propilamina o *terc*-butilamina (Esquema 1.16). De esta forma, empleando un exceso (10 equivalentes) de la amina primaria y llevando a cabo las reacciones a temperatura ambiente en una mezcla $MeOH/CH_2Cl_2$, se obtuvieron cuantitativamente las correspondientes imino-fosfinas, que fueron posteriormente reducidas por tratamiento con $NaBH_4$ en MeOH. Los ligandos amino-aril-fosfina **1.29-1.31a-b** así generados fueron aislados como aceites de color amarillo pálido estables al aire, con unos rendimientos del 76-83%.



Esquema 1.16: Procedimiento general para la preparación de los ligandos amino-aril-fosfina **1.29-1.31a-b**.

El tratamiento de las especies dímeras $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-areno})\}_2]$ (areno = C_6H_6, *p*-cimeno, 1,3,5-$C_6H_3Me_3$, C_6Me_6) con 2.4 equivalentes de

[63] (a) C. A. Ghilardi, S. Midollini, S. Moneti, A. Orlandini, G. Scapacci, *J. Chem. Soc., Dalton Trans.* **1992**, 3371; (b) A. Nikitidis, C. Andersson, *Phosphorus, Sulfur and Silicon* **1993**, *78*, 141; (c) S. Antonaroli, B. Crociani, *J. Organomet. Chem.* **1998**, *560*, 137; (d) P. Crochet, J. Gimeno, S. García-Granda, J. Borge, *Organometallics* **2001**, *20*, 4369; (e) P. Crochet, J. Gimeno, J. Borge, S. García-Granda, *New J. Chem.* **2003**, *27*, 414.

[64] (a) G. P. Schiemenz, H. Kaack, *Justus Liebigs Ann. Chem.* **1973**, *9*, 1480; (b) G. P. Schiemenz, H. Kaack, *Justus Liebigs Ann. Chem.* **1973**, *9*, 1494; (c) J. E. Hoots, T. B. Rauchfuss, D. A. Wrobleski, *Inorg. Synth.* **1982**, *21*, 175; (d) Y. Sun, M. Ahmed, R. Jackstell, M. Beller, W. R. Thiel, *Organometallics* **2004**, *23*, 5260.

estos ligandos, en THF y a temperatura ambiente, nos permitió sintetizar con buenos rendimientos (62-89%) los complejos mononucleares [$RuCl_2$(η^6-areno){κ^1-(*P*)-2-$Ph_2PC_6H_4CH_2NHR$}] (**1.38aa-db**), [$RuCl_2$(η^6-areno){κ^1-(*P*)-3-$Ph_2PC_6H_4CH_2NHR$}] (**1.39aa-db**) y [$RuCl_2$(η^6-areno){κ^1-(*P*)-4-$Ph_2PC_6H_4CH_2NHR$}] (**1.40aa-db**) (Figura 1.11), que se generan por ruptura de los puentes cloruro de los dímeros precursores y coordinación selectiva del átomo de fósforo del ligando a las unidades [$RuCl_2$(η^6-areno)].

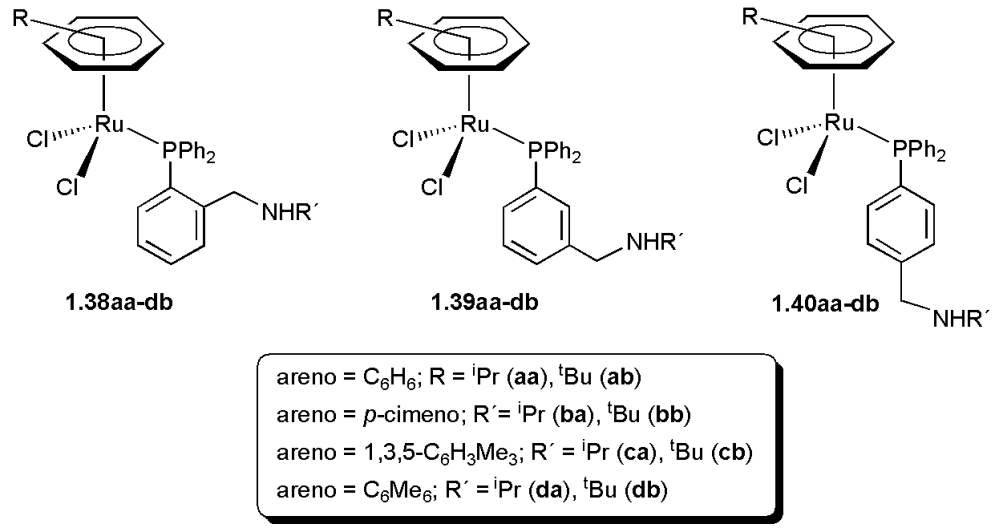


Figura 1.11: Estructura de los complejos (η^6-areno)-rutenio(II) **1.38-1.40aa-db**.

Estos nuevos derivados, aislados como sólidos de color rojo-anaranjado estables al aire, fueron caracterizados empleando las técnicas analíticas y espectroscópicas habituales (IR y RMN de $^{31}P\{^1H\}$, ^1H y $^{13}C\{^1H\}$), avalando los datos obtenidos las formulaciones propuestas para los mismos. El comportamiento redox de estos sistemas fue estudiado mediante voltametría cíclica, y las estructuras de los complejos [$RuCl_2$(η^6-*p*-cimeno){κ^1-(*P*)-2-$Ph_2PC_6H_4CH_2NH_2{}^tBu$}][Cl] (**1.38bb·HCl**), [$RuCl_2$(η^6-*p*-cimeno){κ^1-(*P*)-3-$Ph_2PC_6H_4CH_2NH{}^tBu$}] (**1.39bb**) y [$RuCl_2$(η^6-*p*-cimeno){κ^1-(*P*)-4-$Ph_2PC_6H_4CH_2NH{}^tBu$}] (**1.40bb**) confirmadas de manera inequívoca mediante la técnica de difracción de rayos X de monocristal. Todos los datos de caracterización se encuentran recogidos y discutidos en la correspondiente publicación adjunta, por lo que no serán aquí comentados.

El potencial catalítico de los complejos **1.38-1.40aa-db** fue evaluado tomando nuevamente como transformación modelo la hidratación del benzonitrilo en benzamida, empleando las mismas condiciones de reacción

previamente utilizadas con los derivados **1.33a-d-1.35a-b**, que contenían como ligandos las piridil-fosfinas **1.26-1.28** (Esquema 1.15). Así, encontramos que estos sistemas son capaces de promover selectivamente el proceso de hidratación, generando como único producto de reacción la benzamida deseada con un rendimiento del 43-99% (determinado por CG) tras 24 horas de calentamiento. En particular, los mejores resultados se obtuvieron con los complejos [$RuCl_2(\eta^6$-$C_6Me_6)\{\kappa^1$-(*P*)-2-$Ph_2PC_6H_4CH_2NH^tBu\}$] (**1.38db**), [$RuCl_2(\eta^6$-1,3,5-$C_6H_3Me_3)\{\kappa^1$-(*P*)-3-$Ph_2PC_6H_4CH_2NH^tBu\}$] (**1.39cb**) y [$RuCl_2(\eta^6$-*p*-cimeno)$\{\kappa^1$-(*P*)-4-$Ph_2PC_6H_4CH_2NH^iPr\}$] (**1.40ba**), que fueron capaces de generar la benzamida en más de un 90% de rendimiento tras 7 horas de calentamiento (TOF = 2.6 h^{-1}). Estas actividades, aunque superiores a las mostradas por los derivados con las piridil-fosfinas **1.33a-d-1.35a-b** discutidos previamente, se encuentran muy lejos todavía de las descritas por nuestro grupo de investigación para el complejo rutenio-areno [$RuCl_2(\eta^6$-$C_6Me_6)$(PTA-Bn)] (**1.21d**; ver Figura 1.6) (TOF = 127 h^{-1}).

Por otro lado, aunque los complejos derivados de las amino-aril-fosfinas *orto*-sustituidas resultaron ser, en general, menos activos que sus análogos con sustitución en *meta* y *para*,[65] los datos obtenidos no permitieron establecer una relación directa entre la estructura o naturaleza electrónica de estos complejos y su actividad catalítica. Sin embargo, el hecho de que todos sean más activos que los derivados que contienen trifenilfosfina como ligando, *i.e.* [$RuCl_2(\eta^6$-areno)(PPh_3)] (areno = C_6H_6, *p*-cimeno, 1,3,5-$C_6H_3Me_3$, C_6Me_6; 21-48% de conversión tras 24 h de calentamiento en las mismas condiciones de reacción), parece sugerir la existencia de un efecto cooperativo por parte de las amino-aril-fosfinas. En este sentido, ya que la posición del grupo amino en el anillo aromático (*orto*, *meta* o *para*) no tiene una influencia marcada sobre la actividad catalítica, dicho efecto cooperativo de los ligandos **1.29-1.31a-b** parece no tener relación alguna con el acercamiento efectivo, a través de enlaces de

[65] La formación de anillos quelato estables de 6 miembros, por coordinación intramolecular de los grupos amino al rutenio, podría ser la causa de este comportamiento. En el caso particular del complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{\kappa^1$-(*P*)-2-$Ph_2PC_6H_4CH_2NH^tBu\}$] (**1.38db**), uno de los catalizadores más activos encontrados en este estudio, dicho proceso de quelatación estaría desfavorecido estéricamente debido a la presencia del ligando areno más voluminoso, *i.e.* el hexametilbenceno, y del sustituyente *terc*-butilo en el ligando amino-aril-fosfina.

hidrógeno, de la molécula de agua al nitrilo coordinado. Por otra parte, también observamos que la efectividad de los complejos [$RuCl_2(\eta^6$-areno)(PPh_3)] aumenta considerablemente cuando las reacciones catalíticas se llevan a cabo en presencia de un 5 mol% de *N-iso*-propilbencilamina o *N*-bencil-*terc*-butilamina, es decir, en un medio ligeramente básico. De este modo, podemos concluir que el efecto que proporcionan los ligandos amino-aril-fosfina **1.29-1.31a-b** está más bien relacionado con la activación de la molécula de agua por desprotonación, generándose de esta manera en el medio de reacción el grupo hidroxilo, mucho mejor nucleófilo que el agua (ver Figura 1.12).

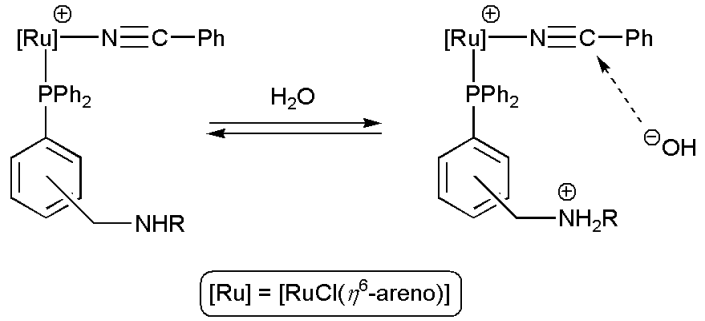


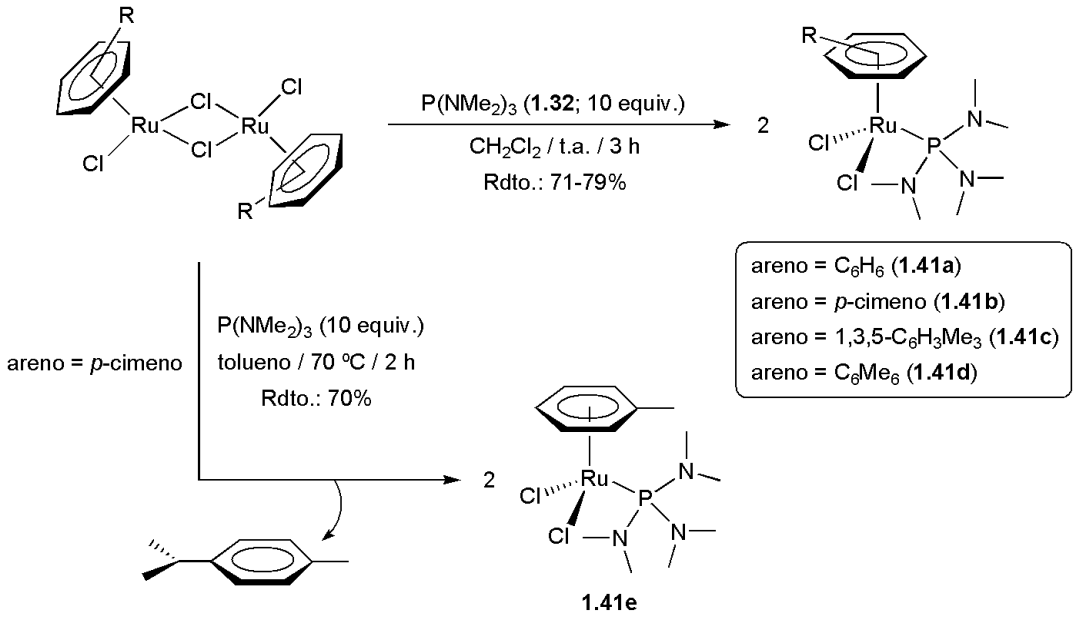
Figura 1.12: Posible efecto de los ligandos amino-aril-fosfina **1.29-1.31a-b** en la reacción de hidratación del benzonitrilo.

1.2.3.- Síntesis, caracterización y evaluación de la actividad catalítica de complejos rutenio(II)-areno derivados de la amino-fosfina $P(NMe_2)_3$ (1.32).

El último ligando potencialmente cooperativo que hemos estudiado es la tris(dimetilamino)fosfina (**1.32**), un compuesto disponible comercialmente a módico precio. Así, por tratamiento del dímero [{RuCl(μ-Cl)(η^6-areno)}$_2$] correspondiente con un exceso (10 equivalentes) de este ligando preparamos, en diclorometano y a temperatura ambiente, los complejos mononucleares [$RuCl_2(\eta^6$-areno){$P(NMe_2)_3$}] (areno = C_6H_6 (**1.41a**), *p*-cimeno (**1.41b**), 1,3,5-$C_6H_3Me_3$ (**1.41c**), C_6Me_6 (**1.41d**)) con buenos rendimientos (71-79%), y los caracterizamos mediante las técnicas analíticas y espectroscópicas habituales (Esquema 1.17).[66] Cabe mencionar

[66] Los derivados **1.41a** y **1.41b** han sido descritos con anterioridad en la bibliografía: (a) H. Werner, R. Werner, *Chem. Ber.* **1982**, *115*, 3766; (b) A. M. A. Boshaala, S. J. Simpson, J. Autschbach, S. Zheng, *Inorg. Chem.* **2008**, *47*, 9279.

en este punto que, en un intento de sintetizar el derivado [$RuCl_2$(η^6-*p*-cimeno){$P(NMe_2)_3$}] (**1.41b**) por reacción del dímero [{RuCl(μ-Cl)(η^6-*p*-cimeno)}$_2$] con la fosfina **1.32** en tolueno a 70 °C, se produjo la formación inesperada del complejo [$RuCl_2$(η^6-tolueno){$P(NMe_2)_3$}] (**1.41e**), cuya estructura fue confirmada mediante difracción de rayos X de monocristal (ver detalles en la correspondiente publicación adjunta).[67]



Esquema 1.17: Síntesis de los complejos [$RuCl_2$(η^6-areno){$P(NMe_2)_3$}] (**1.41a-e**).

Los complejos [$RuCl_2$(η^6-areno){$P(NMe_2)_3$}] (**1.41a-e**) fueron ensayados en la hidratación de benzonitrilo, mostrando, en las mismas condiciones de reacción, una actividad catalítica muy superior a la de sus análogos con piridil-fosfinas (**1.33a-d-1.35a-b**) y amino-aril-fosfinas (**1.38-1.40a-b**) discutidos previamente. De hecho, todos ellos (5 mol%) fueron capaces de generar selectivamente la benzamida deseada con un rendimiento prácticamente cuantitativo (≥ 98%; determinado por CG) tras 1-5 horas de calentamiento a 100 °C. El derivado [$RuCl_2$(η^6-C_6Me_6){$P(NMe_2)_3$}] (**1.41d**), que contiene el ligando η^6-areno más rico electrónicamente, y también el más impedido estéricamente, resultó ser el

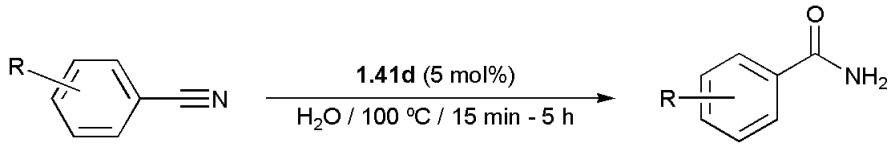
[67] La formación de **1.41e** involucra la sustitución del ligando *p*-cimeno coordinado a rutenio por tolueno, un hecho sorprendente si tenemos en cuenta que: *(i)* las reacciones de sustitución de arenos en complejos de rutenio no suele ocurrir a temperaturas inferiores a los 100 °C, y *(ii)* que, en la mayoría de los casos, estas sustituciones conllevan al desplazamiento de un areno pobre electrónicamente por otro de mayor riqueza electrónica. La alta basicidad de la $P(NMe_2)_3$, que labilizaría el enlace rutenio-*p*-cimeno, podría estar detrás de este resultado tan inesperado.

más activo de todos los complejos estudiados, al convertir cuantitativamente el benzonitrilo en benzamida tras sólo 1 hora de calentamiento (TOF = 20 h^{-1}). Este hecho es coherente con los resultados previos obtenidos por nuestro grupo de investigación al estudiar la actividad catalítica de los sistemas rutenio(II)-areno **1.20-1.23a-d** (ver Figura 1.6), donde se puso de manifiesto que cuanto más voluminoso y rico en densidad electrónica es el ligando areno, mayor es la eficiencia del proceso.[37]

Con objeto de evaluar la utilidad sintética de esta transformación en medio acuoso, decidimos extender nuestro estudio a una familia variada de nitrilos empleando como catalizador el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**). Así, llevando a cabo las reacciones a 100 ºC con disoluciones acuosas 0.33 M en el nitrilo correspondiente y una carga de metal del 5 mol%, encontramos que **1.41d** es capaz de transformar selectivamente un buen número de nitrilos aromáticos, heteroaromáticos, alifátios y *α,β*-insaturados en las amidas correspondientes en tiempos de reacción cortos (de 5 min a 5 h). Dichas amidas pudieron ser aisladas con buenos rendimientos (70-91%; rendimientos superiores al 88% por CG), tras evaporación del disolvente, y posterior purificación cromatográfica. Los detalles completos de este estudio se encuentran recogidos en la correspondiente publicación adjunta, por lo que aquí sólo se comentarán los aspectos más relevantes.

En primer lugar decir que, empleando diferentes benzonitrilos sustituidos, pudimos demostrar la alta tolerancia que presenta el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) hacia grupos funcionales, ya que mostró ser compatible con la presencia en los sustratos de grupos haluro, hidroxilo, nitro, éter, cetona o éster. Por otro lado, merece la pena destacar que las reacciones con estos benzonitrilos pusieron de manifiesto una ligera influencia del patrón de sustitución del anillo aromático en la velocidad del proceso de hidratación. Así, debido probablemente a factores estéricos, los sustratos que presentan sustitución en *orto* requieren tiempos de reacción por lo general más largos, en comparación con aquellos que se encuentran sustituidos en posiciones *meta* o *para*, para generar las amidas finales con rendimientos similares (ejemplos representativos se muestran en el Esquema 1.18). La naturaleza

electrónica del sustituyente afecta igualmente a la velocidad del proceso, siendo más rápidas las reacciones cuanto más deficiente en densidad electrónica es el anillo aromático (ver los ejemplos del Esquema 1.18).



R = 2-Cl (Rdto.: 82%; 1.5 h)	R = 2-OMe (Rdto.: 70%; 5 h)
R = 3-Cl (Rdto.: 90%; 15 min)	R = 3-OMe (Rdto.: 85%; 1.5 h)
R = 4-Cl (Rdto.: 87%; 15 min)	R = 4-OMe (Rdto.: 79%; 2.5 h)

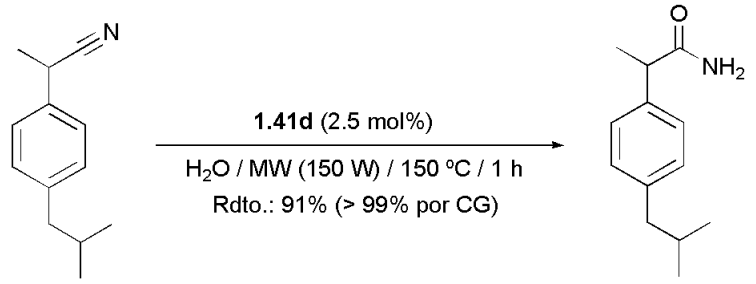
Esquema 1.18: Reactividad observada con algunos benzonitrilos seleccionados.

Cabe destacar también que los valores de TOF alcanzados en la hidratación del 3-bromobenzonitrilo, el pentafluorobenzonitrilo y el fenoxiacetonitrilo (235, 238 y 594 h^{-1}, respectivamente) son comparativamente muy superiores a los obtenidos previamente en nuestro grupo de investigación con el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (**1.21d** en la Figura 1.6) (TOF = 5-20 h^{-1}). Dichos valores, y por tanto la eficiencia del complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**), pudieron ser mejorados drásticamente al emplear irradiación microondas (MW) como fuente de calentamiento (150 W / 150 °C). A modo de ejemplo, llevando a cabo la hidratación del fenoxiacetonitrilo con una carga de catalizador de tan sólo el 0.5 mol% pudo alcanzarse, en estas nuevas condiciones de reacción, un valor de TOF de 11400 h^{-1}, el más alto descrito hasta la fecha para esta transformación catalítica en agua.

Por otro lado, aprovechado la excelente actividad mostrada por el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**), pudimos desarrollar un nuevo método de síntesis, más eficiente y respetuoso con el medioambiente, de la ibuprofenamida, un compuesto con propiedades antiinflamatorias muy interesantes, por hidratación del correspondiente nitrilo comercial, *i.e.* el 2-(isobutilfenil)propionitrilo (Esquema 1.19).[68]

[68] El método convencional de síntesis de la ibuprofenamida involucra la transformación inicial del ibuprofeno en el cloruro de ácido correspondiente, por reacción con cloruro de tionilo, seguido de un tratamiento con amoníaco: (a) R. G. W. Spickett, A. Vega, J. Prieto, J. Moragues, M. Márquez, D. J. Roberts, *Eur. J. Med. Chem.* **1976**, *11*, 7; (b) A. Rajasekaran, P. Sivakumar, B. Jayakar, *Indian J. Pharm. Sci.* **1999**, *61*, 158; (c) A. Doshi, S. D. Samant, S. G. Deshpande, *Indian J.*

Como se comenta en la correspondiente publicación adjunta, con la ayuda de [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) también es posible generar lactamas en agua a partir de *δ*-cetonitrilos, a través de una secuencia tándem de hidratación/ciclocondensación análoga a la desarrollada por S.-I. Murahashi en medio orgánico empleando [$RuH_2(PPh_3)_4$] como catalizador (ver Esquema 1.7).[27,69]



Esquema 1.19: Síntesis catalítica de la ibuprofenamida.

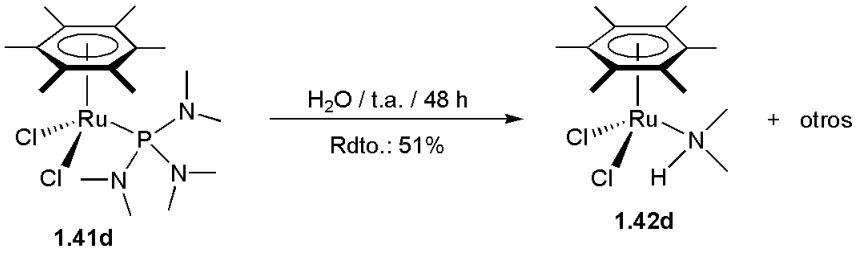
A pesar de la destacable solubilidad y actividad catalítica mostrada por el complejo [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) en agua, debemos reseñar que su estabilidad en este medio es baja. Así, hemos observado que, en disolución acuosa, **1.41d** evoluciona lentamente a temperatura ambiente hacía la formación del derivado [$RuCl_2(\eta^6\text{-}C_6Me_6)(HNMe_2)$] (**1.42d**) y diferentes productos fosforados que no han podido ser identificados (Esquema 1.20). A una temperatura de 100 ºC, esta misma descomposición se observó tras sólo 4-5 horas de calentamiento.[70,71]

Pharm. Sci. **2002**, *64*, 440; (d) A. Doshi, S. G. Deshpande, *Indian J. Pharm. Sci.* **2002**, *64*, 445; (e) M. Allegretti, R. Bertini, M. C. Cesta, C. Bizzarri, R. Di Bitondo, V. Di Cioccio, E. Galliera, V. Berdini, A. Topai, G. Zampella, V. Russo, N. Di Bello, G. Nano, L. Nicolini, M. Locati, P. Fantucci, S. Florio, F. Colotta, *J. Med. Chem.* **2005**, *48*, 4312; (f) C. B. Guo, Z. F. Cai, Z. R. Guo, Z. Q. Feng, F. M. Chu, G. F. Cheng, *Chinese Chem. Lett.* **2006**, *17*, 325; (g) A. Doshi, S. G. Deshpande, *Indian J. Pharm. Sci.* **2007**, *69*, 824.

[69] A pesar de la alta generalidad mostrada por el complejo [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**), debemos hacer notar que una limitación encontrada en nuestro estudio concierne la hidratación de dinitrilos. En los casos ensayados (adiponitrilo, fumaronitrilo y 1,4-dicianobenceno) se obtuvieron productos muy insolubles (presumiblemente polímeros) que no pudieron ser caracterizados.

[70] La formación de **1.42d** implica la liberación inicial al medio de Me_2NH por ruptura hidrolítica de los enlaces P-N del ligando $P(NMe_2)_3$ coordinado. Esta amina desplazaría posteriormente las especies $P(OH)_x(NMe_2)_{3-x}$ (x = 1, 2, 3) resultantes.

[71] (a) Este patrón de descomposición parece ser general ya que las especies [$RuCl_2(\eta^6\text{-}p\text{-cimeno})(NHMe_2)$] (**1.42b**) y [$RuCl_2(\eta^6\text{-}1,3,5\text{-}C_6H_3Me_3)(NHMe_2)$] (**1.42c**) también pudieron ser aisladas cuando disoluciones acuosas de **1.41b-c** se agitaron durante 48 h a temperatura ambiente; (b) Los amino-complejos **1.42b-d** fueron ensayados como potenciales catalizadores en la hidratación del



Esquema 1.20: Formación del amino-complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)(HNMe_2)]$ (**1.42d**) por descomposición de **1.41d**.

Por último, nos gustaría destacar que la utilidad sintética de los complejos $[RuCl_2(\eta^6\text{-areno})\{P(NMe_2)_3\}]$ (**1.41a-e**) no ha pasado desapercibida para otros autores. Así, tras la publicación de nuestros resultados, D. R. Tyler y colaboradores han desarrollado una metodología eficiente para hidratación selectiva de cianohidrinas (*a*-hidroxinitrilos) en las correspondientes *a*-hidroxiamidas empleando nuestros catalizadores.[72] Además los estudios mecanísticos llevados a cabo por estos autores a través de cálculos teóricos DFT confirmaron el efecto cooperativo que ejerce la tris(dimetilamino)fosfina durante las reacciones catalíticas (Figura 1.13).

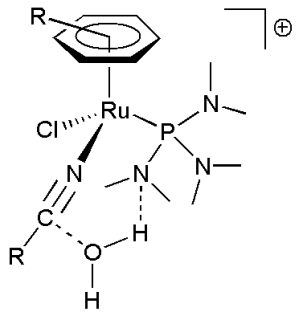


Figura 1.13: Efecto cooperativo del ligando $P(NMe_2)_3$ en los procesos de hidratación.

benzonitrilo, mostrado actividades muy modestas (rendimientos inferiores al 72% tras 24 horas en las condiciones de reacción estandard).

[72] (a) S. M. M. Knapp, T. J. Sherbow, J. J. Juliette, D. R. Tyler, *Organometallics* **2012**, *31*, 2941; (b) S. M. M. Knapp, T. J. Sherbow, R. B. Yelle, L. N. Zakharov, J. J. Juliette, D. R. Tyler, *Organometallics* **2013**, *32*, 824.

CAPÍTULO 1

1.3.- PUBLICACIONES

Los resultados obtenidos en este capítulo han dado lugar a las cuatro publicaciones que se adjuntan:

1) "Arene-ruthenium(II) and bis(allyl)-ruthenium(IV) complexes containing 2-(diphenylphosphanyl)pyridine ligands: Potential catalysts for nitrile hydration reactions?". Rocío García-Álvarez, Sergio E. García-Garrido, Josefina Díez, Pascale Crochet, Victorio Cadierno. *European Journal of Inorganic Chemistry* **2012**, 4218-4230.

2) "Arene-ruthenium(II) complexes containing amino-phosphine ligands as catalysts for nitrile hydration reactions". Rocío García-Álvarez, Josefina Díez, Pascale Crochet, Victorio Cadierno. *Organometallics* **2010**, *29*, 3955-3965.

3) "Ibuprofenamide: A convenient method of synthesis by catalytic hydration of 2-(4-isobutylphenyl)propionitrile in pure aqueous medium". Rocío García-Álvarez, Javier Francos, Pascale Crochet, Victorio Cadierno. *Tetrahedron Letters* **2011**, *52*, 4218-4220.

4) "Arene-ruthenium(II) complexes containing inexpensive tris(dimethylamino)phosphine: Highly efficient catalysts for the selective hydration of nitriles into amides". Rocío García-Álvarez, Josefina Díez, Pascale Crochet, Victorio Cadierno. *Organometallics* **2011**, *30*, 5442-5451.

FULL PAPER

EurJIC European Journal of Inorganic Chemistry

DOI: 10.1002/ejic.201200592

Arene-Ruthenium(II) and Bis(allyl)-Ruthenium(IV) Complexes Containing 2-(Diphenylphosphanyl)pyridine Ligands: Potential Catalysts for Nitrile Hydration Reactions?

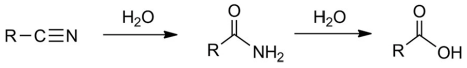
Rocío García-Álvarez,[a] Sergio E. García-Garrido,[a] Josefina Díez,[a] Pascale Crochet,*[a] and Victorio Cadierno*[a]

Keywords: Homogeneous catalysis / Ruthenium / N,P ligands / Amides / Hydration

Neutral arene-ruthenium(II) complexes $[RuCl_2(\eta^6\text{-arene})\{\kappa^1\text{-}(P)\text{-}PPh_2py\}]$ and $[RuCl_2(\eta^6\text{-arene})\{\kappa^1\text{-}(P)\text{-}PPh_2(py\text{-}4\text{-}NMe_2)\}]$ (arene = benzene, *p*-cymene, mesitylene, hexamethylbenzene) have been synthesized and studied as potential catalysts for the selective hydration of nitriles to amides using benzonitrile as a model substrate. The effectiveness of these complexes was low due to the high tendency of the 2-(diphenylphosphanyl)pyridine ligands to form stable κ^2-(*P*,*N*)-chelate rings, as demonstrated by NMR spectroscopy and catalytic experiments performed with the isolated cationic derivatives $[RuCl(\eta^6\text{-arene})\{\kappa^2\text{-}(P,N)\text{-}PN\}][SbF_6]$ [PN = PPh_2py, $PPh_2(py\text{-}4\text{-}NMe_2)$]. Despite its reluctance to adopt a chelating κ^2-(*P*,*N*) coordination mode, cooperative effects of the bulky 2-(diphenylphosphanyl)pyridine ligand $PPh_2(py\text{-}6\text{-}tert\text{-}amyl)$ were not observed in complexes $[RuCl_2(\eta^6\text{-arene})\{\kappa^1\text{-}(P)\text{-}PPh_2(py\text{-}6\text{-}tert\text{-}amyl)\}]$ (arene = benzene, *p*-cymene). The novel bis(allyl)-ruthenium(IV) derivatives $[RuCl(\eta^3{:}\eta^3\text{-}C_{10}H_{16})\{\kappa^2\text{-}(P,N)\text{-}PN\}][SbF_6]$ [PN = PPh_2py, $PPh_2(py\text{-}4\text{-}NMe_2)$] and $[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})\{\kappa^1\text{-}(P)\text{-}PPh_2(py\text{-}6\text{-}tert\text{-}amyl)\}]$ ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl) were also synthesized and fully characterized, and again led to modest conversions in the benzonitrile hydration reaction. Improvements in the catalytic activities of complexes $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{\kappa^1\text{-}(P)\text{-}PPh_2py\}]$, $[RuCl(\eta^6\text{-}p\text{-cymene})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ and $[RuCl(\eta^3{:}\eta^3\text{-}C_{10}H_{16})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ were observed in the presence of excess PPh_2py due to the in situ formation of the catalytically more active dication $[Ru\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}_3]^{2+}$.

Introduction

The hydration of nitriles is an important transformation because the resulting amides present a huge number of applications in synthetic organic chemistry, as well as industrial and pharmaceutical interest.[1] For example, the large-scale production of acrylamide, nicotinamide and 5-cyanovaleramide is currently based on this reaction.[2] In addition to a higher chemoselectivity, that is, amides are not further hydrolysed to the corresponding carboxylic acids (see Scheme 1), transition-metal catalysed nitrile hydration reactions offer other advantages over the conventional acid- and base-promoted transformations,[3] such as milder reaction conditions and higher tolerance to other functional groups.[4] Moreover, despite the significant progress achieved in enzymatic nitrile hydration reactions and their commercial success,[2] the narrow substrate specificity and high isolation costs of the currently available enzymes make the metal-based methodologies the simplest and most powerful alternatives to carry out these transformations.[5] Several homogeneous[4] and heterogeneous[6] systems have been described with the former showing greater synthetic applicability. Among them, Murahashi's ruthenium[7] and Parkins' platinum[8] complexes, $[RuH_2(PPh_3)_4]$ and $[PtH(PMe_2OH)\{(PMe_2O)_2H\}]$, respectively, are the most widely employed due to their remarkable activity and excellent functional group tolerance. The Rh^I-based systems $[\{Rh(\mu\text{-OMe})(cod)\}_2]/PCy_3$ (cod = 1,5-cyclooctadiene)[9] and [RhBr(pin)(cod)] [pin = 1-isopropyl-3-(5,7-dimethyl-1,8-naphthyrid-2-yl)imidazol-2-ylidene][10] also deserve to be highlighted due to their effectiveness under ambient conditions.



Scheme 1. Nitrile hydration and amide hydrolysis reactions.

Although different reaction pathways have been proposed for the metal-catalysed nitrile hydration processes, coordination of the nitrile to the metal is a common prerequisite for most of them.[4] Through this coordination, the C≡N unit becomes more electrophilic and susceptible to nucleophilic attack by water, thus improving the kinetics of

[a] Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, Julián Clavería 8, 33006 Oviedo, Spain
Fax: +34-985-103-446
E-mail: crochetpascale@uniovi.es
vcm@uniovi.es
Homepage: http://www.unioviedo.es/comorca

the hydration process in comparison with hydrolysis (Scheme 1). Recent works have also suggested that this key nucleophilic addition step can be facilitated by the presence of functionalized ligands able to activate the water molecule through a secondary hydrogen-bond interaction (Figure 1).[10,11] Such a cooperative effect of the ligand represents a new example of the so-called "bifunctional catalysis", that is, the metal ion acts as a Lewis acid and the ligand as a Lewis base, a concept widely exploited in homogeneous catalysis during recent years.[12]

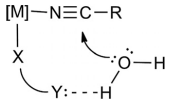


Figure 1. Simplified representation of the cooperative effect of the ligand.

In this context, Oshiki and co-workers reported that the ruthenium(II) complex *cis*-[Ru(acac)$_2${κ^1-(*P*)-PPh$_2$py}$_2$] (acac = acetylacetonate), which contains the well-known and commercially available heteroditopic phosphane 2-(diphenylphosphanyl)pyridine (PPh$_2$py, **1**; Figure 2),[13] is an excellent bifunctional catalyst for the selective hydration of nitriles to amides under neutral conditions.[11b,11h] The directing effect of the uncoordinated pyridyl unit of the PPh$_2$py ligands allowed impressive turnover frequency (TOF) values of up to 20900 h^{-1} to be obtained with this complex. Further studies by the same group employing [Ru(η^3-2-methylallyl)$_2$(cod)]/PR$_3$ systems also indicated the greater effectiveness of the related ligand PPh$_2$(py-4-NMe$_2$) (**2**; Figure 2) over the unsubstituted PPh$_2$py (**1**) due to the increased electron density on the nitrogen atom of the pyridyl unit generated by the presence of the electron-donating dimethylamino group (i.e., greater hydrogen-bond acceptor character).[11k]

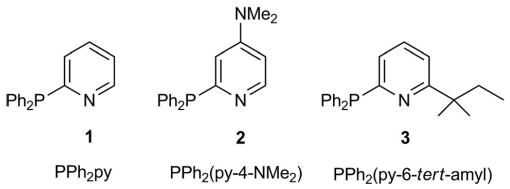


Figure 2. Structure of the 2-(diphenylphosphanyl)pyridine ligands **1**–**3**.

In recent years our group has been active in this field, describing different series of arene-ruthenium(II) (**A**–**C**; Figure 3) and bis(allyl)-ruthenium(IV) complexes (**D**,**E**; Figure 3), all containing potential hydrogen-bond acceptor phosphane ligands that are able to promote efficiently the selective hydration of nitriles to amides.[11e–11g,11i–11j] As an extension of these studies, and inspired by the work of Oshiki,[11b,11h,11k] we decided to investigate the catalytic activities of related arene-ruthenium(II)[14] and bis(allyl)-ruthenium(IV) complexes derived from the 2-(diphenylphosphanyl)pyridine ligands **1**–**3** (Figure 2) to assess whether cooperative effects also operate in these systems. The results of this study are presented herein.

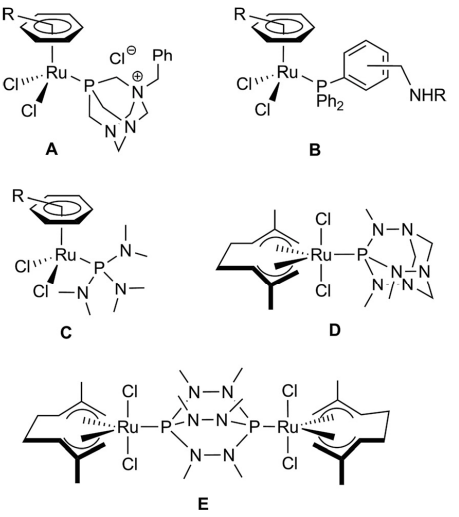
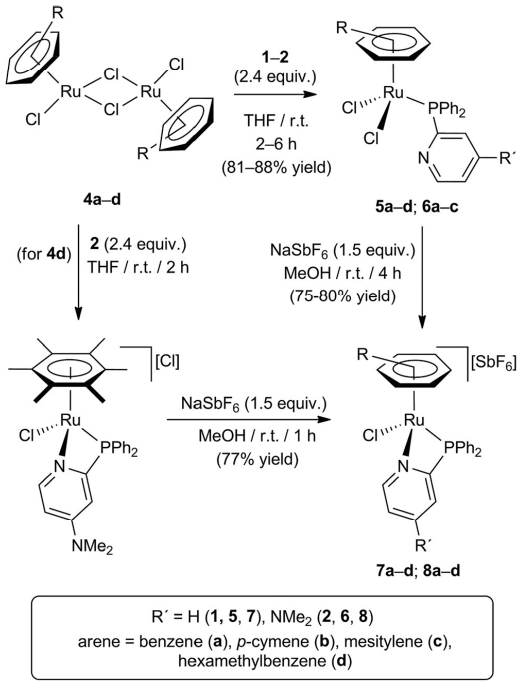


Figure 3. Structures of some Ru^{II} and Ru^{IV} catalysts previously described by us.

Results and Discussion

Our investigations started with the preparation of the neutral complexes [RuCl$_2$(η^6-arene){κ^1-(*P*)-PPh$_2$py}] [arene = benzene (**5a**), *p*-cymene (**5b**), mesitylene (**5c**), hexamethylbenzene (**5d**)] and [RuCl$_2$(η^6-arene){κ^1-(*P*)-PPh$_2$(py-4-NMe$_2$)}] [arene = benzene (**6a**), *p*-cymene (**6b**), mesitylene (**6c**)] through the classical cleavage of the chloride bridges in the dimeric precursors [{RuCl(μ-Cl)(η^6-arene)}$_2$] (**4a**–**d**) with 2.4 equiv. of the corresponding 2-(diphenylphosphanyl)pyridine ligand **1** or **2** (Scheme 2). The reactions, which were conducted in tetrahydrofuran at room temperature, delivered the desired complexes **5a**–**d** and **6a**–**c** in high yields (81–88%). In contrast, all attempts to generate the neutral complex [RuCl$_2$(η^6-hexamethylbenzene){κ^1-(*P*)-PPh$_2$(py-4-NMe$_2$)}] (**6d**) by the reaction of dimer **4d** with phosphane **2** in different solvents (THF, CH$_2$Cl$_2$, 1,2-dichloroethane or methanol) failed, the reactions leading instead to the rapid and selective formation of the cationic species [RuCl(η^6-hexamethylbenzene){κ^2-(*P*,*N*)-PPh$_2$(py-4-NMe$_2$)}][Cl] by direct chelation of the ligand. This complex was isolated as the corresponding hexafluoroantimonate salt **8d** after Cl$^-$/SbF$_6^-$ counter-anion exchange with a methanolic solution of NaSbF$_6$ at room temperature. The related cationic complexes [RuCl(η^6-arene){κ^2-(*P*,*N*)-PPh$_2$py}]-[SbF$_6$] [arene = benzene (**7a**), *p*-cymene (**7b**), mesitylene (**7c**), hexamethylbenzene (**7d**)] and [RuCl(η^6-arene){κ^2-(*P*,*N*)-PPh$_2$(py-4-NMe$_2$)}][SbF$_6$] [arene = benzene (**8a**), *p*-cymene (**8b**), mesitylene (**8c**)] were also synthesized in high

yields (75–80%) by treatment of the isolated complexes **5a–d** and **6a–c**, respectively, with $NaSbF_6$ in methanol (Scheme 2).



Scheme 2. Synthesis of the (η^6-arene)ruthenium(II) complexes **5–8a–d** containing the 2-(diphenylphosphanyl)pyridine ligands **1** or **2** coordinated in a κ^1-(*P*) or κ^2-(*P*,*N*) manner.

Complexes **5a**,**b**,**d** and **7a**,**b**,**d** containing the more classical Ph_2Ppy ligand **1** have previously been reported in the literature.[15] The spectroscopic data obtained for the new mesitylene analogues **5c** and **7c** are comparable to those described for **5a**,**b**,**d** and **7a**,**b**,**d** and deserve no further comment. For compounds **6a–c** and **8a–d**, which represent rare examples of isolated metal complexes containing the dimethylamino-substituted 2-(diphenylphosphanyl)pyridine ligand **2**,[16] characterization was straightforward from their analytical and spectroscopic data (see the Exp. Sect.). In particular, the $^{31}P\{^1H\}$ NMR spectra are very informative, showing for the neutral complexes **6a–c** a strong downfield shift of the Ph_2P signal (δ_P = 21.9–28.3 ppm) with respect to that shown by the free phosphane **2** (δ_P = –2.8 ppm) as a consequence of the coordination of this group to ruthenium. In contrast, important shielding was observed for the Ph_2P resonances when moving from **6a–c** to **8a–d** (δ_P from –19.3 to –13.2 ppm for **8a–d**), in agreement with the formation of a strained four-membered chelate ring.[17] The ^1H and $^{13}C\{^1H\}$ NMR spectra also show the signals expected for η^6-coordinated arene groups and the PPh_2(py-4-NMe_2) ligand. For the latter, characteristic NMe_2 singlet resonances were observed at δ_H = 2.78–3.08 ppm and δ_C = 38.6–39.6 ppm. In addition, the structure of the cationic complex [RuCl(η^6-mesitylene){κ^2-(*P*,*N*)-PPh_2(py-4-NMe_2)}][SbF_6] (**8c**) was unambiguously confirmed by X-ray diffraction analysis. X-ray quality crystals were obtained by slow diffusion of diethyl ether into a saturated solution of **8c** in acetone. An ORTEP view of the molecule, along with selected structural parameters, is shown in Figure 4.[18] The expected pseudo-octahedral three-legged piano-stool geometry around the ruthenium atom was observed, with the interligand angles P(1)–Ru(1)–Cl(1), P(1)–Ru(1)–N(1) and Cl(1)–Ru(1)–N(1) and those between the centroid of the mesitylene ring C* and the legs typical of a pseudo-octahedron. Remarkably, the bond lengths and angles found within the four-membered ruthenacycle [Ru(1)–P(1)–C(10)–N(1)] are almost identical (±0.03 Å or ±0.1°) to those previously observed in the solid-state crystal structures of the complexes [$RuCl_2$(η^6-*p*-cymene){κ^2-(*P*,*N*)-PPh_2py}]$^+$ (**7b**)[15a,15d] and [$RuCl_2$(η^6-hexamethylbenzene){κ^2-(*P*,*N*)-PPh_2py}]$^+$ (**7d**),[15c] which indicates a negligible structural effect of the dimethylamino substituent on the 2-(diphenylphosphanyl)pyridine ligand.

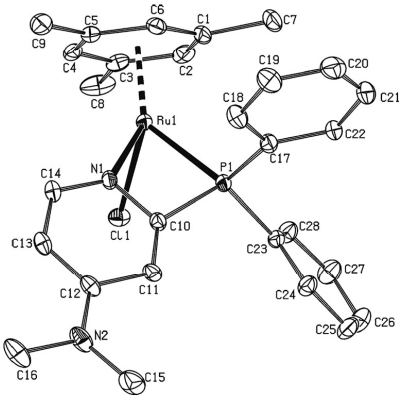
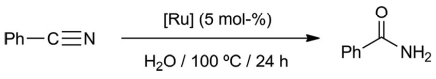


Figure 4. ORTEP-type view of the structure of [RuCl(η^6-mesitylene){κ^2-(*P*,*N*)-PPh_2(py-4-NMe_2)}][SbF_6] (**8c**) showing the crystallographic labeling scheme. Hydrogen atoms and the SbF_6^- anion have been omitted for clarity. Thermal ellipsoids are drawn at the 10% probability level. Selected bond lengths [Å] and angles [°]: Ru(1)–P(1) 2.332(2), Ru(1)–Cl(1) 2.405(2), Ru(1)–N(1) 2.146(5), Ru(1)–C* 1.720(4), P(1)–C(10) 1.820(5), P(1)–C(17) 1.813(7), P(1)–C(23) 1.805(6), C(10)–N(1) 1.371(7), C(12)–N(2) 1.361(8), C(15)–N(2) 1.435(2), C(16)–N(2) 1.47(1), C*–Ru(1)–P(1) 135.2(1), C*–Ru(1)–N(1) 136.5(3), C*–Ru(1)–Cl(1) 128.2(3), P(1)–Ru(1)–Cl(1) 86.27(6), P(1)–Ru(1)–N(1) 66.3(1), Cl(1)–Ru(1)–N(1) 81.6(1), Ru(1)–P(1)–C(10) 85.7(2), P(1)–C(10)–N(1) 99.6(4), C(10)–N(1)–Ru(1) 106.0(3). C* denotes the centroid of the mesitylene ring [C(1)–C(2)–C(3)–C(4)–C(5)–C(6)].

The catalytic potential of the synthesized complexes for nitrile hydration reactions was investigated by using benzonitrile as the model substrate. In a typical experiment, the corresponding ruthenium catalyst (5 mol-%) was added to a 0.33 M aqueous solution of benzonitrile and the mixture was heated in an oil bath at 100 °C for 24 h.

As shown in Table 1, the effectiveness of the neutral derivatives [$RuCl_2(\eta^6$-arene)$\{\kappa^1$-(*P*)-$PPh_2py\}$] (**5a**–**d**; entries 1–4) and [$RuCl_2(\eta^6$-arene)$\{\kappa^1$-(*P*)-PPh_2(py-4-$NMe_2)\}$] (**6a**–**c**; entries 5–8), potential candidates to operate through a bifunctional mechanism, was very low.[19] Thus, in the best case, a maximum conversion of 69% was reached with complex [$RuCl_2(\eta^6$-$C_6Me_6)\{\kappa^1$-(*P*)-$PPh_2py\}$] (**5d**; entry 4).[20] In contrast to the observations made by Oshiki and co-workers,[11k] the presence of the dimethylamino substituent on the pyridyl ring does not exert any beneficial effect as no marked differences in reactivity were found between complexes **5a**–**c** and **6a**–**c** (entries 1–3 vs. 5–7). Note also that the catalytic activities of **5a**–**d** and **6a**–**c** were only slightly higher than those shown by the analogous complexes [$RuCl_2(\eta^6$-arene)(PPh_3)] (**9a**–**d**; entries 16–19), in which the presence of the triphenylphosphane ligand eliminates the possibility of secondary hydrogen-bond interactions with the nucleophilic water molecules. This indicates that cooperative effects of the 2-(diphenylphosphanyl)pyridine ligands are negligible in our complexes.[21] Interestingly, inspection of the crude reaction mixtures by $^{31}P\{^1H\}$ NMR spectroscopy showed, in all cases, the major presence of the corresponding cationic species [$RuCl(\eta^6$-arene)$\{\kappa^2$-(*P*,*N*)-$PPh_2py\}]^+$ (**7a**–**d**) and [$RuCl(\eta^6$-arene)$\{\kappa^2$-(*P*,*N*)-PPh_2(py-4-$NMe_2)\}]^+$ (**8a**–**c**) in solution. These complexes are less active than **5a**–**d** and **6a**–**c**, as assessed by performing the catalytic hydration of benzonitrile with the isolated hexafluoroantimonate salts of **7**,**8a**–**d** (Scheme 2) under identical reaction conditions (entries 8–15; conversions ≤37% after 24 h of heating). We must also note that, despite the hemilabile character usually associated with phosphanylpyridine ligands,[13,22] all attempts to generate the compounds [$RuCl(\eta^6$-*p*-cymene)$(N{\equiv}CPh)\{\kappa^1$-(*P*)-$PPh_2py\}][SbF_6]$ and [$RuCl(\eta^6$-*p*-cymene)$(N{\equiv}CPh)\{\kappa^1$-(*P*)-PPh_2(py-4-$NMe_2)\}][SbF_6]$ by treating complexes **7**,**8b** with excess benzonitrile (up to 50 equiv.) were unsuccessful.[23] Consequently, the low reactivity observed for **5a**–**c** and **6a**–**c** can be attributed to the stability of the four-membered chelate rings generated by κ^2-(*P*,*N*) coordination of the ligands, a process thermodynamically favoured by the high polarity of the catalytic reaction media.[24]

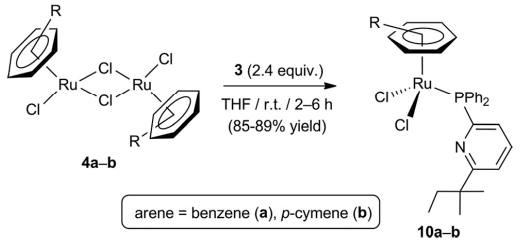
Table 1. Catalytic hydration of benzonitrile using the arene-ruthenium(II) complexes **5**–**10a**–**d**.[a]



Entry	Catalyst	Yield[b] [%]
1	[$RuCl_2(\eta^6$-$C_6H_6)\{\kappa^1$-(*P*)-$PPh_2py\}$] (**5a**)	55
2	[$RuCl_2(\eta^6$-*p*-cym)$\{\kappa^1$-(*P*)-$PPh_2py\}$] (**5b**)	57
3	[$RuCl_2(\eta^6$-mes)$\{\kappa^1$-(*P*)-$PPh_2py\}$] (**5c**)	67
4	[$RuCl_2(\eta^6$-$C_6Me_6)\{\kappa^1$-(*P*)-$PPh_2py\}$] (**5d**)	69
5	[$RuCl_2(\eta^6$-$C_6H_6)\{\kappa^1$-(*P*)-PPh_2(py-4-$NMe_2)\}$] (**6a**)	45
6	[$RuCl_2(\eta^6$-*p*-cym)$\{\kappa^1$-(*P*)-PPh_2(py-4-$NMe_2)\}$] (**6b**)	65
7	[$RuCl_2(\eta^6$-mes)$\{\kappa^1$-(*P*)-PPh_2(py-4-$NMe_2)\}$] (**6c**)	60
8	[$RuCl(\eta^6$-$C_6H_6)\{\kappa^2$-(*P*,*N*)-$PPh_2py\}]^+$ (**7a**)	7
9	[$RuCl(\eta^6$-*p*-cym)$\{\kappa^2$-(*P*,*N*)-$PPh_2py\}]^+$ (**7b**)	16
10	[$RuCl(\eta^6$-mes)$\{\kappa^2$-(*P*,*N*)-$PPh_2py\}]^+$ (**7c**)	11
11	[$RuCl(\eta^6$-$C_6Me_6)\{\kappa^2$-(*P*,*N*)-$PPh_2py\}]^+$ (**7d**)	2
12	[$RuCl(\eta^6$-$C_6H_6)\{\kappa^2$-(*P*,*N*)-PPh_2(py-4-$NMe_2)\}]^+$ (**8a**)	28
13	[$RuCl(\eta^6$-*p*-cym)$\{\kappa^2$-(*P*,*N*)-PPh_2(py-4-$NMe_2)\}]^+$ (**8b**)	37
14	[$RuCl(\eta^6$-mes)$\{\kappa^2$-(*P*,*N*)-PPh_2(py-4-$NMe_2)\}]^+$ (**8c**)	32
15	[$RuCl(\eta^6$-$C_6Me_6)\{\kappa^2$-(*P*,*N*)-PPh_2(py-4-$NMe_2)\}]^+$ (**8d**)	22
16[c]	[$RuCl_2(\eta^6$-$C_6H_6)(PPh_3)$] (**9a**)	45
17[c]	[$RuCl_2(\eta^6$-*p*-cym)(PPh_3)] (**9b**)	45
18[c]	[$RuCl_2(\eta^6$-mes)(PPh_3)] (**9c**)	21
19[c]	[$RuCl_2(\eta^6$-$C_6Me_6)(PPh_3)$] (**9d**)	48
20	[$RuCl_2(\eta^6$-$C_6H_6)\{\kappa^1$-(*P*)-PPh_2(py-6-*tert*-amyl)$\}$] (**10a**)	28
21	[$RuCl_2(\eta^6$-*p*-cym)$\{\kappa^1$-(*P*)-PPh_2(py-6-*tert*-amyl)$\}$] (**10b**)	37

[a] Reactions performed under N_2 at 100 °C with 1 mmol of benzonitrile (0.33 M in water). Substrate/Ru ratio: 100:5. [b] Yield of benzamide determined by GC. [c] Data taken from ref.[11f]

To avoid the chelation of the pyridyl unit, we decided to explore related arene-ruthenium(II) complexes with the 2-(diphenylphosphanyl)pyridine ligand PPh_2(py-6-*tert*-amyl) (**3**; Figure 2). This commercially available phosphane, developed by Hintermann and co-workers, previously proved useful in the ruthenium-catalysed anti-Markovnikov hydration of terminal alkynes through bifunctional reaction pathways.[25] The presence of the bulky *tert*-amyl substituent adjacent to the nitrogen atom was expected to suppress the coordination ability of its now sterically shielded lone pair. As shown in Scheme 3, treatment of THF solutions of dimers [{$RuCl(\mu$-Cl)$(\eta^6$-arene)$\}_2$] [arene = benzene (**4a**), *p*-cymene (**4b**)] with 2.4 equiv. of **3** at room temperature delivered the expected mononuclear κ^1-(*P*) complexes **10a**,**b**, which were isolated as air-stable orange solids in high yields (85–89%).[26]



Scheme 3. Synthesis of the (η^6-arene)ruthenium(II) complexes **10a**,**b** containing the 2-(diphenylphosphanyl)pyridine ligand **3**.

Complexes **10a**,**b** were characterized by elemental analyses and multinuclear NMR (^1H, $^{31}P\{^1H\}$ and $^{13}C\{^1H\}$) spectroscopy, the data obtained being fully consistent with the structural proposals (see the Exp. Sect. for details). In particular, the monodentate κ^1-(*P*) coordination of the phosphane ligand **3** is reflected in the $^{31}P\{^1H\}$ NMR spectra by the appearance of a singlet signal at δ_P = 20.1–25.0 ppm, a chemical shift range that fits well with that observed for compounds **5a**–**d** and **6a**–**c**. The structure of the benzene complex [$RuCl_2(\eta^6$-benzene)$\{\kappa^1$-(*P*)-PPh_2(py-6-*tert*-amyl)$\}$] (**10a**) was also unambiguously confirmed by single-crystal X-ray diffraction. An ORTEP-type drawing of the molecule is depicted in Figure 5; selected bond lengths and angles are listed in the caption. The ruthenium atom is coordinated to two terminal chlorides, the η^6-benzene ligand and the phosphorus atom of **3**, all arranged in a

typical pseudo-octahedral three-legged piano-stool geometry. The Ru(1)–Cl(1) [2.389(1) Å], Ru(1)–Cl(2) [2.407(1) Å] and Ru(1)–P(1) [2.3521(9) Å] bond lengths observed are very similar (±0.03 Å) to those described previously for [$RuCl_2(\eta^6$-*p*-cymene){κ^1-(*P*)-PPh_2py}] (**5b**)[15a,15d] and [$RuCl_2(\eta^6$-hexamethylbenzene){κ^1-(*P*)-PPh_2py}] (**5d**),[15c] which again suggests negligible effects of the pyridyl substituent on the structure of this family of arene-ruthenium complexes. On the other hand, we would also like to note that, to the best of our knowledge, **10a** is the first structurally characterized complex containing the bulky 2-(diphenylphosphanyl)pyridine ligand **3**.[27]

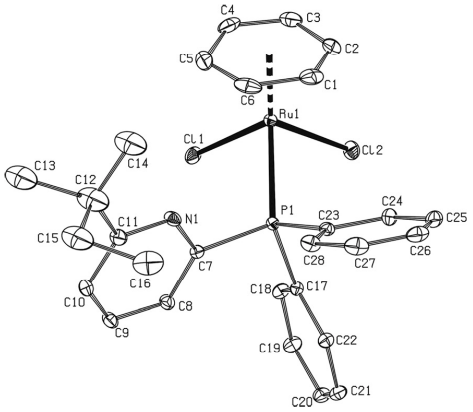
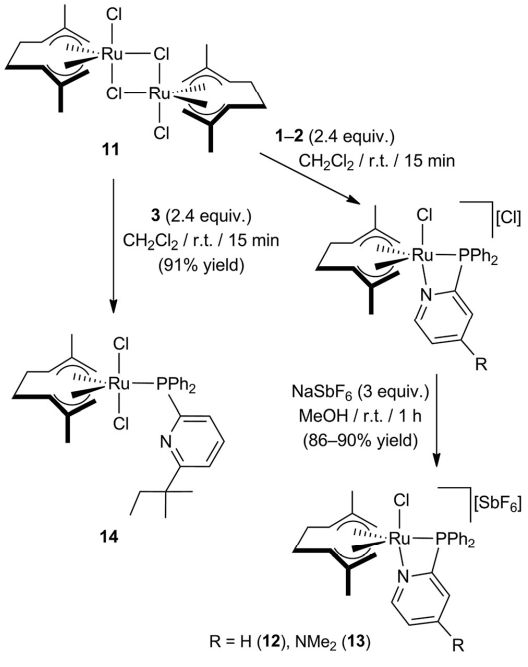


Figure 5. ORTEP-type view of the structure of [$RuCl_2(\eta^6$-benzene){κ^1-(*P*)-PPh_2(py-6-*tert*-amyl)}] (**10a**) showing the crystallographic labeling scheme. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are drawn at the 10% probability level. Selected bond lengths [Å] and angles [°]: Ru(1)–P(1) 2.3521(9), Ru(1)–Cl(1) 2.389(1), Ru(1)–Cl(2) 2.407(1), Ru(1)–C* 1.6928(3), P(1)–C(7) 1.843(4), P(1)–C(17) 1.828(4), P(1)–C(23) 1.819(4), C(7)–N(1) 1.339(5), C*–Ru(1)–P(1) 128.82(2), C*–Ru(1)–Cl(1) 126.07(3), C*–Ru(1)–Cl(2) 124.70(3), P(1)–Ru(1)–Cl(1) 86.99(4), P(1)–Ru(1)–Cl(2) 87.83(3), Cl(1)–Ru(1)–Cl(2) 89.79(4), Ru(1)–P(1)–C(7) 114.4(1), P(1)–C(7)–N(1) 115.7(3). C* = centroid of the benzene ring [C(1)–C(2)–C(3)–C(4)–C(5)–C(6)].

To determine whether the chelation of **3** could interfere during catalysis, the reactivities of complexes [$RuCl_2(\eta^6$-arene){κ^1-(*P*)-PPh_2(py-6-*tert*-amyl)}] (**10a**,**b**) towards $NaSbF_6$ were first explored. In contrast to the behaviour shown by **5a**–**d** and **6a**–**c** (Scheme 2), complexes **10a**,**b** remained unchanged when methanolic solutions were treated with a large excess (10 equiv.) of $NaSbF_6$, even after prolonged periods at reflux. This clearly indicates that, in solution, the equilibrium [$RuCl_2(\eta^6$-arene){κ^1-(*P*)-PPh_2(py-6-*tert*-amyl)}] ⇌ [$RuCl(\eta^6$-arene){κ^2-(*P*,*N*)-PPh_2(py-6-*tert*-amyl)}][Cl] is completely displaced to the left. However, despite the reluctance of PPh_2(py-6-*tert*-amyl) to adopt a chelating κ^2-(*P*,*N*) coordination mode, the catalytic activities of complexes **10a**,**b** in the hydration of benzonitrile were unexpectedly disappointing. Thus, as shown in Table 1 (entries 20 and 21), only yields of 28–37% of benzamide could be reached with 5 mol-% of these complexes after 24 h of heating at 100 °C. These results, which are worse than those obtained with complexes [$RuCl_2(\eta^6$-arene){κ^1-(*P*)-PPh_2py}] (**5a**–**d**; entries 1–4), [$RuCl_2(\eta^6$-arene){κ^1-(*P*)-PPh_2(py-4-NMe_2)}] (**6a**–**c**; entries 5–7) and [$RuCl_2(\eta^6$-arene)(PPh_3)] (**9a**–**d**; entries 16–19), rule out any cooperative effect of the phosphane ligand **3**. Steric congestion around the Lewis acid metal centre, which prevents the approach of the benzonitrile molecule, may be responsible for the low catalytic activities shown by **10a**,**b**.

As commented in the introduction to this article, previous studies from our group have demonstrated the high potential of catalytic systems consisting of bis(allyl)-ruthenium(IV) complexes [$RuCl_2(\eta^3$:η^3-$C_{10}H_{16}$)(L)] ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl; L = phosphane ligand) for nitrile hydration processes (e.g., compound **D** in Figure 3).[11g] That is why we also decided to explore the reactivity of dimer [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] (**11**) towards phosphanes **1**–**3** and the catalytic behaviour of the resulting complexes.[28] As shown in Scheme 4, although the treatment of **11** with a two-fold excess of ligand **1** or **2** resulted in the rapid and direct formation of the corresponding cationic chelate complexes, isolated as the hexafluoroantimonate salts [$RuCl(\eta^3$:η^3-$C_{10}H_{16}$){κ^2-(*P*,*N*)-PPh_2py}][SbF_6] (**12**) and [$RuCl(\eta^3$:η^3-$C_{10}H_{16}$){κ^2-(*P*,*N*)-PPh_2(py-4-NMe_2)}][SbF_6] (**13**), the neutral derivative [$RuCl_2(\eta^3$:η^3-$C_{10}H_{16}$){κ^1-(*P*)-PPh_2(py-6-*tert*-amyl)}] (**14**) was cleanly obtained by using the bulky phosphane **3**. As previously observed with



Scheme 4. Synthesis of the bis(allyl)-ruthenium(IV) complexes **12**–**14**.

its arene-ruthenium(II) counterparts **10a**,**b**, methanolic solutions of complex **14** did not react with $NaSbF_6$, which confirms the reluctance of **3** to undergo κ^2-(*P*,*N*) coordination. In addition, similarly to **7**,**8b**, no chelate ring opening occurred when **12** or **13** was treated with benzonitrile.

The new compounds **12**–**14**, isolated as air-stable yellow solids in yields of 86–91%, were characterized by elemental analyses and multinuclear NMR spectroscopy (see the Exp. Sect.). The different coordination adopted by the 2-(diphenylphosphanyl)pyridine ligands **1**–**3** was readily evidenced in the $^{31}P\{^1H\}$ NMR spectra, which show for **12** and **13** singlet signals (δ_P = –39.1 and –38.3 ppm) at much higher fields than observed for **14** (δ_P = 25.8 ppm). The ^1H and $^{13}C\{^1H\}$ NMR spectra of these compounds are also very informative. Thus, as expected for the formation of a simple equatorial adduct, a unique set of signals for the two allylic moieties of **14** was observed, which suggests that the two halves of the 2,7-dimethylocta-2,6-diene-1,8-diyl skeleton are in equivalent environments. In contrast, for **12** and **13**, the two halves of the 2,7-dimethylocta-2,6-diene-1,8-diyl ligand are inequivalent, as clearly reflected by the appearance 10 different signals in the $^{13}C\{^1H\}$ NMR spectra. Doubling of the allylic resonances for **12** and **13** is in complete accord with the loss of C_2 symmetry in these chelate complexes. The structure of $[RuCl(\eta^3:\eta^3\text{-}C_{10}H_{16})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ (**12**) was fully confirmed by X-ray crystallographic studies (Figure 6). The geometry about the ruthenium atom in **12** is best described as a highly distorted trigonal bipyramid by considering the allyl groups as monodentate ligands bound to the metal through their centres of mass (C* and C**; see caption to Figure 6). The chloride ligand and pyridyl nitrogen atom occupy the axial positions [Cl(1)–Ru–N(1) bond angle of 154.9(1)°], whereas the octadienediyl and diphenylphosphanyl units are located at equatorial sites. Both allyl groups of the organic $C_{10}H_{16}$ fragment are η^3-bound to the ruthenium atom with Ru–C and C–C distances in the ranges 2.199(6)–2.249(6) and 1.40(1)–1.41(1) Å, respectively. These values, together with the internal allylic C(1)–C(2)–C(4) and C(7)–C(8)–C(10) angles [115.1(7) and 113.2(6)°, respectively], compare well with those observed in other structures containing the "$Ru(\eta^3:\eta^3\text{-}C_{10}H_{16})$" unit.[29]

When applied to the catalytic hydration of benzonitrile under conditions identical to those employed with **5**–**10a**–**d** (Table 1), the Ru^{IV} derivatives **12**–**14** also showed very low activities (Table 2). In contrast to the former cases, the best result was obtained with the neutral complex $[RuCl_2(\eta^3:\eta^3\text{-}C_{10}H_{16})\{\kappa^1\text{-}(P)\text{-}PPh_2(py\text{-}6\text{-}tert\text{-}amyl)\}]$ (**14**), which led to the selective formation of benzamide in 62% yield after 24 h of heating (entry 3). However, this yield does not differ much from that reached with $[RuCl_2(\eta^3:\eta^3\text{-}C_{10}H_{16})(PPh_3)]$ (**15**; entry 4), which again suggests a lack of a cooperative effect of ligand **3** during the catalytic event.

To gain more information on the catalytic behaviour of our systems, some additional experiments were performed with complexes $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{\kappa^1\text{-}(P)\text{-}PPh_2py\}]$ (**5b**), $[RuCl(\eta^6\text{-}p\text{-cymene})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ (**7b**) and $[RuCl(\eta^3:\eta^3\text{-}C_{10}H_{16})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ (**12**) as representative models (see Table 3). We observed that the performances shown by the arene derivatives **5b** and **7b** were reduced when benzonitrile was hydrated in the presence of 50 equiv. (per Ru) of free *p*-cymene (entry 2 vs. 1, and 7 vs. 6). These observations suggest that the vacant sites required for the coordination of the substrate may be generated through the dissociation of the arene ligand. On the other hand, remarkable improvements in the catalytic activities of these complexes occurred when 1 or 2 equiv. (per Ru) of the

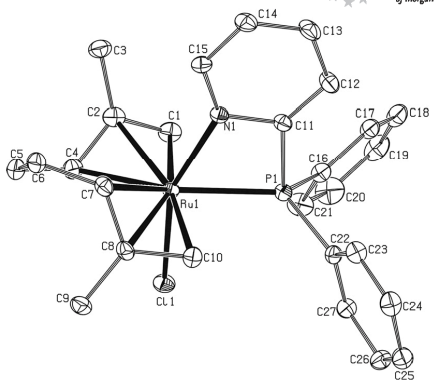
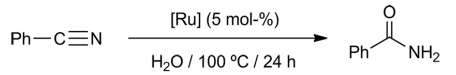


Figure 6. ORTEP-type view of the structure of $[RuCl(\eta^3:\eta^3\text{-}C_{10}H_{16})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ (**12**) showing the crystallographic labeling scheme. Hydrogen atoms and the SbF_6^- anion have been omitted for clarity. Thermal ellipsoids are drawn at the 10% probability level. Selected bond lengths [Å] and angles [°]: Ru(1)–Cl(1) 2.414(1), Ru(1)–P(1) 2.364(1), Ru(1)–N(1) 2.130(4), Ru(1)–C* 1.9729(4), Ru(1)–C** 1.9674(4), Ru(1)–C(1) 2.199(6), Ru(1)–C(2) 2.231(7), Ru(1)–C(4) 2.249(6), Ru(1)–C(7) 2.229(5), Ru(1)–C(8) 2.216(5), Ru(1)–C(10) 2.211(6), C(1)–C(2) 1.40(1), C(2)–C(4) 1.41(1), C(7)–C(8) 1.408(9), C(8)–C(10) 1.405(9), P(1)–C(11) 1.816(5), P(1)–C(16) 1.825(5), P(1)–C(22) 1.802(6), C(11)–N(1) 1.359(7), Cl(1)–Ru(1)–N(1) 154.9(1), Cl(1)–Ru(1)–P(1) 87.43(5), Cl(1)–Ru(1)–C* 90.92(4), Cl(1)–Ru(1)–Cl** 97.39(4), P(1)–Ru(1)–N(1) 67.4(1), P(1)–Ru(1)–C* 117.52(4), P(1)–Ru(1)–C** 115.08(4), N(1)–Ru(1)–C* 100.1(1), N(1)–Ru(1)–C** 93.9(1), C*–Ru–C** 127.02(2), Ru(1)–P(1)–C(11) 83.8(2), P(1)–C(11)–N(1) 103.0(4), C(1)–C(2)–C(4) 115.1(7), C(7)–C(8)–C(10) 113.2(6). C* and C** denote the centroids of the allyl units [C(1)–C(2)–C(4), and C(7)–C(8)–C(10), respectively].

Table 2. Catalytic hydration of benzonitrile using the bis(allyl)-ruthenium(IV) complexes **12**–**15**.[a]

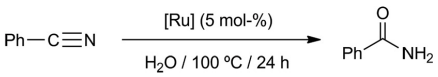


Entry	Catalyst	Yield[b] [%]
1	$[RuCl(\eta^3:\eta^3\text{-}C_{10}H_{16})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}]^+$ (**12**)	7
2	$[RuCl(\eta^3:\eta^3\text{-}C_{10}H_{16})\{\kappa^2\text{-}(P,N)\text{-}PPh_2(py\text{-}4\text{-}NMe_2)\}]^+$ (**13**)	34
3	$[RuCl_2(\eta^3:\eta^3\text{-}C_{10}H_{16})\{\kappa^1\text{-}(P)\text{-}PPh_2(py\text{-}6\text{-}tert\text{-}amyl)\}]$ (**14**)	62
4	$[RuCl_2(\eta^3:\eta^3\text{-}C_{10}H_{16})(PPh_3)]$ (**15**)	56

[a] Reactions performed under N_2 at 100 °C with 1 mmol of benzonitrile (0.33 M in water). Substrate/Ru ratio: 100:5. [b] Yield of benzamide determined by GC.

free 2-(diphenylphosphanyl)pyridine ligand **1** were introduced into the reaction media (entries 3 and 4 vs. 1, and 8 and 9 vs. 6). A beneficial effect of the addition of free phosphane was also observed with the bis(allyl)-ruthenium(IV) derivative **12** (entries 12 and 13 vs. 11). In particular, in the presence of 2 equiv. of PPh_2py, the quantitative formation of benzamide could be reached after 24 h of heating with the three complexes **5b**, **7b** and **12** (entries 4, 9 and 13). The role of the free phosphane as a simple base was discarded because the activities shown by **5b** and **7b** remained almost unaltered in the presence of 2 equiv. (per Ru) of pyridine (entries 5 vs. 1, and 10 vs. 6).

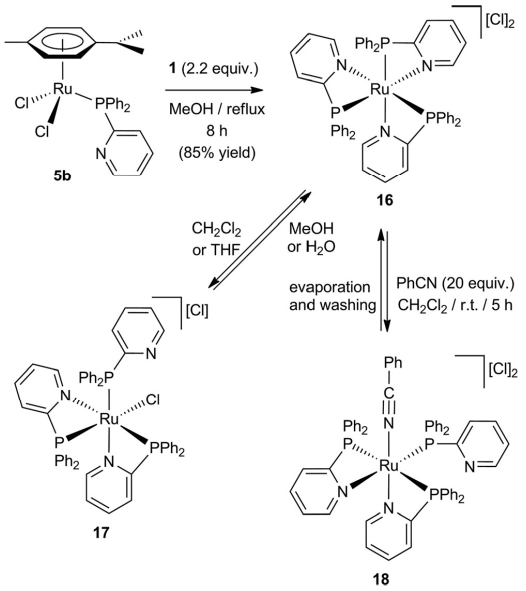
Table 3. Catalytic hydration of benzonitrile with complexes **5b**, **7b** and **12** in the presence of different additives.[a]



Entry	Catalyst	Additive	Yield[b] [%]
1	**5b**	none	57
2	**5b**	*p*-cymene (250 mol-%)	21
3	**5b**	PPh_2py (**1**; 5 mol-%)	99
4	**5b**	PPh_2py (**1**; 10 mol-%)	>99
5	**5b**	py (10 mol-%)	58
6	**7b**	none	16
7	**7b**	*p*-cymene (250 mol-%)	2
8	**7b**	PPh_2py (**1**; 5 mol-%)	89
9	**7b**	PPh_2py (**1**; 10 mol-%)	>99
10	**7b**	py (10 mol-%)	15
11	**12**	none	7
12	**12**	PPh_2py (**1**; 5 mol-%)	61
13	**12**	PPh_2py (**1**; 10 mol-%)	>99

[a] Reactions performed under N_2 at 100 °C with 1 mmol of benzonitrile (0.33 M in water). Substrate/Ru ratio: 100:5. [b] Yield of benzamide determined by GC.

For a better understanding of the role of the PPh_2py ligand **1** added during the catalysis, the reactivity of complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{\kappa^1\text{-}(P)\text{-}PPh_2py\}]$ (**5b**) towards **1** was explored. As shown in Scheme 5, treatment of a methanolic solution of **5b** with 2.2 equiv. of **1** at reflux resulted in the clean formation of the new octahedral derivative $[Ru\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}_3][Cl]_2$ (**16**) by displacement of the *p*-cymene ligand. Complex **16** was isolated as an air-stable yellow solid in 85% yield and characterized by elemental analysis and multinuclear NMR spectroscopy (see the Exp. Sect.). In accord with the chemical equivalence of the three PPh_2 units, a unique singlet resonance is observed in the $^{31}P\{^1H\}$ NMR spectrum of this complex, the chemical shift observed (δ_P = –4.1 ppm) being coherent with $\kappa^2\text{-}(P,N)$ coordination. As shown by $^{31}P\{^1H\}$ NMR spectroscopy, the $[Ru\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}_3]^{2+}$ dication was also formed as the major species when methanolic solutions of $[RuCl(\eta^6\text{-}p\text{-cymene})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ (**7b**) and $[RuCl(\eta^3\text{:}\eta^3\text{-}C_{10}H_{16})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ (**12**) were heated at reflux with an excess of PPh_2py.[30] However, in these cases, other byproducts were also generated, which prevented its isolation in pure form.



Scheme 5. Synthesis and behaviour in solution of the octahedral ruthenium(II) complex **16**.

Interestingly, when the dicationic complex **16** was dissolved in non-polar solvents, such as dichloromethane or tetrahydrofuran, it readily evolved into the known monocationic derivative $fac\text{-}[RuCl\{\kappa^1\text{-}(P)\text{-}PPh_2py\}\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}_2][Cl]$ (**17**) by coordination of one of the chloride counter-anions to ruthenium (Scheme 5).[31] This is clearly evidenced in the $^{31}P\{^1H\}$ NMR spectra in which the singlet at –4.1 ppm splits into three new signals at –8.0 [dd, $^2J(P,P)$ = 33.1, 27.7 Hz], –6.4 (dd, $^2J_{P,P}$ = 27.7, 27.7 Hz) and 47.5 (dd, $^2J_{P,P}$ = 33.1, 27.7 Hz) ppm. Remarkably, such a chelate ring-opening process is reversible and **16** was instantaneously recovered when **17** was dissolved in polar media (methanol or water). Hemilabile behaviour was also observed for **16** when a dichloromethane solution of this complex was treated with excess benzonitrile, the $^{31}P\{^1H\}$ NMR spectrum of the mixture showing, after 5 h at room temp., the formation of $mer\text{-}[Ru(NCPh)\{\kappa^1\text{-}(P)\text{-}PPh_2py\}\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}_2][Cl]_2$ (**18**) as the major product [a characteristic ABX spin system is observed with signals at –7.5 (m) and 47.3 (t) ppm].[32] Work up of the mixture regenerated **16** quantitatively (Scheme 5).

In complete accord with the catalytic results collected in Table 3, the dicationic complex $[Ru\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}_3][Cl]_2$ (**16**) proved effective in the hydration of benzonitrile, leading to the quantitative formation of benzamide after 24 h.[33] The higher reactivity of **16** in comparison with the other complexes containing $\kappa^2\text{-}(P,N)$-coordinated 2-(diphenylphosphanyl)pyridines studied in this work most probably stems from its hemilabile character. However, we must note that the activity of this complex was still far from that previously reported by us with the ruthenium catalysts

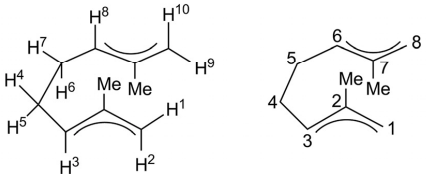
A–**E** depicted in Figure 3,[11e–11g,11i–11j] which were able to effect the complete hydration of benzonitrile in only 1–5 h under identical reaction conditions (a conversion of only 36% after 7 h was observed for **16**).

Conclusions

In the search for cooperative effects of ligands, several arene-ruthenium(II) and bis(allyl)-ruthenium(IV) complexes with electronically and sterically varied 2-(diphenylphosphanyl)pyridines have been synthesized, structurally characterized and investigated as potential catalysts for the selective hydration of nitriles to amides. In contrast to the previous work of Oshiki and co-workers with this type of phosphane ligands,[11b,11h,11k] our results from the hydration of the benzonitrile model substrate ruled out the involvement of bifunctional pathways during the catalytic events. In fact, the high tendency of PPh_2py (**1**) and PPh_2(py-4-NMe_2) (**2**) to adopt chelating coordination results in the formation of species with very low activity, whereas in the case of PPh_2(py-6-*tert*-amyl) (**3**) the presence of the bulky *tert*-amyl substituent seems to prevent the approach of the substrate to the Lewis acid metal centre, also leading to poor results in the catalysis. Although improvements in the catalytic activities of complexes $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{\kappa^1\text{-}(P)\text{-}PPh_2py\}]$, $[RuCl(\eta^6\text{-}p\text{-cymene})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ and $[RuCl(\eta^3{:}\eta^3\text{-}C_{10}H_{16})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ were observed in the presence of excess PPh_2py due to the in situ formation of the more active dication $[Ru\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}_3]^{2+}$, the results obtained are still far from the benchmarks already described in the literature for this catalytic transformation. Overall, the results described herein demonstrate that cooperative effects of ligands in homogeneous catalysis depend not only on the ligand structure, but also on the metal fragment to which they are attached. For the particular case of 2-(diphenylphosphanyl)pyridine ligands, hemilability seems to be a key factor that must be taken into account when designing catalysts with these ligands.

Experimental Section

General: Synthetic procedures were performed under dry nitrogen using vacuum-line and standard Schlenk techniques. Solvents were dried by standard methods and distilled under nitrogen before use. The phosphane ligand **2**[34] and the ruthenium(II) complexes $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})\}_2]$ (**4a**–**d**),[35] $[RuCl_2(\eta^6\text{-arene})\{\kappa^1\text{-}(P)\text{-}PPh_2py\}]$ (**5a**,**b**,**d**),[15] $[RuCl(\eta^6\text{-arene})\{\kappa^2\text{-}(P,N)\text{-}PPh_2py\}][SbF_6]$ (**7a**,**b**,**d**),[15] $[RuCl_2(\eta^6\text{-arene})(PPh_3)]$ (**9a**–**d**),[35a,36] $[\{RuCl(\mu\text{-}Cl)(\eta^3{:}\eta^3\text{-}C_{10}H_{16})\}_2]$ (**11**),[37] and $[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(PPh_3)]$ (**15**)[38] were prepared by following the methods reported in the literature. The rest of the reagents employed in this work were obtained from commercial suppliers and used as received. C, H and N analyses were carried out with a Perkin–Elmer 2400 microanalyser. NMR spectra were recorded with Bruker DPX300 or AV400 instruments. Chemical shifts are given in ppm, relative to internal tetramethylsilane (^1H and ^{13}C), and external 85% aqueous H_3PO_4 solutions (^{31}P). The coupling constants *J* are given in Hz. DEPT experiments were carried out for all the compounds reported in this paper. The numbering of the H and C atoms of the 2,7-dimethylocta-2,6-diene-1,8-diyl skeleton is given below.



$[RuCl_2(\eta^6\text{-mesitylene})\{\kappa^1\text{-}(P)\text{-}PPh_2py\}]$ (5c): A solution of dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-mesitylene})\}_2]$ (**4c**) (0.292 g, 0.5 mmol) in tetrahydrofuran (40 mL) was treated with the phosphane ligand **1** (0.316 g, 1.2 mmol) at room temperature for 3 h. The solvent was then removed under reduced pressure to give an orange solid, which was washed with hexanes (3 × 20 mL) and dried in vacuo. Yield 0.461 g (83%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 29.4 (s) ppm. ^1H NMR ($CDCl_3$): δ = 1.90 (s, 9 H, $C_6H_3Me_3$), 4.91 (s, 3 H, $C_6H_3Me_3$), 7.25–7.96 (m, 13 H, CH_{arom}), 8.70 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 18.0 (s, $C_6H_3Me_3$), 86.1 (s, CH of mes), 103.7 (s, C of mes), 123.8 and 130.2 (s, CH_{arom}), 127.6 (br., CH_{arom}), 131.7 (d, $^3J_{P,C}$ = 23.1 Hz, CH_{arom}), 133.0 (d, $^1J_{P,C}$ = 45.3 Hz, C_{arom}), 135.1 (d, $^2J_{P,C}$ = 8.0 Hz, CH_{arom}), 148.5 (d, $^3J_{P,C}$ = 15.1 Hz, CH_{arom}), 158.8 (d, $^1J_{P,C}$ = 68.4 Hz, C_{arom}) ppm. $C_{26}H_{26}Cl_2NPRu$ (555.45): calcd. C 56.22, H 4.72, N 2.52; found C 56.34, H 4.77, N 2.69.

$[RuCl_2(\eta^6\text{-arene})\{\kappa^1\text{-}(P)\text{-}PPh_2(py\text{-}4\text{-}NMe_2)\}]$ [arene = benzene (6a), *p*-cymene (6b), mesitylene (6c)]: A solution of the appropriate dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})\}_2]$ (**4a**–**c**) (0.5 mmol) in tetrahydrofuran (40 mL) was treated with the phosphane ligand **2** (0.367 g, 1.2 mmol) at room temperature for 2 (**6b**,**c**) or 6 h (**6a**). The solvent was then removed under reduced pressure to give an orange solid, which was washed with hexanes (3 × 20 mL) and dried in vacuo.

6a: Yield 0.467 g (84%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 26.5 (s) ppm. ^1H NMR ($CDCl_3$): δ = 2.78 [s, 6 H, $N(CH_3)_2$], 5.57 (s, 6 H, C_6H_6), 6.43 (m, 2 H, CH_{arom}), 7.35 (m, 6 H, CH_{arom}), 7.90 (m, 4 H, CH_{arom}), 8.37 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 38.6 [s, $N(CH_3)_2$], 89.1 (d, $^2J_{P,C}$ = 3.0 Hz, C_6H_6), 106.4 and 130.3 (s, CH_{arom}), 114.1 (d, $^2J_{P,C}$ = 22.1 Hz, CH_{arom}), 127.8 (d, $^3J_{P,C}$ = 12.0 Hz, CH_{arom}), 133.2 (d, $^1J_{P,C}$ = 46.2 Hz, C_{arom}), 134.7 (d, $^2J_{P,C}$ = 8.0 Hz, CH_{arom}), 149.3 (d, $^3J_{P,C}$ = 16.0 Hz, CH_{arom}), 153.6 (d, $^3J_{P,C}$ = 11.1 Hz, C_{arom}), 156.8 (d, $^1J_{P,C}$ = 69.4 Hz, C_{arom}) ppm. $C_{25}H_{25}Cl_2N_2PRu$ (556.44): calcd. C 53.96, H 4.53, N 5.03; found C 54.15, H 4.44, N 5.21.

6b: Yield 0.496 g (81%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 21.9 (s) ppm. ^1H NMR ($CDCl_3$): δ = 0.97 [d, $^3J_{H,H}$ = 6.9 Hz, 6 H, $CH(CH_3)_2$], 1.75 (s, 3 H, CH_3), 2.64 [sept., $^3J_{H,H}$ = 6.9 Hz, 1 H, $CH(CH_3)_2$], 2.80 [s, 6 H, $N(CH_3)_2$], 5.36 and 5.48 (d, $^3J_{H,H}$ = 6.3 Hz, 2 H each, CH of cym), 6.50 (m, 2 H, CH_{arom}), 7.36 (m, 6 H, CH_{arom}), 8.04 (m, 4 H, CH_{arom}), 8.40 (d, $^3J_{H,H}$ = 6.1 Hz, 1 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 16.9 (s, CH_3), 21.5 [s, $CH(CH_3)_2$], 30.1 [s, $CH(CH_3)_2$], 38.6 [s, $N(CH_3)_2$], 85.4 (d, $^2J_{P,C}$ = 5.0 Hz, CH of cym), 91.0 (d, $^2J_{P,C}$ = 3.0 Hz, CH of cym), 94.8 and 109.0 (s, C of cym), 106.3 and 130.0 (s, CH_{arom}), 114.3 (d, $^2J_{P,C}$ = 19.1 Hz, CH_{arom}), 127.5 (d, $^3J_{P,C}$ = 11.0 Hz, CH_{arom}), 132.4 (d, $^1J_{P,C}$ = 43.7 Hz, C_{arom}), 134.9 (d, $^2J_{P,C}$ = 8.0 Hz, CH_{arom}), 148.8 (d, $^3J_{P,C}$ = 18.1 Hz, CH_{arom}), 153.4 (d, $^3J_{P,C}$ = 11.7 Hz, C_{arom}), 157.8 (d, $^1J_{P,C}$ = 74.4 Hz, C_{arom}) ppm. $C_{29}H_{33}Cl_2N_2PRu$ (612.54): calcd. C 56.86, H 5.43, N 4.57; found C 56.93, H 5.32, N 4.71.

6c: Yield 0.526 g (88%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 28.3 (s) ppm. ^1H NMR ($CDCl_3$): δ = 1.90 (s, 9 H, $C_6H_3Me_3$), 2.89 [s, 6 H, $N(CH_3)_2$], 4.90 (s, 3 H, $C_6H_3Me_3$), 6.40 (m, 2 H, CH_{arom}), 7.36 (m, 6 H, CH_{arom}), 8.03 (m, 4 H, CH_{arom}), 8.31 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 18.0 (s, $C_6H_3Me_3$), 38.9 [s, $N(CH_3)_2$], 85.9 (s, CH of mes), 105.6 (s, C of mes), 106.4 and 129.9 (s, CH_{arom}), 115.8 (d, $^2J_{P,C}$ = 28.2 Hz, CH_{arom}), 127.4 (d, $^3J_{P,C}$ = 13.0 Hz, CH_{arom}), 133.8 (d, $^1J_{P,C}$ = 45.3 Hz, C_{arom}), 135.0 (d, $^2J_{P,C}$ = 9.0 Hz, CH_{arom}), 148.7 (d, $^3J_{P,C}$ = 16.1 Hz, CH_{arom}), 153.4 (d, $^3J_{P,C}$ = 14.1 Hz, C_{arom}), 157.5 (d, $^1J_{P,C}$ = 62.8 Hz, C_{arom}) ppm. $C_{28}H_{31}Cl_2N_2PRu$ (598.52): calcd. C 56.19, H 5.22, N 4.68; found C 55.92, H 5.40, N 4.60.

[RuCl(η⁶-mesitylene){κ²-(*P*,*N*)-PPh₂py}][SbF₆] (7c): An orange solution of complex **5c** (0.278 g, 0.5 mmol) in methanol (20 mL) was treated with $NaSbF_6$ (0.194 g, 0.75 mmol) at room temperature for 4 h. The solvent was then removed under reduced pressure to give a yellow solid, which was dissolved in CH_2Cl_2 (10 mL), filtered through Kieselguhr and the filtrate concentrated to around 3 mL. Addition of hexanes (30 mL) led to the precipitation of a yellow microcrystalline solid, which was washed with hexanes (3 × 20 mL) and vacuum-dried. Yield 0.287 g (76%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –12.3 (s) ppm. ^1H NMR ($CDCl_3$): δ = 2.20 (s, 9 H, $C_6H_3Me_3$), 5.22 (s, 3 H, $C_6H_3Me_3$), 7.15–8.04 (m, 13 H, CH_{arom}), 8.78 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR ([D₆]acetone): δ = 18.3 (s, $C_6H_3Me_3$), 82.6 (s, CH of mes), 107.5 (s, C of mes), 121.6 (d, $^1J_{P,C}$ = 48.3 Hz, C_{arom}), 129.1 and 129.8 (d, $^3J_{P,C}$ = 11.1 Hz, CH_{arom}), 129.3 and 139.6 (d, $^2J_{P,C}$ = 4.0 Hz, CH_{arom}), 130.1 (d, $^1J_{P,C}$ = 55.3 Hz, C_{arom}), 130.4, 132.3 and 132.9 (s, CH_{arom}), 132.2 (d, $^3J_{P,C}$ = 11.5 Hz, CH_{arom}), 135.3 (d, $^2J_{P,C}$ = 7.1 Hz, CH_{arom}), 153.9 (d, $^3J_{P,C}$ = 14.0 Hz, CH_{arom}), 168.3 (d, $^1J_{P,C}$ = 63.4 Hz, C_{arom}) ppm. $C_{26}H_{26}ClF_6NPRuSb$ (755.73): calcd. C 41.32, H 3.47, N 1.85; found C 41.46, H 3.39, N 2.01.

[RuCl(η⁶-arene){κ²-(*P*,*N*)-PPh₂(py-4-NMe₂)}][SbF₆] [arene = benzene (8a), *p*-cymene (8b), mesitylene (8c)]: Compounds **8a–c**, isolated as air-stable yellow solids, were prepared as described for **7c** starting from the appropriate neutral complex [$RuCl_2$(η⁶-arene){κ¹-(*P*)-PPh_2(py-4-NMe_2)}] (**6a–c**) (0.5 mmol) and $NaSbF_6$ (0.194 g, 0.75 mmol).

8a: Yield 0.284 g (75%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –18.6 (s) ppm. ^1H NMR ($CDCl_3$): δ = 2.97 [s, 6 H, $N(CH_3)_2$], 5.75 (s, 6 H, C_6H_6), 6.57 and 6.78 (m, 1 H each, CH_{arom}), 7.39–7.92 (m, 10 H, CH_{arom}), 8.28 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 39.6 [s, $N(CH_3)_2$], 87.4 (s, C_6H_6), 111.5 (br., 2 C, CH_{arom}), 129.6 and 130.0 (d, $^3J_{P,C}$ = 15.0 Hz, CH_{arom}), 130.2 (d, $^1J_{P,C}$ = 58.3 Hz, C_{arom}), 131.4 and 134.9 (d, $^2J_{P,C}$ = 9.0 Hz, CH_{arom}), 132.2 and 133.0 (s, CH_{arom}), 133.6 (d, $^1J_{P,C}$ = 57.6 Hz, C_{arom}), 152.4 (d, $^3J_{P,C}$ = 12.1 Hz, CH_{arom}), 154.4 (d, $^3J_{P,C}$ = 4.0 Hz, C_{arom}), 166.1 (d, $^1J_{P,C}$ = 40.2 Hz, C_{arom}) ppm. $C_{25}H_{25}ClF_6N_2PRuSb$ (756.72): calcd. C 39.68, H 3.33, N 3.70; found C 39.54, H 3.42, N 3.83.

8b: Yield 0.325 g (80%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –19.3 (s) ppm. ^1H NMR ($CDCl_3$): δ = 1.18 [d, $^3J_{H,H}$ = 6.6 Hz, 3 H, $CH(CH_3)_2$], 1.26 [d, $^3J_{H,H}$ = 7.1 Hz, 3 H, $CH(CH_3)_2$], 2.03 (s, 3 H, CH_3), 2.63 [m, 1 H, $CH(CH_3)_2$], 2.92 [s, 6 H, $N(CH_3)_2$], 5.18 and 5.73 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H each, CH of cym), 5.50 and 5.61 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H each, CH of cym), 6.57 and 6.80 (m, 1 H each, CH_{arom}), 7.42–7.90 (m, 10 H, CH_{arom}), 8.17 (d, $^3J_{H,H}$ = 6.6 Hz, 1 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 18.2 (s, CH_3), 21.8 and 22.7 [s, $CH(CH_3)_2$], 30.9 [s, $CH(CH_3)_2$], 39.5 [s, $N(CH_3)_2$], 83.9 and 87.1 (d, $^2J_{P,C}$ = 3.0 Hz, CH of cym), 85.8 and 89.5 (d, $^2J_{P,C}$ = 5.0 Hz, CH of cym), 101.8 and 107.6 (s, C of cym), 111.4 (d, $^2J_{P,C}$ = 4.8 Hz, CH_{arom}), 111.6 (d, $^4J_{P,C}$ = 3.0 Hz, CH_{arom}), 129.3 (d, $^1J_{P,C}$ = 45.2 Hz, C_{arom}), 129.5 and 130.0 (d, $^3J_{P,C}$ = 11.1 Hz, CH_{arom}), 129.8 (d, $^1J_{P,C}$ = 47.5 Hz, C_{arom}), 131.4 and 134.9 (d, $^2J_{P,C}$ = 10.0 Hz, CH_{arom}), 132.1 and 132.8 (d, $^4J_{P,C}$ = 3.0 Hz, CH_{arom}), 151.5 (d, $^3J_{P,C}$ = 18.1 Hz, CH_{arom}), 154.4 (d, $^3J_{P,C}$ = 5.0 Hz, C_{arom}), 166.6 (d, $^1J_{P,C}$ = 59.0 Hz, C_{arom}) ppm. $C_{29}H_{33}ClF_6N_2PRuSb$ (812.83): calcd. C 42.85, H 4.09, N 3.45; found C 42.70, H 4.18, N 3.66.

8c: Yield 0.311 g (78%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –13.2 (s) ppm. ^1H NMR ($CDCl_3$): δ = 2.17 (s, 9 H, $C_6H_3Me_3$), 3.08 [s, 6 H, $N(CH_3)_2$], 5.08 (s, 3 H, $C_6H_3Me_3$), 6.50 and 6.78 (m, 1 H each, CH_{arom}), 7.45–7.91 (m, 10 H, CH_{arom}), 8.11 (d, $^3J_{H,H}$ = 6.4 Hz, 1 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 18.9 (s, $C_6H_3Me_3$), 39.5 [s, $N(CH_3)_2$], 82.3 (s, CH of mes), 105.9 (s, C of mes), 110.7 (d, $^2J_{P,C}$ = 4.5 Hz, CH_{arom}), 111.6 (d, $^4J_{P,C}$ = 3.0 Hz, CH_{arom}), 121.5 (d, $^1J_{P,C}$ = 46.0 Hz, C_{arom}), 129.2 and 129.7 (d, $^3J_{P,C}$ = 12.1 Hz, CH_{arom}), 130.0 (d, $^1J_{P,C}$ = 49.1 Hz, C_{arom}), 131.9 and 135.0 (d, $^2J_{P,C}$ = 10.3 Hz, CH_{arom}), 132.3 and 132.9 (d, $^4J_{P,C}$ = 3.0 Hz, CH_{arom}), 151.0 (d, $^3J_{P,C}$ = 18.2 Hz, CH_{arom}), 154.4 (d, $^3J_{P,C}$ = 5.3 Hz, C_{arom}), 166.8 (d, $^1J_{P,C}$ = 63.4 Hz, C_{arom}) ppm. $C_{28}H_{31}ClF_6N_2PRuSb$ (798.80): calcd. C 42.10, H 3.91, N 3.51; found C 42.23, H 3.86, N 3.69.

[RuCl(η⁶-hexamethylbenzene){κ²-(*P*,*N*)-PPh₂(py-4-NMe₂)}][SbF₆] (8d): A solution of dimer [{RuCl(μ-Cl)(η⁶-hexamethylbenzene)}₂] (**4d**; 0.334 g, 0.5 mmol) in tetrahydrofuran (40 mL) was treated with the phosphane ligand **2** (0.367 g, 1.2 mmol) at room temperature for 2 h. Methanol (10 mL) and $NaSbF_6$ (0.388 g, 1.5 mmol) were then added and the resulting mixture was stirred at room temperature for 1 h. After this time, solvents were removed under reduced pressure and CH_2Cl_2 (10 mL) was added. The resulting suspension was filtered through Kieselguhr and the filtrate concentrated to around 3 mL. Addition of hexanes (30 mL) led to the precipitation of a yellow microcrystalline solid, which was washed with diethyl ether (3 × 10 mL) and vacuum-dried. Yield 0.647 g (77%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –8.5 (s) ppm. ^1H NMR ($CDCl_3$): δ = 2.05 (s, 18 H, C_6Me_6), 3.01 [s, 6 H, $N(CH_3)_2$], 6.46 and 6.79 (m, 1 H each, CH_{arom}), 7.19 (m, 2 H, CH_{arom}), 7.54–7.79 (m, 8 H, CH_{arom}), 7.92 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 15.6 (s, C_6Me_6), 39.4 [s, $N(CH_3)_2$], 96.9 (d, $^1J_{P,C}$ = 3.0 Hz, C_6Me_6), 110.4 (d, $^2J_{P,C}$ = 5.0 Hz, CH_{arom}), 111.0 (d, $^4J_{P,C}$ = 3.0 Hz, CH_{arom}), 123.6 (d, $^1J_{P,C}$ = 44.2 Hz, C_{arom}), 128.4 (d, $^1J_{P,C}$ = 48.2 Hz, C_{arom}), 129.0 and 129.8 (d, $^3J_{P,C}$ = 11.1 Hz, CH_{arom}), 132.0 and 132.7 (d, $^4J_{P,C}$ = 3.0 Hz, CH_{arom}), 132.2 and 135.1 (d, $^2J_{P,C}$ = 9.5 Hz, CH_{arom}), 148.0 (d, $^3J_{P,C}$ = 18.1 Hz, CH_{arom}), 154.5 (d, $^3J_{P,C}$ = 5.0 Hz, C_{arom}), 167.4 (d, $^1J_{P,C}$ = 62.4 Hz, C_{arom}) ppm. $C_{31}H_{37}ClF_6N_2PRuSb$ (840.88): calcd. C 44.28, H 4.44, N 3.33; found C 44.36, H 4.29, N 3.45.

[$RuCl_2$(η⁶-arene){κ¹-(*P*)-PPh_2(py-6-*tert*-amyl)}] [arene = benzene (10a), *p*-cymene (10b)]: Complexes **10a,b**, isolated as air-stable orange solids, were prepared as described for **6a,b** starting from the appropriate dimer [{RuCl(μ-Cl)(η⁶-arene)}₂] (**4a,b**) (0.5 mmol) and the phosphane ligand **3** (0.400 g, 1.2 mmol).

10a: Yield 0.519 g (89%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 25.0 (s) ppm. ^1H NMR ($CDCl_3$): δ = 0.79 (t, $^3J_{H,H}$ = 8.0 Hz, 3 H, CH_2CH_3), 1.41 [s, 6 H, $C(CH_3)_2$], 1.83 (q, $^3J_{H,H}$ = 8.0 Hz, 2 H, CH_2CH_3), 5.55 (s, 6 H, C_6H_6), 7.12–7.60 (m, 9 H, CH_{arom}), 7.92 (m, 4 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 9.0 (s, CH_2CH_3), 27.2 [s, $C(CH_3)_2$], 35.9 (s, CH_2CH_3), 41.3 [s, $C(CH_3)_2$], 89.0 (d, $^2J_{P,C}$ = 3.0 Hz, C_6H_6), 120.9 and 130.4 (s, CH_{arom}), 127.7 (d, $^3J_{P,C}$ = 12.0 Hz, CH_{arom}), 127.8 (d, $^3J_{P,C}$ = 22.9 Hz, CH_{arom}), 133.0 (d, $^1J_{P,C}$ = 48.3 Hz, C_{arom}), 134.8 (d, $^2J_{P,C}$ = 9.0 Hz, CH_{arom}), 135.8 (d, $^2J_{P,C}$ = 8.0 Hz, CH_{arom}), 156.8 (d, $^1J_{P,C}$ = 71.4 Hz, C_{arom}),

168.0 (d, $^3J_{P,C}$ = 15.1 Hz, C_{arom}) ppm. $C_{28}H_{30}Cl_2NPRu$ (583.50): calcd. C 57.64, H 5.18, N 2.40; found C 57.50, H 5.31, N 2.59.

10b: Yield 0.544 g (85%). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 20.1 (s) ppm. ^1H NMR ($CDCl_3$): δ = 0.79 (t, $^3J_{H,H}$ = 8.6 Hz, 3 H, CH_2CH_3), 0.92 [d, $^3J_{H,H}$ = 6.2 Hz, 6 H, $CH(CH_3)_2$], 1.43 [s, 6 H, $C(CH_3)_2$], 1.63 (s, 3 H, CH_3), 1.85 (q, $^3J_{H,H}$ = 8.6 Hz, 2 H, CH_2CH_3), 2.62 [sept., $^3J_{H,H}$ = 6.2 Hz, 1 H, $CH(CH_3)_2$], 5.21 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H, CH of cym), 5.45 (dd, $^3J_{H,H}$ = 6.5, $^3J_{P,H}$ = 2.0 Hz, 2 H, CH of cym), 7.25–7.54 (m, 9 H, CH_{arom}), 8.11 (m, 4 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 9.1 (s, CH_2CH_3), 16.8 (s, CH_3), 21.3 [s, $CH(CH_3)_2$], 27.2 [s, $C(CH_3)_2$], 30.0 [s, $CH(CH_3)_2$], 35.9 (s, CH_2CH_3), 41.3 [s, $C(CH_3)_2$], 85.1 (d, $^2J_{P,C}$ = 5.0 Hz, CH of cym), 90.9 (s, CH of cym), 94.5 and 110.2 (s, C of cym), 120.6 and 130.0 (s, CH_{arom}), 127.4 (d, $^3J_{P,C}$ = 12.1 Hz, CH_{arom}), 128.2 (d, $^3J_{P,C}$ = 24.1 Hz, CH_{arom}), 134.3 (d, $^1J_{P,C}$ = 44.3 Hz, C_{arom}), 135.0 (d, $^2J_{P,C}$ = 10.0 Hz, CH_{arom}), 135.6 (d, $^2J_{P,C}$ = 8.0 Hz, CH_{arom}), 158.3 (d, $^1J_{P,C}$ = 67.4 Hz, C_{arom}), 167.3 (d, $^3J_{P,C}$ = 13.1 Hz, C_{arom}) ppm. $C_{32}H_{38}Cl_2NPRu$ (639.61): calcd. C 60.09, H 5.99, N 2.19; found C 60.20, H 5.87, N 2.34.

[RuCl(η^3:η^3-$C_{10}H_{16}$){κ^2-(*P*,*N*)-PPh_2py}][SbF_6] (12) and [RuCl(η^3:η^3-$C_{10}H_{16}$){κ^2-(*P*,*N*)-PPh_2(py-4-NMe_2)}][SbF_6] (13): A solution of dimer [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] (**11**; 0.308 g, 0.5 mmol) in dichloromethane (40 mL) was treated with the appropriate phosphane ligand **1** or **2** (1.2 mmol) at room temperature for 15 min. The solvent was then removed under reduced pressure to give a yellow solid, which was washed with hexanes (3 × 20 mL) and dried in vacuo. The resulting solid was dissolved in CH_2Cl_2/MeOH (20 mL, 1:1, v/v) and treated with $NaSbF_6$ (0.776 g, 3 mmol) at room temperature. After stirring for 1 h, the solvents were removed under reduced pressure and CH_2Cl_2 (10 mL) was added. The resulting suspension was filtered through Kieselguhr and the filtrate concentrated to around 3 mL. The addition of hexanes (30 mL) led to the precipitation of a yellow microcrystalline solid, which was washed with diethyl ether (3 × 10 mL) and vacuum-dried.

12: Yield 0.663 g (86%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = –39.1 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 1.99 and 2.35 (s, 3 H each, CH_3), 2.33 (d, $^3J_{P,H}$ = 7.9 Hz, 1 H, 2-H or 2-H), 2.98 (m, 2 H, 4-H and 6-H), 3.29 (m, 2 H, 5-H and 7-H), 3.44 (d, $^3J_{P,H}$ = 5.1 Hz, 1 H, 2-H or 10-H), 3.70 (d, $^3J_{P,H}$ = 8.3 Hz, 1 H, 1-H or 9-H), 3.75 and 4.73 (m, 1 H each, 3-H and 8-H), 3.83 (d, $^3J_{P,H}$ = 6.8 Hz, 1 H, 1-II or 9-II), 7.51–8.25 (m, 14 II, CII_{arom}) ppm. $^{13}C\{^1II\}$ NMR (CD_2Cl_2): δ = 19.7 (s, 2 C, CH_3), 33.8 and 37.1 (s, C-4 and C-5), 71.2 (d, $^2J_{P,C}$ = 3.1 Hz, C-1 or C-8), 71.5 (d, $^2J_{P,C}$ = 4.1 Hz, C-1 or C-8), 102.9 (d, $^2J_{P,C}$ = 5.6 Hz, C-3 or C-6), 115.7 (d, $^2J_{P,C}$ = 11.2 Hz, C-3 or C-6), 119.0 and 119.3 (s, C-2 and C-7), 128.3 (d, $^1J_{P,C}$ = 49.7 Hz, C_{arom}), 129.9 and 130.1 (d, $^3J_{P,C}$ = 11.0 Hz, CH_{arom}), 131.3 (s, CH_{arom}), 131.7–132.7 (m, C_{arom} and CH_{arom}), 141.0 (d, $^2J_{P,C}$ = 3.5 Hz, CH_{arom}), 153.6 (d, $^3J_{P,C}$ = 13.3 Hz, CH_{arom}), 164.2 (d, $^1J_{P,C}$ = 57.8 Hz, C_{arom}) ppm. $C_{27}H_{30}ClF_6NPRuSb$ (771.78): calcd. C 42.02, H 3.92, N 1.81; found C 42.06, H 4.13, N 2.01.

13: Yield 0.733 g (90%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = –38.3 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 2.01 and 2.33 (s, 3 H each, CH_3), 2.95–3.29 (m, 6 H, 2-H, 4-H, 5-H, 6-H, 7-H and 10-H), 3.15 (s, 6 H, $N(CH_3)_2$), 3.49 and 4.52 (m, 1 H each, 3-H and 8-H), 3.67 (d, $^3J_{P,H}$ = 7.9 Hz, 1 H, 1-H or 9-H), 3.72 (d, $^3J_{P,H}$ = 6.4 Hz, 1 H, 1-H or 9-H), 6.70, 6.94 and 7.15 (m, 1 H each, CH_{arom}), 7.47–7.71 (m, 8 H, CH_{arom}), 8.11 (m, 2 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 19.3 and 19.7 (s, CH_3), 33.3 and 36.5 (s, C-4 and C-5), 40.0 [s, $N(CH_3)_2$], 71.2 (d, $^2J_{P,C}$ = 3.7 Hz, C-1 or C-8), 71.6 (d, $^2J_{P,C}$ = 4.4 Hz, C-1 or C-8), 101.1 (d, $^2J_{P,C}$ = 5.9 Hz, C-3 or C-6), 112.2 (d, $^4J_{P,C}$ = 1.5 Hz, CH_{arom}), 113.4 (d, $^2J_{P,C}$ = 11.8 Hz, C-3 or C-6), 114.4 (d, $^2J_{P,C}$ = 4.4 Hz, CH_{arom}), 116.8 (d, $^2J_{P,C}$ = 2.2 Hz, C-2 or C-7), 118.6 (d, $^2J_{P,C}$ = 1.5 Hz, C-2 or C-7), 128.7 (d, $^1J_{P,C}$ = 47.4 Hz, C_{arom}), 128.9 (d, $^1J_{P,C}$ = 48.1 Hz, C_{arom}), 129.6 and 129.9 (d, $^3J_{P,C}$ = 12.4 Hz, CH_{arom}), 131.8–132.4 (m, CH_{arom}), 149.3 (d, $^3J_{P,C}$ = 14.8 Hz, CH_{arom}), 155.0 (d, $^3J_{P,C}$ = 5.1 Hz, C_{arom}), 162.3 (d, $^1J_{P,C}$ = 59.2 Hz, C_{arom}) ppm. $C_{29}H_{35}ClF_6N_2PRuSb$ (814.84): calcd. C 42.75, H 4.33, N 3.44; found C 42.84, H 4.21, N 3.62.

[$RuCl_2$(η^3:η^3-$C_{10}H_{16}$){κ^1-(*P*)-PPh_2(py-6-*tert*-amyl)}] (14): A solution of dimer [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] (**11**; 0.308 g, 0.5 mmol) in dichloromethane (40 mL) was treated with the phosphane ligand **3** (0.400 g, 1.2 mmol) at room temperature for 15 min. The solvent was then removed under reduced pressure to give a yellow solid, which was washed with hexanes (3 × 20 mL) and dried in vacuo. Yield 0.583 g (91%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 25.8 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 0.75 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH_2CH_3), 1.41 and 1.42 [s, 3 H each, $C(CH_3)_2$], 1.87 (q, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2CH_3), 2.24 (s, 6 H, CH_3), 2.64 (m, 2 H, 4-H and 6-H), 2.91 (d, $^3J_{P,H}$ = 3.3 Hz, 2 H, 2-H and 10-H), 3.46 (m, 2 H, 5-H and 7-H), 4.70 (d, $^3J_{P,H}$ = 8.9 Hz, 2 H, 1-H and 9-H), 5.16 (m, 2 H, 3-H and 8-H), 7.10–7.44 (m, 9 H, CH_{arom}), 8.03 (m, 4 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 9.5 (s, CH_2CH_3), 20.8 (s, CH_3), 27.6 and 27.8 [s, $C(CH_3)_2$], 36.3 (s, CH_2CH_3), 37.2 (s, C-4 and C-5), 41.7 [s, $C(CH_3)_2$], 67.0 (d, $^2J_{P,C}$ = 5.2 Hz, C-1 and C-8), 108.8 (d, $^2J_{P,C}$ = 9.8 Hz, C-3 and C-6), 119.8 and 127.7 (s, CH_{arom}), 125.8 (s, C-2 and C-7), 127.0 (d, $^3J_{P,C}$ = 10.3 Hz, CH_{arom}), 127.7 (d, $^3J_{P,C}$ = 10.6 Hz, CH_{arom}), 129.6 and 130.1 (d, $^4J_{P,C}$ = 1.8 Hz, CH_{arom}), 134.3 (d, $^1J_{P,C}$ = 44.4 Hz, C_{arom}), 135.1 (d, $^3J_{P,C}$ = 14.1 Hz, CH_{arom}), 135.8 (d, $^1J_{P,C}$ = 46.3 Hz, C_{arom}), 136.2 (d, $^2J_{P,C}$ = 7.4 Hz, CH_{arom}), 137.3 (d, $^2J_{P,C}$ = 8.0 Hz, CH_{arom}), 160.0 (d, $^1J_{P,C}$ = 65.2 Hz, C_{arom}), 167.1 (d, $^3J_{P,C}$ = 13.4 Hz, C_{arom}) ppm. $C_{32}H_{40}Cl_2NPRu$ (641.62): calcd. C 59.90, H 6.28, N 2.18; found C 60.03, H 6.16, N 2.25.

[Ru{κ^2-(*P*,*N*)-PPh_2py}$_3$][Cl]$_2$ (16): A solution of complex [$RuCl_2$(η^6-*p*-cymene){κ^1-(*P*)-PPh_2py}] (**5b**; 0.285 g, 0.5 mmol) and the phosphane ligand **1** (0.290 g, 1.1 mmol) was heated at reflux in methanol (30 mL) for 8 h. The colour of the solution progressively changed from orange to yellow. After cooling the mixture, the solvent was removed under vacuum and the solid residue was washed with hexanes (3 × 20 mL) and diethyl ether (10 mL) and dried in vacuo. Yield 0.409 g (85%). $^{31}P\{^1H\}$ NMR (CD_3OD): δ = –4.1 (s) ppm. ^1H NMR (CD_3OD): δ = 6.71 (br., 6 H, CH_{arom}), 7.12–7.91 (m, 30 H, CH_{arom}), 8.19–8.35 (m, 6 H, CH_{arom}) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD): δ = 126.7 (m, C_{arom}), 128.9 (m, CH_{arom}), 129.4 (m, CH_{arom}), 130.1 (s, CH_{arom}), 131.6 (s, CH_{arom}), 132.2 (m, CH_{arom}), 132.6 (s, CH_{arom}), 132.9 (m, CH_{arom}), 139.9 (s, CH_{arom}), 151.6 (m, CH_{arom}), 171.0 (s, C_{arom}) ppm. $C_{51}H_{42}Cl_2N_3P_3Ru$ (961.81): calcd. C 63.69, H 4.40, N 4.37; found C 63.55, H 4.28, N 4.56.

General Procedure for the Catalytic Hydration of Benzonitrile: Under nitrogen, benzonitrile (0.103 g, 1 mmol), water (3 mL), the corresponding ruthenium complex (0.05 mmol; 5 mol-% of Ru) and additive (when indicated) were introduced into a sealed tube and the reaction mixture was stirred at 100 °C for 24 h. Conversion was determined by GC, analysing a sample of around 20 μL of the crude reaction mixture, which was extracted with CH_2Cl_2 (3 mL). The identity of the resulting benzamide was assessed by comparison with a commercially available pure sample.

X-ray Crystal Structure Determinations of Complexes 8c, 10a and 12: Crystals of **8c** and **12** suitable for X-ray diffraction analysis were obtained by the slow diffusion of diethyl ether into saturated solutions of the complexes in acetone or dichloromethane, respec-

Table 4. Crystal data and structure refinement details for **8c**, **10a** and **12**.

	8c	**10a**	**12**
Chemical formula	$Ru_2C_{56}H_{62}F_{12}N_4Cl_2P_2Sb_2$	$RuC_{28}H_{30}Cl_2NP$	$RuC_{27}H_{30}F_6ClNPSb$
Molecular mass	1597.58	583.47	771.76
T [°K]	293(2)	293(2)	293(2)
Wavelength [Å]	1.5418	1.5418	1.5418
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	$Pca2_1$	$P2_1/c$	$P2_1/c$
Crystal size [mm]	0.196 × 0.057 × 0.031	0.32 × 0.20 × 0.18	0.254 × 0.204 × 0.093
a [Å]	25.393(5)	10.0028(3)	10.4788(2)
b [Å]	15.340(5)	11.8993(3)	16.0744(2)
c [Å]	16.063(5)	22.2935(4)	18.0987(3)
α [°]	90	90	90
β [°]	90	97.803(2)	105.461(2)
γ [°]	90	90	90
Z	4	4	4
V [Å^3]	6257(3)	2628.9(2)	2938.23(8)
$\rho_{calcd.}$ [g cm^{-3}]	1.696	1.474	1.745
μ [mm^{-1}]	12.529	7.390	13.304
F(000)	3152	1192	1520
θ range [°]	2.88–74.75	4.00–74.77	3.74–74.73
Index ranges	$-31 \le h \le 31$	$-11 \le h \le 11$	$-8 \le h \le 13$
	$-18 \le k \le 13$	$-14 \le k \le 14$	$-19 \le k \le 18$
	$-19 \le l \le 13$	$-27 \le l \le 27$	$-22 \le l \le 22$
Completeness to θ_{max} [%]	98.0	96.7	95.6
No. of data collected	29535	19302	13656
No. of unique data	9878 (R_{int} = 0.0286)	5218 (R_{int} = 0.0432)	5757 (R_{int} = 0.0418)
No. parameters/restraints	731/0	280/0	361/0
Refinement method		full-matrix least-squares on F^2	
Goodness of fit on F^2	1.063	1.077	1.013
Weight function (a, b)	0.0783, 0.5490	0.0990, 3.1526	0.1138, 0.0000
R_1[a] [$I > 3\sigma(I)$]	0.0395	0.0555	0.0549
wR_2[a] [$I > 3\sigma(I)$]	0.1058	0.1495	0.1484
R_1 (all data)	0.0414	0.0568	0.0632
wR_2 (all data)	0.1093	0.1517	0.1624
Largest diff peak and hole [e Å^{-3}]	0.474 and –0.723	1.365 and –2.424	1.715 and –1.009

[a] $R_1 = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

tively. Crystals of **10a** were grown by the slow diffusion of *n*-pentane into a saturated solution of the complex in tetrahydrofuran. For all crystals, data collection was performed with a Oxford Diffraction Xcalibur Nova single-crystal diffractometer using Cu-K_α radiation (λ = 1.5418 Å). Images were collected at a fixed crystal-detector distance of 63 mm by using the oscillation method with 1° oscillation and variable exposure time per image (2–8 s for **8c**, 8–30 s for **10a** and 1.5–2.5 s for **12**). The data collection strategy was calculated with the program CrysAlis Pro CCD.[39] Data reduction and cell refinement was performed with the program CrysAlis Pro RED.[39] An empirical absorption correction was applied by using the SCALE3 ABSPACK algorithm as implemented in the program CrysAlis Pro RED.[39] The software package WINGX[40] was used for space group determination, structure solution and refinement. The structures of complexes **8c** and **12** were solved by Patterson interpretation and phase expansion by using SIR92.[41] The structure of **10a** was solved by direct methods using DIRDIF.[42] Isotropic least-squares refinement on F^2 was performed by using SHELXL97.[43] During the final stages of the refinements, all the positional parameters and the anisotropic temperature factors of all the non-hydrogen atoms were refined. The coordinates of the hydrogen atoms were geometrically located and their coordinates were refined riding on their parent atoms (except for H1A, H1B, H10A and H10B for **12**, which were found from different Fourier maps and included in a refinement with isotropic parameters). The function minimized was $[\Sigma w(F_o^2 - F_c^2)/\Sigma w(F_o^2)]^{1/2}$ in which $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ (a and b values are given in Table 4) with $\sigma(F_o^2)$ from counting statistics and $P = [\text{Max}(F_o^2,0) + 2F_c^2]/3$. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[44] Geometrical calculations were performed with PARST.[45] The crystallographic plots were prepared by using PLATON.[46] Selected crystal and refinement data are presented in Table 4.

CCDC-884153 (for **8c**), -884154 (for **10a**) and -884155 (for **12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

Financial support by the Spanish Ministerio de Ciencia e Innovación (MICINN) (project numbers CTQ2010-14796/BQU, CTQ2009-08746/BQU and CSD2007-00006) and the Gobierno del Principado de Asturias (FICYT project FC-11-COF11-13) is gratefully acknowledged. S.E.G.-G. also thanks the MICINN and the European Social Fund for the award of a "Ramón y Cajal" contract.

[1] See, for example: a) J. Zabicky (Ed.), *The Chemistry of Amides*, Wiley, New York, **1970**; b) A. Greenberg, C. M. Breneman, J. F. Liebman (Eds.), *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*, Wiley, New York, **2000**; c) B. L. Deopura, B. Gupta, M. Joshi, R.

Alagirusami (Eds.), *Polyesters and Polyamides*, CRC Press, Boca Raton, **2008**; d) I. Johansson, *Kirk-Othmer Encyclopedia of Chemical Technology*, Wiley, New York, **2004**, vol. 2, pp. 442–463.

[2] See, for example: a) H. Yamada, M. Kobayashi, *Biosci. Biotechnol. Biochem.* **1996**, *60*, 1391–1400; b) S. van Pelt, F. van Rantwijk, R. A. Sheldon, *Focus in Catalysis Applications* (supplement to *Chimica Oggi/Chemistry Today*), Teknoscienze Srl, Milano, Italy, **2008**, vol. 26, pp. 2–4; c) S. Sanchez, A. L. Demain, *Org. Process Res. Dev.* **2011**, *15*, 224–230; d) B. Li, J. Su, J. Tao, *Org. Process Res. Dev.* **2011**, *15*, 291–293.

[3] a) P. D. Bailey, T. J. Mills, R. Pettecrew, R. A. Price, in: *Comprehensive Organic Functional Group Transformations II* (Eds.: A. R. Katritzky, R. J. K. Taylor), Elsevier, Oxford, **2005**, vol. 5, pp. 201–294; b) D. Döpp, H. Döpp (Eds.), *Methoden Org. Chem. Houben Weyl*, Thieme, Stuttgart, Germany, **1985**, vol. E5(2), pp. 1024–1031.

[4] For reviews on the metal-catalysed hydration of nitriles, see: a) A. W. Parkins, *Platinum Met. Rev.* **1996**, *40*, 169–174; b) V. Y. Kukushkin, A. J. L. Pombeiro, *Chem. Rev.* **2002**, *102*, 1771–1802; c) N. A. Bokach, V. Y. Kukushkin, *Russ. Chem. Bull.* **2005**, *74*, 153 170; d) V. Y. Kukushkin, A. J. L. Pombeiro, *Inorg. Chim. Acta* **2005**, *358*, 1–21; e) T. J. Ahmed, S. M. M. Knapp, D. R. Tyler, *Coord. Chem. Rev.* **2011**, *255*, 949–974.

[5] a) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405–3415; b) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Laezer Jr, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420; c) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

[6] For selected examples, see: a) K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani, K. Kaneda, *Chem. Commun.* **2001**, 461–462; b) K. Yamaguchi, M. Matsushita, N. Mizuno, *Angew. Chem.* **2004**, *116*, 1602–1606; *Angew. Chem. Int. Ed.* **2004**, *43*, 1576–1580; c) T. Mitsudome, Y. Mikami, H. Mori, S. Arita, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Chem. Commun.* **2009**, 3258–3260; d) V. Polshettiwar, R. S. Varma, *Chem. Eur. J.* **2009**, *15*, 1582–1586; e) M. Tamura, H. Wakasugi, K.-I. Shimizu, A. Satsuma, *Chem. Eur. J.* **2011**, *17*, 11428–11431; f) S. E. García-Garrido, J. Francos, V. Cadierno, J. M. Basset, V. Polshettiwar, *ChemSusChem* **2011**, *4*, 104–111; g) A. Y. Kim, H. S. Bae, S. Park, S. Park, S. H. Park, *Catal. Lett.* **2011**, *141*, 685–690; h) K.-I. Shimizu, N. Imaiida, K. Sawabe, A. Satsuma, *Appl. Catal. A* **2012**, *421–422*, 114–120; i) Y. Gangarajula, B. Gopal, *Chem. Lett.* **2012**, *41*, 101–103; j) R. B. N. Baig, R. S. Varma, *Chem. Commun.* **2012**, *48*, 6220–6222.

[7] See, for example: a) S.-I. Murahashi, T. Naota, E. Saito, *J. Am. Chem. Soc.* **1986**, *108*, 7846–7847; b) S.-I. Murahashi, S. Sasao, E. Saito, T. Naota, *J. Org. Chem.* **1992**, *57*, 2521–2523; c) S.-I. Murahashi, S. Sasao, E. Saito, T. Naota, *Tetrahedron* **1993**, *49*, 8805–8826; d) S.-I. Murahashi, T. Naota, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1805–1824; e) A. J. M. van Dijk, T. Heyligen, R. Duchateau, J. Meuldijk, C. E. Koning, *Chem. Eur. J.* **2007**, *13*, 7664–7672.

[8] See, for example: a) T. Ghaffar, A. W. Parkins, *Tetrahedron Lett.* **1995**, *36*, 8657–8660; b) J. Akinsaya, A. W. Parkins, J. W. Steed, *Org. Process Res. Dev.* **1998**, *2*, 274–276; c) T. Ghaffar, A. W. Parkins, *J. Mol. Catal. A* **2000**, *160*, 249–261; d) A. Papakyprianou, A. W. Parkins, P. D. Prince, J. W. Steed, *Org. Prep. Proced. Int.* **2002**, *34*, 436–440; e) X.-B. Jiang, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Org. Chem.* **2004**, *69*, 2327–2331; f) M. North, A. W. Parkins, A. N. Shariff, *Tetrahedron Lett.* **2004**, *45*, 7625–7627; g) T. J. Greshock, R. L. Funk, *Org. Lett.* **2006**, *8*, 2643–2645; h) X. Jiang, N. Williams, J. K. De Brabander, *Org. Lett.* **2007**, *9*, 227–230; i) T. Kan, Y. Kawamoto, T. Asakawa, T. Furuta, T. Fukuyama, *Org. Lett.* **2008**, *10*, 169–171; j) R. A. Jones, M. J. Krische, *Org. Lett.* **2009**, *11*, 1849–1851; k) L. E. Brown, Y. R. Landaverry, J. R. Davies, K. A. Milinkevich, S. Ast, J. S. Carlson, A. G. Oliver, J. P. Konopelski, *J. Org. Chem.* **2009**, *74*, 5405–5410; l) C.-K. Mai, M. F. Sammons, T. Sammakia, *Angew. Chem.* **2010**, *122*, 2447–2450; *Angew. Chem. Int. Ed.* **2010**, *49*, 2397–2400.

[9] A. Goto, K. Endo, S. Saito, *Angew. Chem.* **2008**, *120*, 3663–3665; *Angew. Chem. Int. Ed.* **2008**, *47*, 3607–3609.

[10] P. Daw, A. Sinha, S. M. W. Rahaman, S. Dinda, J. K. Bera, *Organometallics* **2012**, *31*, 3790–3797.

[11] a) W. K. Fung, X. Huang, M. L. Man, S. M. Ng, M. Y. Hung, Z. Lin, C. P. Lau, *J. Am. Chem. Soc.* **2003**, *125*, 11539–11544; b) T. Oshiki, H. Yamashita, K. Sawada, M. Utsunomiya, K. Takahashi, K. Takai, *Organometallics* **2005**, *24*, 6287–6290; c) C. W. Leung, W. Zheng, D. Wang, S. M. Ng, C. H. Yeung, Z. Zhou, Z. Lin, C. P. Lau, *Organometallics* **2007**, *26*, 1924–1933; d) T. Šmejkal, B. Breit, *Organometallics* **2007**, *26*, 2461–2464; e) V. Cadierno, J. Francos, J. Gimeno, *Chem. Eur. J.* **2008**, *14*, 6601–6605; f) R. García-Álvarez, J. Díez, P. Crochet, V. Cadierno, *Organometallics* **2010**, *29*, 3955–3965; g) V. Cadierno, J. Díez, J. Francos, J. Gimeno, *Chem. Eur. J.* **2010**, *16*, 9808–9817; h) T. Oshiki, I. Hyodo, A. Ishizuka, *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 41–51; i) R. García-Álvarez, P. Crochet, V. Cadierno, *Tetrahedron Lett.* **2011**, *52*, 4218–4220; j) R. García-Álvarez, J. Díez, P. Crochet, V. Cadierno, *Organometallics* **2011**, *30*, 5442–5451; k) M. Murahaka, I. Hyodo, W. Okumura, T. Oshiki, *Catal. Today* **2011**, *164*, 552–555; l) W.-C. Lee, B. J. Frost, *Green Chem.* **2012**, *14*, 62–66; m) S. M. M. Knapp, T. J. Sherbow, J. J. Juliette, D. R. Tyler, *Organometallics* **2012**, *31*, 2941–2944.

[12] For leading accounts and reviews on bifunctional catalysts, see: a) D. B. Grotjahn, *Chem. Eur. J.* **2005**, *11*, 7146–7153; b) A. S. Borovik, *Acc. Chem. Res.* **2005**, *38*, 54–61; c) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406; d) T. Ikariya, A. J. Blacker, *Acc. Chem. Res.* **2007**, *40*, 1300–1308; e) D. B. Grotjahn, *Dalton Trans.* **2008**, 6497–6508; f) D. B. Grotjahn, *Chem. Lett.* **2010**, *39*, 908–914; g) D. B. Grotjahn, *Pure Appl. Chem.* **2010**, *82*, 635–647; h) T. Ikariya, I. D. Gridnev, *Top. Catal.* **2010**, *53*, 894–901; i) D. B. Grotjahn, *Top. Catal.* **2010**, *53*, 1009–1014.

[13] For reviews on the coordination chemistry of phosphanylpyridine ligands, see: a) G. R. Newkome, *Chem. Rev.* **1993**, *93*, 2067–2089; b) Z.-Z. Zhang, H. Cheng, *Coord. Chem. Rev.* **1996**, *147*, 1–39; c) P. Espinet, K. Soulantica, *Coord. Chem. Rev.* **1999**, *193–195*, 499–556; d) A. P. Sadimenko, *Adv. Heterocycl. Chem.* **2011**, *104*, 391–475.

[14] In addition to our work, arene-ruthenium(II) catalysts for nitrile hydration reactions have also been described in: a) S. M. Ashraf, I. Berger, A. A. Nazarov, C. G. Hartinger, M. P. Koroteev, E. E. Nifant'ev, B. K. Keppler, *Chem. Biodiversity* **2008**, *5*, 1640–1644; b) S. M. Ashraf, W. Kandioller, M.-G. Mendoza-Ferri, A. A. Nazarov, C. G. Hartinger, B. K. Keppler, *Chem. Biodiversity* **2008**, *5*, 2060–2066; c) A. Cavarzan, A. Scarso, G. Strukul, *Green Chem.* **2010**, *12*, 790–794; d) H. B. Ammar, X. Miao, C. Fischmeister, L. Toupet, P. H. Dixneuf, *Organometallics* **2010**, *29*, 4234–4238; e) S. Kamezaki, S. Akiyama, Y. Kayaki, S. Kuwata, T. Ikariya, *Tetrahedron: Asymmetry* **2010**, *21*, 1169–1172.

[15] a) I. Moldes, E. de la Encarnación, J. Ros, A. Alvarez-Larena, J. F. Piniella, *J. Organomet. Chem.* **1998**, *566*, 165–174; b) D. Drommi, C. G. Arena, F. Nicolò, G. Bruno, F. Faraone, *J. Organomet. Chem.* **1995**, *485*, 115–121; c) P. Govindaswamy, Y. A. Mozharivskyj, M. R. Kollipara, *Polyhedron* **2004**, *23*, 3115–3123; d) R. Lalrempuia, P. J. Carroll, M. R. Kollipara, *J. Chem. Sci.* **2004**, *116*, 21–27.

[16] To the best of our knowledge only a dinuclear Cu^{I} complex, namely $[Cu_2I_2\{PPh_2(py\text{-}4\text{-}NMe_2)\}_3]$, has previously been isolated in the context of a patented work directed towards the design of copper complexes for optoelectronic applications: U. Monkowius, T. Scher, T. Hofbeck, T. Baumann, T. Grab, *PCT Int. Appl.* WO2010/149748, **2010**.

[17] P. E. Garrou, *Chem. Rev.* **1981**, *81*, 229–266.

[18] The crystals measured contain two independent molecules in the asymmetric unit with very similar structural parameters.

For brevity, only one conformer is represented in Figure 4, and only its bond lengths and angles are presented.

[19] Complexes **5a–d** and **6a–c** are poorly soluble in water. However, reasons of solubility cannot be evoked to explain the modest activities of these complexes because reactions performed in the presence of the surfactants sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTABr) did not lead to an improvement in the benzamide yields.

[20] The hydrolysis of benzamide to benzoic acid was not observed in any of the catalytic reactions listed in Tables 1–3.

[21] This contrasts with the dramatic rate acceleration observed by Oshiki et al. in the hydration of nitriles catalysed by the octahedral Ru^{II} complexes *cis*-$[Ru(acac)_2(PR_3)_2]$ when moving from PPh_3 to PPh_2py; see ref.[11b]

[22] For general reviews on hemilabile coordination complexes, see: a) C. S. Slone, D. A. Weinberger, C. A. Mirkin, *Prog. Inorg. Chem.* **1999**, *48*, 233–250; b) S. E. Angell, C. W. Rogers, Y. Zhang, M. O. Wolf, W. E. Jones Jr, *Coord. Chem. Rev.* **2006**, *250*, 1829–1841; c) M. Bassetti, *Eur. J. Inorg. Chem.* **2006**, 4473–4482.

[23] a) Complexes **7–8b** were recovered unchanged when the reactions were performed at room temp. in different solvents (THF, CH_2Cl_2 or MeOH). In refluxing methanol, after prolonged reaction periods, partial decomposition was observed by release of the *p*-cymene ligand; b) variable-temperature $^{31}P\{^1H\}$ NMR experiments in CD_3CN were also performed with complexes **7–8b**. No chelate ring opening was observed over the 293–353 K temperature range.

[24] Disappointing results have recently been reported from a study of the alkyne hydration processes with bifunctional $CpRu^{II}$ catalysts containing imidazole-based P,N ligands due to their high tendency to block the metal by chelation: P. C. Kunz, I. Thiel, A. L. Noffke, G. J. Reib, F. Mohr, B. Spingler, *J. Organomet. Chem.* **2012**, *697*, 33–40.

[25] a) T. Kribber, A. Labonne, L. Hintermann, *Synthesis* **2007**, 2809–2818; b) A. Labonne, L. Zani, L. Hintermann, C. Bolm, *J. Org. Chem.* **2007**, *72*, 5704–5708; c) L. Hintermann, L. Xiao, A. Labonne, *Angew. Chem.* **2008**, *120*, 8370–8374; *Angew. Chem. Int. Ed.* **2008**, *47*, 8246–8250; d) L. Hintermann, T. T. Dang, A. Labonne, T. Kribber, L. Xiao, P. Naumov, *Chem. Eur. J.* **2009**, *15*, 7167–7179; e) F. Boeck, T. Kribber, L. Xiao, L. Hintermann, *J. Am. Chem. Soc.* **2011**, *133*, 8138–8141.

[26] Attempts to generate related complexes starting from dimers $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})\}_2]$ [arene = mesitylene (**4c**), hexamethylbenzene (**4d**)] failed. The starting materials were recovered untouched, even after 24 h of heating at reflux in THF. The steric repulsion between the *tert*-amyl group of the phosphane and the methyl substituents in the η^6-coordinated arenes may be behind this lack of reactivity.

[27] In fact, despite its commented utility in catalysis, the coordination chemistry of this phosphane remains unexplored because only the cyclopentadienyl-ruthenium(II) complex $[RuCp(N{\equiv}CMe)\{\kappa^1\text{-}(P)\text{-}PPh_2(py\text{-}6\text{-}tert\text{-}amyl)\}_2][PF_6]$ has previously been isolated. See the Supporting Information of ref.[25e]

[28] For reviews on the coordination chemistry of this dimer and catalytic applications of its derivatives, see: a) V. Cadierno, P. Crochet, S. E. García-Garrido, J. Gimeno, *Curr. Org. Chem.* **2006**, *10*, 165–183; b) C. Bruneau, M. Achard, *Coord. Chem. Rev.* **2012**, *256*, 525–536.

[29] See, for example: a) V. Cadierno, P. Crochet, J. Díez, J. García-Álvarez, S. E. García-Garrido, J. Gimeno, S. García-Granda, M. A. Rodríguez, *Inorg. Chem.* **2003**, *42*, 3293–3307; b) V. Cadierno, P. Crochet, J. Díez, J. García-Álvarez, S. E. García-Garrido, S. García-Granda, J. Gimeno, M. A. Rodríguez, *Dalton Trans.* **2003**, 3240–3249; c) C. Xu, S. A. Pullarkat, L. Y. Goh, *Aust. J. Chem.* **2009**, *62*, 1537–1543; d) R. K. Gupta, A. K. Singh, M. Yadav, P. Kumar, S. K. Singh, P. Li, Q. Xu, D. S. Pandey, *J. Organomet. Chem.* **2010**, *695*, 1924–1931; e) J. Díez, J. Gimeno, I. Merino, E. Rubio, F. J. Suárez, *Inorg. Chem.* **2011**, *50*, 4868–4881; f) L. Bellarosa, J. Díez, J. Gimeno, A. Lledós, F. J. Suárez, G. Ujaque, C. Vicent, *Chem. Eur. J.* **2012**, *18*, 7749–7765.

[30] In the case of **12**, a Ru^{IV}/Ru^{II} reduction takes place, the excess of the phosphane ligand **1** probably acting as the reducing agent. We note that such a redox chemistry is well documented for $[\{RuCl(\mu\text{-}Cl)(\eta^3{:}\eta^3\text{-}C_{10}H_{16})\}_2]$ (**11**) and its derivatives (see ref.[28]). For selected examples, see: a) V. Cadierno, S. E. García-Garrido, J. Gimeno, *J. Am. Chem. Soc.* **2006**, *128*, 15094–15095; b) S. Y. Ng, G. K. Tan, L. L. Koh, W. K. Leong, L. Y. Goh, *Organometallics* **2007**, *26*, 3352–3361; c) V. Cadierno, J. Francos, J. Gimeno, *Chem. Commun.* **2010**, *46*, 4175–4177; d) V. Cadierno, J. Francos, S. E. García-Garrido, J. Gimeno, *Green Chem. Lett. Rev.* **2011**, *4*, 55–61.

[31] a) The preparation of complex **17** by the reaction of $[RuCl_2(cod)]_n$ with 3 equiv. of PPh_2py in refluxing methanol has been described in: D. Drommi, F. Nicolò, C. G. Arena, G. Bruno, F. Faraone, R. Gobetto, *Inorg. Chim. Acta* **1994**, *221*, 109–116; b) the X-ray crystal structure of this compound has also been determined: K. Wajda-Hermanowicz, Z. Ciunik, A. Kochel, *Inorg. Chem.* **2006**, *45*, 3369–3377.

[32] Simulation of this spectrum by using the gNMR v.4.1 software (Adept Scientific plc) led to $^2J_{P,P}$ coupling constants of 250 (*trans*) and 30 Hz (*cis*).

[33] a) High conversions (90–99%) were also attained in the hydration of 4-fluorobenzonitrile, 4-chlorobenzonitrile and 4-methylbenzonitrile with complex **16** (5 mol-%) after heating for 24 h at 100 °C; b) for comparative purposes, the hydration of benzonitrile (0.33 M solutions) by complex **16** (5 mol-%) was also studied in *i*PrOH/H_2O (2:1, v/v) and 1,2-dichloroethane/H_2O (2:1, v/v). In these organic media the conversions to benzamide were remarkably lower than that reached in pure water (23–35% after 24 h at 100 °C).

[34] D. Cuperly, P. Gros, Y. Fort, *J. Org. Chem.* **2002**, *67*, 238–241.

[35] a) M. A. Bennett, A. K. Smith, *J. Chem. Soc., Dalton Trans.* **1974**, 233–241; b) M. A. Bennett, T.-N. Huang, T. W. Matheson, A. K. Smith, *Inorg. Synth.* **1982**, *21*, 74–78; c) J. W. Hull, W. L. Gladfelter, *Organometallics* **1984**, *3*, 605–613.

[36] a) H. Werner, H. Kletzin, *J. Organomet. Chem.* **1982**, *228*, 289–300; b) D. L. Davies, J. Fawcett, R. Krafczyk, D. R. Russell, K. Singh, *J. Chem. Soc., Dalton Trans.* **1998**, 2349–2352.

[37] a) L. Porri, M. C. Gallazzi, A. Colombo, G. Allegra, *Tetrahedron Lett.* **1965**, *47*, 4187–4189; b) A. Salzer, A. Bauer, S. Geyser, F. Podewils, G. C. Turpin, R. D. Ernst, *Inorg. Synth.* **2004**, *34*, 59–65.

[38] R. A. Head, J. F. Nixon, J. R. Swain, C. M. Woodard, *J. Organomet. Chem.* **1974**, *76*, 393–400.

[39] *CrysAlis*^{Pro} *CCD*, CrysAlis^{Pro} RED, Oxford Diffraction Ltd., Abingdon, **2008**.

[40] L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, *32*, 837–838.

[41] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435–436.

[42] P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, S. García-Granda, R. O. Gould, J. M. M. Smits, C. Smykalla, *The DIRDIF Program System*, Technical Report of the Crystallographic Laboratory, University of Nijmegen, The Netherlands, **1999**.

[43] G. M. Sheldrick, *SHELXL97: Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, **1997**.

[44] *Tables for X-ray Crystallography*, Kynoch Press, Birmingham, **1974**, vol. IV (present distributor: Kluwer Academic Publishers, Dordrecht, The Netherlands).

[45] M. Nardelli, *Comput. Chem.* **1983**, *7*, 95–97.

[46] A. L. Spek, *PLATON: A Multipurpose Crystallographic Tool*, University of Utrecht, The Netherlands, **2007**.

Received: May 30, 2012
Published Online: August 3, 2012

ORGANOMETALLICS
Article

Organometallics **2010,** *29,* 3955–3965 3955
DOI: 10.1021/om1006227

Arene−Ruthenium(II) Complexes Containing Amino−Phosphine Ligands as Catalysts for Nitrile Hydration Reactions

Rocío García-Álvarez, Josefina Díez, Pascale Crochet,* and Victorio Cadierno*

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles" (Unidad Asociada al CSIC), Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain

Received June 29, 2010

Three different series of novel mononuclear arene-ruthenium(II) complexes containing amino-phosphine ligands, namely, $[RuCl_2\{\kappa^1(P)\text{-}2\text{-}Ph_2PC_6H_4CH_2NHR\}(\eta^6\text{-arene})]$, $[RuCl_2\{\kappa^1(P)\text{-}3\text{-}Ph_2PC_6H_4CH_2NHR\}(\eta^6\text{-arene})]$, and $[RuCl_2\{\kappa^1(P)\text{-}4\text{-}Ph_2PC_6H_4CH_2NHR\}(\eta^6\text{-arene})]$ (arene = C_6H_6, *p*-cymene, 1,3,5-$C_6H_3Me_3$, C_6Me_6; R = ^{i}Pr, ^{t}Bu; all combinations), have been synthesized and fully characterized. These readily accessible species are efficient catalysts for the selective hydration of organonitriles into amides under challenging reaction conditions, i.e., pure aqueous medium in the absence of any cocatalyst, being much more active than their corresponding nonfunctionalized triphenylphosphine counterparts $[RuCl_2(PPh_3)(\eta^6\text{-arene})]$. The results obtained in this study indicate that the (amino-phosphine)ruthenium(II) complexes operate through a "bifunctional catalysis" mechanism in which the ruthenium center acts as a Lewis acid, activating the nitrile molecule, and the P-donor ligand acts as a Brønsted base, the pendant amino group generating the real nucleophile of the hydration process, i.e., the OH^- group.

Introduction

Hydration of nitriles is one of the most appealing routes presently available for the large-scale production of amides, which are versatile synthetic intermediates used in the manufacture of several pharmacological products, polymers, detergents, lubricants, and drug stabilizers.[1] As an example, hydration of acrylonitrile produces annually more than 2×10^5 tons of acrylamide, representing the main industrial route for this chemical.[2,3] Traditionally, these hydration processes have been catalyzed by strong acids and bases under harsh conditions, methods that are not compatible with many sensitive functional groups.[4] In addition, the base-catalyzed reactions usually cause overhydrolysis of the amides into the corresponding carboxylic acids, a kinetically favored reaction compared to the hydration one (see Scheme 1).[1,4] Although under acidic conditions it is possible to stop the process at the amide stage, in these cases it is necessary to control carefully the temperature and stoichiometry employed in order to avoid the formation of polymeric side products.[5] It is also important to note that, from an industrial perspective, the final neutralization step required in either the acid- or base-catalyzed reactions leads to extensive salt formation with inconvenient product contamination and pollution effects.

To circumvent all these limitations, several protocols using enzymes,[2,6] heterogeneous catalysts,[7] and transition-metal complexes[8] have been developed. In particular, a large variety of homogeneous catalysts highly selective toward amide formation have been described,[9] with Murahashi's ruthenium dihydride $[RuH_2(PPh_3)_4]$,[10] Parkins's platinum hydride $[PtH(PMe_2OH)\{(PMe_2O)_2H\}]$,[11] the acetylacetonate complex *cis*-$[Ru(acac)_2(PPh_2py)_2]$,[12] and the Rh(I)-based system $[\{Rh(\mu\text{-OMe})(cod)\}_2]/PCy_3$ (cod = 1,5-cyclooctadiene),[9h] showing remarkable activities under mild conditions. In

*To whom correspondence should be addressed. E-mail: crochetpascale@uniovi.es (P.C.); vcm@uniovi.es (V.C.).

(1) See, for example: (a) *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970. (b) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Greenberg, A.; Breneman, C. M.; Liebman, J. F., Eds.; Wiley: New York, 2000. (c) *Polyesters and Polyamides*; Deopura, B. L.; Gupta, B.; Joshi, M.; Alagirusami, R., Eds.; CRC Press: Boca Raton, 2008. (d) Johansson, I. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley: New York, 2004; Vol. *2*, pp 442−463.

(2) Yamada, H.; Kobayashi, M. *Biosci., Biotechnol., Biochem.* **1996**, *60*, 1391.

(3) Hydration of 3-cyanopyridine and adiponitrile into nicotinamide and 5-cyanovaleramide, respectively, are other relevant examples of the industrial applications of this process. See: van Pelt, S.; van Rantwijk, F.; Sheldon, R. A. In *Focus in Catalysis Applications* (supplement to Chim. Oggi **2008**, 26); pp 2−4.

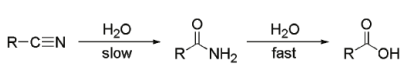
(4) See, for example: (a) Bailey, P. D.; Mills, T. J.; Pettecrew, R.; Price, R. A. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. *5*, pp 201−294. (b) *Methoden Org. Chem. (Houben Weyl)*; Dopp, D.; Dopp, H., Eds.; Thieme Verlag: Stuttgart, 1985; Vol. *E5* (2), pp 1024−1031.

(5) See, for example: (a) Edward, J. T.; Meacock, S. C. R. *J. Chem. Soc.* **1957**, 2000. (b) Steynberg, P. J.; Denga, Z.; Steyn, R.; Bezuidenhout, B. C.; Stark, N. L. Int. Pat. Appl. WO 0026178, 2000.

(6) For selected reviews covering the use of enzymes in catalytic nitrile hydrations, see: (a) Kobayashi, M.; Shimizu, S. *Curr. Opin. Chem. Biol.* **2000**, *4*, 95. (b) Endo, I.; Nojori, M.; Tsujimura, M.; Nakasako, M.; Nagashima, S.; Yohda, M.; Odaka, M. *J. Inorg. Biochem.* **2001**, *83*, 247. (c) Mylerová, V.; Martínková, L. *Curr. Org. Chem.* **2003**, *7*, 1279. (d) Kovacs, J. A. *Chem. Rev.* **2004**, *104*, 825. (e) De Santis, G.; Di Cosimo, R. In *Biocatalysis for the Pharmaceutical Industry: Discovery, Development and Manufacturing*; Tao, J.; Lin, G.-Q.; Liese, A., Eds.; Wiley-VCH: Weinheim, 2009; pp 153−181.

Published on Web 08/03/2010

Scheme 1. Nitrile Hydration and Amide Hydrolysis Reactions



addition to these examples, all operating in organic media, some metal complexes able to promote selective nitrile hydrations directly in water have also been disclosed, mainly thanks to the use of hydrosoluble ligands or surfactants.[13]

From a mechanistic point of view, although different reaction pathways have been proposed for these metal-catalyzed transformations, coordination of the nitrile to the metal is a common prerequisite for all of them.[8−13] In this way, the C≡N unit becomes more electrophilic and susceptible to nucleophilic attack by water (or the hydroxyl group if basic conditions are used), thus improving the kinetics of the hydration process versus the hydrolysis (see Scheme 1). Recent work has also suggested that this nucleophilic addition step can be facilitated by the presence of functionalized ligands able to activate the water molecule via hydrogen bonding (see Figure 1).[9m,12,13a,g,i] Such a cooperative effect of the ligand represents a new example of the so-called "bifunctional catalysis"; that is, the metal ion acts as a Lewis acid and the ligand as a Lewis base, a concept largely exploited in homogeneous catalysis during the last years.[14]

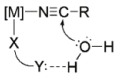


Figure 1. Cooperative effect of the ligand.

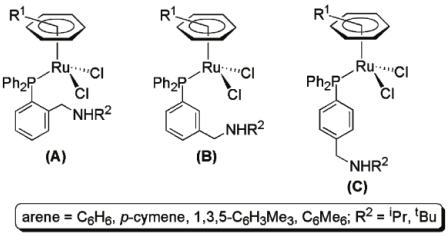


Figure 2. Structure of the (η^6-arene)-Ru(II) complexes synthesized in this work.

With this mechanistic idea in mind, and continuing with our interest in this key catalytic transformation,[13g,i] we wondered about the potential of (η^6-arene)-Ru(II) complexes **A**−**C**, containing readily accessible amino-phosphine ligands (Figure 2), as catalysts for the selective hydration of nitrile to amides.[15] We reasoned that, while the presence of a pendant amino group on these P-donor ligands would ensure the activation of the water molecule via hydrogen bonding, the exact location of the amino substituent on the aromatic ring should drastically affect the efficiency of these catalysts, conditioning the effective approach of the activated hydrogen-bonded water molecule to the coordinated nitrile. In this way, very useful information on the real operativity of a bifunctional catalysis mechanism could be easily gained experimentally. Results from this study are presented herein.

Results and Discussion

Synthesis of the Amino-phosphine Ligands. Amino-phosphine ligands **7**−**9a**,**b** have been synthesized following classical

(7) See, for example: (a) Rao, C. G. *Synth. Commun.* **1982**, *12*, 177. (b) Liu, K.-T.; Shih, M.-H.; Huang, H.-W.; Hu, C.-J. *Synthesis* **1988**, 715. (c) Breuilles, P.; Leclerc, R.; Uguen, D. *Tetrahedron Lett.* **1994**, *35*, 1401. (d) Wilgus, C. P.; Downing, S.; Molitor, E.; Bains, S.; Pagni, R. M.; Kabalka, G. W. *Tetrahedron Lett.* **1995**, *36*, 3469. (e) Sebti, S.; Rhihil, A.; Saber, A.; Hanafi, N. *Tetrahedron Lett.* **1996**, *37*, 6555. (f) Mori, K.; Yamaguchi, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2001**, 461. (g) Solhy, A.; Smahi, A.; El Badaoui, H.; Elaabar, B.; Amoukal, A.; Tikad, A.; Sebti, S.; Macquarrie, D. J. *Tetrahedron Lett.* **2003**, *44*, 4031. (h) Yamaguchi, K.; Matsushita, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1576. (i) Bazi, F.; El Badaoui, H.; Tamani, S.; Sokori, S.; Solhy, A.; Macquarrie, D. J.; Sebti, S. *Appl. Catal. A: Gen.* **2006**, *301*, 211. (j) Polshettiwar, V.; Varma, R. S. *Chem.—Eur. J.* **2009**, *15*, 1582. (k) Mitsudome, T.; Mikami, Y.; Mori, H.; Arita, S.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.* **2009**, 3258. (l) Ishizuka, A.; Nakazaki, Y.; Oshiki, T. *Chem. Lett.* **2009**, *38*, 360.

(8) For reviews covering the field of metal-mediated and metal-catalyzed nitrile hydration, see: (a) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *358*, 1. (b) Bokach, N. A.; Kukushkin, V. Y. *Russ. Chem. Rev.* **2005**, *74*, 153. (c) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771.

(9) For recent examples, see: (a) Oshiki, T.; Hyodo, I.; Ishizuka, A. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 41. (b) Crisóstomo, C.; Crestani, M. G.; García, J. J. *Inorg. Chim. Acta* **2010**, *363*, 1092. (c) Ramón, R. S.; Marion, N.; Nolan, S. P. *Chem.—Eur. J.* **2009**, *15*, 8695. (d) Crestani, M. G.; García, J. J. *J. Mol. Catal. A: Chem.* **2009**, *299*, 26. (e) Mola, J.; Pujol, D.; Rodríguez, M.; Romero, I.; Sala, X.; Katz, N.; Parella, T.; Benet-Buchholz, J.; Fontrodona, X.; Llobet, A. *Aust. J. Chem.* **2009**, *62*, 1675. (f) Crestani, M. G.; Steffen, A.; Kenwright, A. M.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Organometallics* **2009**, *28*, 2904. (g) Martín, M.; Horváth, H.; Sola, E.; Kathó, A.; Joó, F. *Organometallics* **2009**, *28*, 561. (h) Goto, A.; Endo, K.; Saito, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3607. (i) Leung, C. W.; Zheng, W.; Zhou, Z.; Lin, Z.; Lau, C. P. *Organometallics* **2008**, *27*, 4957. (j) Yi, C. S.; Zeczycki, T. N.; Lindeman, S. V. *Organometallics* **2008**, *27*, 2030. (k) Thallaj, N. K.; Przybilla, J.; Welter, R.; Mandon, D. *J. Am. Chem. Soc.* **2008**, *130*, 2414. (l) Crisóstomo, C.; Crestani, M. G.; García, J. J. *J. Mol. Catal. A: Chem.* **2007**, *266*, 139. (m) Šmejkal, T.; Breit, B. *Organometallics* **2007**, *26*, 2461. (n) Crestani, M. G.; Arévalo, A.; García, J. J. *Adv. Synth. Catal.* **2006**, *348*, 732.

(10) (a) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521. (b) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* **1993**, *49*, 8805. (c) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225.

(11) (a) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657. (b) Akisanya, J.; Parkins, A. W.; Steed, J. W. *Org. Process Res. Dev.* **1998**, *2*, 274. (c) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A: Chem.* **2000**, *160*, 249. (d) Jiang, X.-B.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Org. Chem.* **2004**, *69*, 2327.

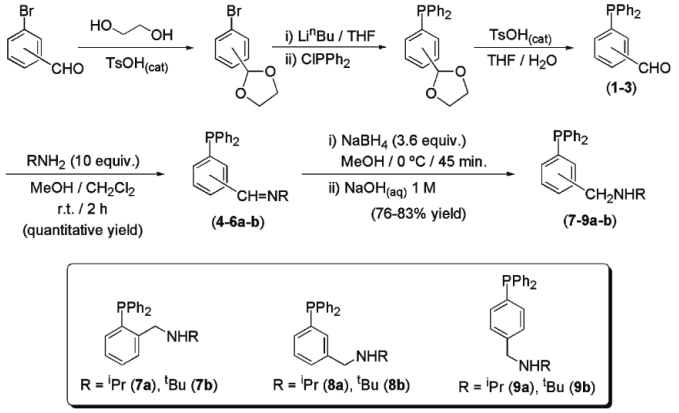
(12) Oshiki, T.; Yamashita, H.; Sawada, K.; Utsunomiya, M.; Takahashi, K.; Takai, K. *Organometallics* **2005**, *24*, 6287.

(13) See, for example: (a) Chin, C. S.; Kim, S. Y.; Joo, K.-S.; Won, G.; Chong, D. *Bull. Korean Chem. Soc.* **1999**, *20*, 535. (b) Djoman, M. C. K.-B.; Ajjou, A. N. *Tetrahedron Lett.* **2000**, *41*, 4845. (c) Kopylovich, M. N.; Kakushkin, V. Y.; Haukka, M.; Fraústo da Silva, J. J. R.; Pombeiro, A. J. L. *Inorg. Chem.* **2002**, *41*, 4798. (d) Breno, K. L.; Pluth, M. D.; Tyler, D. R. *Organometallics* **2003**, *22*, 1203. (e) Breno, K. L.; Pluth, M. D.; Landorf, C. W.; Tyler, D. R. *Organometallics* **2004**, *23*, 1738. (f) Ahmed, T. J.; Zakharov, L. N.; Tyler, D. R. *Organometallics* **2007**, *26*, 5179. (g) Cadierno, V.; Francos, J.; Gimeno, J. *Chem.—Eur. J.* **2008**, *14*, 6601. (h) Cavarzan, A.; Scarso, A.; Struckul, G. *Green Chem.* **2010**, *12*, 790. (i) Cadierno, V.; Díez, J.; Francos, J.; Gimeno, J. *Chem.−Eur. J.* **2010**, in press (DOI: 10.1002/chem.201001152).

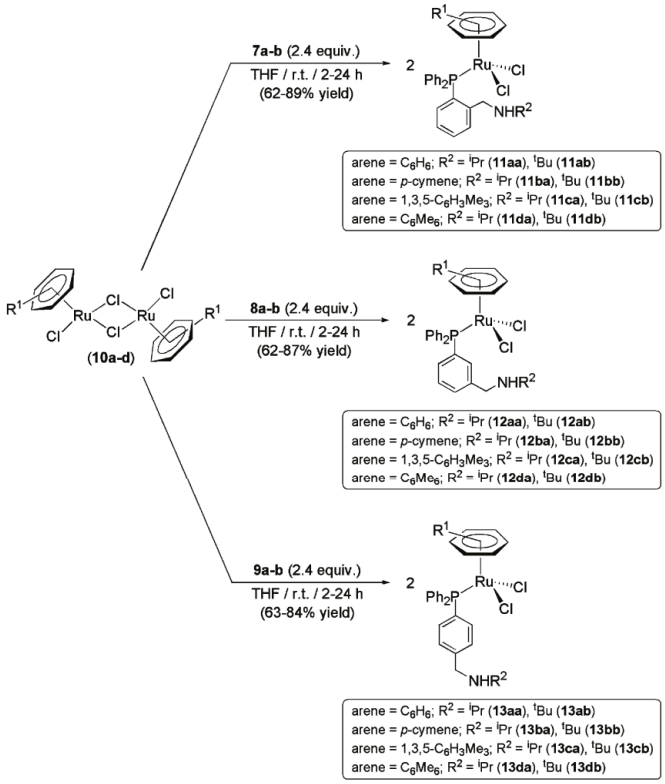
(14) The transfer hydrogenation processes through an outer-sphere mechanism, described by Noyori and co-workers, and the selective hydration of alkynes to aldehydes (*anti*-Markovnikov addition), developed by Grotjahn's group, are probably the most illustrative and successful examples of this concept. See, for example: (a) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (c) Grotjahn, D. B. *Chem.—Eur. J.* **2005**, *11*, 7146. (d) Borovik, A. S. *Acc. Chem. Res.* **2005**, *38*, 54. (e) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393. (f) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300. (g) Grotjahn, D. B. *Dalton Trans.* **2008**, 6497. (h) Grotjahn, D. B. *Pure Appl. Chem.* **2010**, *82*, 635.

(15) The effectiveness of arene-ruthenium(II) complexes in nitrile hydration reactions has been largely demonstrated. See refs 13g, 13h, and: (a) Ashraf, S. M.; Kandioller, W.; Mendoza-Ferri, M.-G.; Nazarov, A. A.; Hartinger, C. G.; Keppler, B. K. *Chem. Biodiversity* **2008**, *5*, 2060. (b) Ashraf, S. M.; Berger, I.; Nazarov, A. A.; Hartinger, C. G.; Koroteev, M. P.; Nifant'ev, E. E.; Keppler, B. K. *Chem. Biodiversity* **2008**, *5*, 1640.

Scheme 2. General Procedure for the Preparation of Amino-phosphine Ligands 7−9a,b



Scheme 3. Synthesis of the Mononuclear (η^6-Arene)ruthenium(II) Complexes 11aa−13db



methodologies (see Scheme 2),[16] based on the condensation of known (formylphenyl)diphenylphosphines **1**−**3**[17] with isopropylamine or *tert*-butylamine. In this way, the corresponding phosphine-substituted Schiff bases **4**−**6a**,**b** were quantitatively formed and subjected to reduction of the C=N bond by means

(16) (a) Ghilardi, C. A.; Midollini, S.; Moneti, S.; Orlandini, A.; Scapacci, G. *J. Chem. Soc., Dalton Trans.* **1992**, 3371. (b) Nikitidis, A.; Andersson, C. *Phosphorus, Sulfur Silicon* **1993**, *78*, 141. (c) Antonaroli, S.; Crociani, B. *J. Organomet. Chem.* **1998**, *560*, 137. (d) Crochet, P.; Gimeno, J.; García-Granda, S.; Borge, J. *Organometallics* **2001**, *20*, 4369. (e) Crochet, P.; Gimeno, J.; Borge, J.; García-Granda, S. *New J. Chem.* **2003**, *27*, 414.

(17) (a) Schiemenz, G. P.; Kaack, H. *Justus Liebigs Ann. Chem.* **1973**, *9*, 1480. (b) Schiemenz, G. P.; Kaack, H. *Justus Liebigs Ann. Chem.* **1973**, *9*, 1494. (c) Hoots, J. E.; Rauchfuss, T. B.; Wrobleski, D. A. *Inorg. Synth.* **1982**, *21*, 175. (d) Sun, Y.; Ahmed, M.; Jackstell, R.; Beller, M.; Thiel, W. R. *Organometallics* **2004**, *23*, 5260.

of $NaBH_4$/MeOH, thus affording the desired amino-phosphines **7**−**9a**,**b** as air-stable, pale yellow oils in 62−89% yield. Characterization of the novel compounds 3-$Ph_2PC_6H_4CH{=}NR$ (**5a**,**b**), 4-$Ph_2PC_6H_4CH{=}NR$ (**6a**,**b**), 3-$Ph_2PC_6H_4CH_2NHR$ (**8a**,**b**), and 4-$Ph_2PC_6H_4CH_2NHR$ (**9a**,**b**) was straightforward following their analytical and spectroscopic data (details are given in the Experimental Section). Significant features are (i) ($^{31}P\{^1H\}$ NMR) the presence of a singlet signal at ca. −5 ppm, (ii) (^1H NMR) the appearance of singlet or broad resonances at ca. 8 (**5**−**6a**,**b**) and 4 ppm (**8**−**9a**,**b**), respectively, attributed to the iminic CH=N and methylenic CH_2N protons, and (iii) ($^{13}C\{^1H\}$ NMR) the presence of characteristic singlet signals at *ca.* 155 (**5**−**6a**,**b**) and 51 (**8**−**9a**,**b**) ppm for the iminic and methylenic carbons, respectively.

Synthesis of the Arene-ruthenium(II) Complexes. The ability of dimers [{RuCl(μ-Cl)(η^6-arene)}$_2$] to form mononuclear ruthenium(II) species of general composition [$RuCl_2$(η^6-arene)L] (L = $2e^-$ donor ligand) via cleavage of the chloride bridges is well known.[18] In accord, we have found that the reaction of [{RuCl(μ-Cl)(η^6-arene)}$_2$] (arene = C_6H_6 (**10a**),[19] *p*-cymene (**10b**),[20] 1,3,5-$C_6H_3Me_3$ (**10c**),[21] C_6Me_6 (**10d**)[20]) with 2.4 equiv of the amino-phosphine ligands **7**−**9a**,**b**, in tetrahydrofuran at room temperature, leads to the selective formation of the novel mononuclear Ru(II) derivatives **11aa**−**13db** (see Scheme 3).

Complexes **11aa**−**13db**, isolated as air-stable orange solids in 62−89% yield, are soluble in polar solvents, such as dichloromethane, chloroform, THF, alcohols, and even water (ca. 1 mg/mL), and insoluble in *n*-alkanes and diethyl ether. The formulation proposed for these species is based on analytical data, as well as IR and multinuclear NMR ($^{31}P\{^1H\}$, ^1H, and $^{13}C\{^1H\}$) spectroscopy (details are given in the Experimental Section). In particular, the $^{31}P\{^1H\}$ NMR spectra of all these derivatives exhibit a singlet resonance (δ 23.7−33.4 ppm) strongly deshielded with respect to that of the corresponding free amino-phosphine ($\Delta\delta$ = 29−39 ppm), thus supporting the selective P-coordination of the ligands to ruthenium. Their ^1H and $^{13}C\{^1H\}$ NMR spectra are also consistent with the proposed structures, showing the expected resonances for the corresponding amino-phosphine and η^6-coordinated arene groups. At this point, we must note that, although the N−H proton of the amino-phosphine ligands was not detected in any case by ^1H NMR spectroscopy, the presence of this group was confirmed by the appearance of a characteristic ν(N−H) absorption band at 3174−3317 cm^{-1} in the IR spectra.

Moreover, the structure of the *p*-cymene complexes [$RuCl_2\{\kappa^1(P)$-2-$Ph_2PC_6H_4CH_2NH^tBu\}(\eta^6$-*p*-cymene)] (**11bb**), [$RuCl_2\{\kappa^1(P)$-3-$Ph_2PC_6H_4CH_2NH^tBu\}(\eta^6$-*p*-cymene)] (**12bb**), and [$RuCl_2\{\kappa^1(P)$-4-$Ph_2PC_6H_4CH_2NH^tBu\}(\eta^6$-*p*-cymene)] (**13bb**) could be unequivocally confirmed by means of X-ray diffraction methods. Single crystals suitable for X-ray analysis were obtained by slow diffusion of *n*-pentane into saturated solutions of these compounds in dichloromethane. ORTEP views of the molecules, along with selected structural parameters, are shown in Figures 3−5. The unexpected protonation of the amino group of **11bb** by traces of HCl present in dichloromethane occurred during crystallization, and consequently the structure of the corresponding ammonium salt [$RuCl_2\{\kappa^1(P)$-2-$Ph_2PC_6H_4CH_2NH_2^tBu\}(\eta^6$-*p*-cymene)]-[Cl] (**11bb·HCl**) was obtained (Figure 3). The three molecules exhibit an usual pseudooctahedral three-legged piano-stool geometry around the metal with values of the interligand angles Cl(1)−Ru−P(1), Cl(2)−Ru−P(1), and Cl(1)−Ru−Cl(2), and those between the centroid of the *p*-cymene ring C* and the legs, typical of a pseudo-octahedron. The observed N(1)−C(29) and N(1)−C(30) bond distances (1.446(5)−1.530(3) Å) fall also within the expected range for a nitrogen−carbon (sp^3) single bond.[22]

Complexes **11aa**−**13db** were further studied by means of cyclic voltammetry (CV). Two independent electrochemical processes were in all cases observed (representative cyclic voltammograms are shown in Figure 6). The first oxidation wave observed in the voltammograms, which corresponds to the oxidation of the amino group,[23] is irreversible and disappears after successive scans, while the second one is reversible, or quasi-reversible, and corresponds to the Ru^{2+}/Ru^{3+}

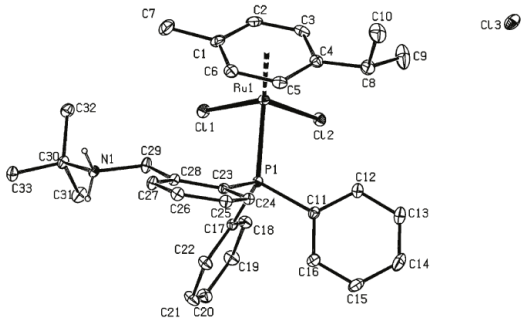


Figure 3. ORTEP-type view of the structure of complex **11bb**·HCl showing the crystallographic labeling scheme. Hydrogen atoms, except those on N(1), have been omitted for clarity. Thermal ellipsoids are drawn at the 10% probability level. Selected bond distances (Å) and angles (deg): Ru−C* = 1.7179(2); Ru−Cl(1) = 2.4025(8); Ru−Cl(2) = 2.4061(7); Ru−P(1) = 2.3743(7); C(29)−N(1) = 1.489(4); N(1)−C(30) = 1.530(3); C*−Ru−Cl(1) = 124.09(2); C*−Ru−Cl(2) = 126.21(2); C*−Ru−P(1) = 128.579(18); Cl(1)−Ru−Cl(2) = 85.42(3); Cl(1)−Ru−P(1) = 89.61(2); Cl(2)−Ru−P(1) = 90.11(2); C(11)−P(1)−C(17) = 97.88(12); C(11)−P(1)−C(23) = 103.38(12); C(11)−P(1)−Ru(1) = 116.74(10); C(17)−P(1)−C(23) = 105.49(12); C(17)−P(1)−Ru(1) = 120.82(9); C(23)−P(1)−Ru(1) = 110.46(8); C(28)−C(29)−N(1) = 113.5(2); C(29)−N(1)−C(30) = 117.1(3). C* denotes the centroid of the *p*-cymene ring (C(1), C(2), C(3), C(4), C(5), and C(6)).

(18) For reviews on the chemistry of [{RuCl(μ-Cl)(η^6-arene)}$_2$] dimers see: (a) Le Bozec, H.; Touchard, D.; Dixneuf, P. H. *Adv. Organomet. Chem.* **1989**, *29*, 163. (b) Bennett, M. A. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. *7*, pp 549−602. (c) Bennett, M. A. *Coord. Chem. Rev.* **1997**, *166*, 225. (d) Pigge, F. C.; Coniglio, J. J. *Curr. Org. Chem.* **2001**, *5*, 757. (e) Kündig, E. P. *Top. Organomet. Chem.* **2004**, *7*, 3. (f) Gimeno, J.; Cadierno, V.; Crochet, P. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H.; Mingos, D. M. P., Eds.; Elsevier: Oxford, 2007; Vol. *6*, pp 465−550. (g) Therrien, B. *Coord. Chem. Rev.* **2009**, *253*, 493.

(19) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233.

(20) Bennett, M. A.; Huang, T.-N.; Matheson, T. W.; Smith, A. K. *Inorg. Synth.* **1982**, *21*, 74.

(21) Hull, J. W.; Gladfelter, W. L. *Organometallics* **1984**, *3*, 605.

(22) See for example: (a) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1. (b) Allen, F. H.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. In *International Tables for X-Ray Crystallography*; Prince, E., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2004; Vol. *C*, p 790.

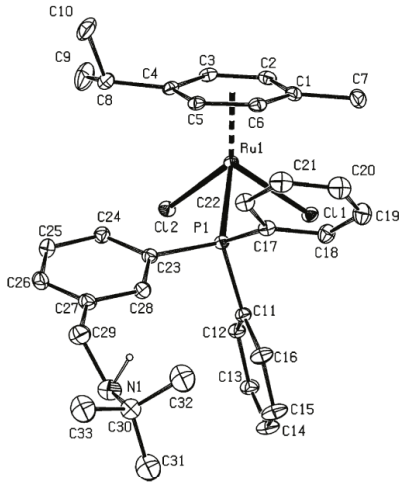


Figure 4. ORTEP-type view of the structure of complex **12bb** showing the crystallographic labeling scheme. Hydrogen atoms, except that on N(1), have been omitted for clarity. Thermal ellipsoids are drawn at the 10% probability level. Selected bond distances (Å) and angles (deg): Ru−C* = 1.7114(2); Ru−Cl(1) = 2.4090(7); Ru−Cl(2) = 2.4232(7); Ru−P(1) = 2.3743(7); C(29)−N(1) = 1.448(7); N(1)−C(30) = 1.500(7); C*−Ru−Cl(1) = 124.72(2); C*−Ru−Cl(2) = 126.31(2); C*−Ru−P(1) = 127.945(19); Cl(1)−Ru−Cl(2) = 88.63(3); Cl(1)−Ru−P(1) = 86.39(2); Cl(2)−Ru−P(1) = 90.27(3); C(11)−P(1)−C(17) = 104.18(15); C(11)−P(1)−C(23) = 101.64(14); C(11)−P(1)−Ru(1) = 120.08(10); C(17)−P(1)−C(23) = 104.55(15); C(17)−P(1)−Ru(1) = 107.76(11); C(23)−P(1)−Ru(1) = 116.97(10); C(27)−C(29)−N(1) = 114.3(4); C(29)−N(1)−C(30) = 116.2(5). C* denotes the centroid of the *p*-cymene ring (C(1), C(2), C(3), C(4), C(5), and C(6)).

redox system. Formal potentials ($E^{\circ\prime}$) of the latter, given versus the $[Cp_2Fe]/[Cp_2Fe]^+$ redox couple,[24] are collected in Table 1. In complete accord with the increasing electron-releasing properties of the arene ring, within the three series of complexes studied, $E^{\circ\prime}$ values decrease in the sequence C_6H_6 > *p*-cymene ≈ 1,3,5-$C_6H_3Me_3$ > C_6Me_6. Similar trends have been previously reported for related (η^6-arene)ruthenium(II)

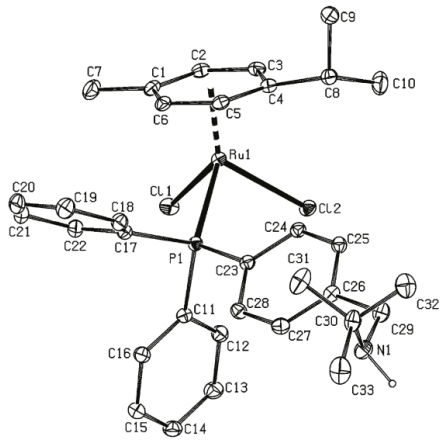


Figure 5. ORTEP-type view of the structure of complex **13bb** showing the crystallographic labeling scheme. Hydrogen atoms, except that on N(1), have been omitted for clarity. Thermal ellipsoids are drawn at the 10% probability level. Selected bond distances (Å) and angles (deg): Ru−C* = 1.7235(2); Ru−Cl(1) = 2.4061(7); Ru−Cl(2) = 2.4236(7); Ru−P(1) = 2.3606(7); C(29)−N(1) = 1.446(5); N(1)−C(30) = 1.479(5); C*−Ru−Cl(1) = 124.87(2); C*−Ru−Cl(2) = 127.65(2); C*−Ru−P(1) = 128.800(18); Cl(1)−Ru−Cl(2) = 87.67(3); Cl(1)−Ru−P(1) = 85.89(3); Cl(2)−Ru−P(1) = 88.36(2); C(11)−P(1)−C(17) = 101.87(13); C(11)−P(1)−C(23) = 101.41(13); C(11)−P(1)−Ru(1) = 121.86(9); C(17)−P(1)−C(23) = 105.92(13); C(17)−P(1)−Ru(1) = 108.53(10); C(23)−P(1)−Ru(1) = 115.48(9); C(26)−C(29)−N(1) = 115.0(3); C(29)−N(1)−C(30) = 117.8(3). C* denotes the centroid of the *p*-cymene ring (C(1), C(2), C(3), C(4), C(5), and C(6)).

complexes.[25] These observations are also consistent with theoretical studies that indicate that the HOMO energy level decreases when substituting Me by H in an arene−metal complex.[26] It is also worthy of note that the exact location of the CH_2NHR substituent on the aromatic ring of the P-donor ligands exerts some influence on the formal potentials of these complexes, those derived from the *para*-substituted phosphines being, in general, more easily oxidized than their *meta*- and *ortho*-substituted counterparts (in the order $E^{\circ\prime}_{para} < E^{\circ\prime}_{meta} < E^{\circ\prime}_{ortho}$).

Catalytic Hydration of Nitriles in Aqueous Medium. The catalytic potential of the novel (η^6-arene)ruthenium(II) complexes **11aa**−**13bd** was then evaluated using the hydration of benzonitrile into benzamide as model reaction. In a typical experiment, the ruthenium precursor (5 mol % of Ru) was added to a 0.33 M aqueous solution of benzonitrile and the mixture heated in an oil bath at 100 °C. The course of the reaction was monitored by regular sampling and analysis by gas chromatography (GC). The results obtained are summarized in Table 2.

All complexes synthesized proved to be active catalysts in this transformation, providing benzamide as the unique reaction product (benzoic acid was not detected by GC in the crude reaction mixtures) in 43−99% GC yield after 24 h of heating (entries 1−24). Among them, complexes $[RuCl_2\{\kappa^1(P)\text{-}2\text{-}Ph_2PC_6H_4CH_2NH^tBu\}(\eta^6\text{-}C_6Me_6)]$ (**11db**), $[RuCl_2\{\kappa^1(P)\text{-}3\text{-}Ph_2PC_6H_4CH_2NH^tBu\}(\eta^6\text{-}1,3,5\text{-}C_6H_3Me_3)]$ (**12cb**), and $[RuCl_2\{\kappa^1(P)\text{-}4\text{-}Ph_2PC_6H_4CH_2NH^iPr\}(\eta^6\text{-}p\text{-cymene})]$

(23) Related irreversible oxidations were observed when cyclic voltammograms of *N*-isopropylbenzylamine (E_{pa} = 1.72 V) and *N*-benzyl-*tert*-butylamine (E_{pa} = 1.81 V) were run under identical experimental conditions.

(24) (a) Gritzner, G.; Kuta, J. *Pure Appl. Chem.* **1984**, *56*, 461. (b) Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877.

(25) See, for example: (a) Devanne, D.; Dixneuf, P. H. *J. Organomet. Chem.* **1990**, *390*, 371. (b) Le Bozec, H.; Ouzzine, K.; Dixneuf, P. H. *Organometallics* **1991**, *10*, 2768. (c) Dussel, R.; Pilette, D.; Dixneuf, P. H.; Fehlhammer, W. P. *Organometallics* **1991**, *10*, 3287. (d) Kücükbay, H.; Cetinkaya, B.; Guesmi, S.; Dixneuf, P. H. *Organometallics* **1996**, *15*, 2434. (e) Mai, J.-F.; Yamamoto, Y. *J. Organomet. Chem.* **1998**, *560*, 223. (f) Yamamoto, Y.; Nakamura, H.; Mai, J.-F. *J. Organomet. Chem.* **2001**, *640*, 10. (g) Bhalla, R.; Boxwell, C. J.; Duckett, S. B.; Dyson, P. J.; Humphrey, D. G.; Steed, J. W.; Suman, P. *Organometallics* **2002**, *21*, 924. (h) Valerga, P.; Puerta, M. C.; Pandey, D. S. *J. Organomet. Chem.* **2002**, *648*, 27. (i) Cadierno, V.; Crochet, P.; García-Álvarez, J.; García-Garrido, S. E.; Gimeno, J. *J. Organomet. Chem.* **2002**, *663*, 32. (j) Lastra-Barreira, B.; Díez, J.; Crochet, P. *Green Chem.* **2009**, *11*, 1681.

(26) (a) Singewald, E. T.; Slone, C. S.; Stern, C. L.; Mirkin, C. A.; Yap, G. P. A.; Liable-Sands, L. M.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 3048. (b) Bowyer, W. J.; Merket, J. W.; Geiger, W. E.; Rheingold, A. L. *Organometallics* **1989**, *8*, 191.

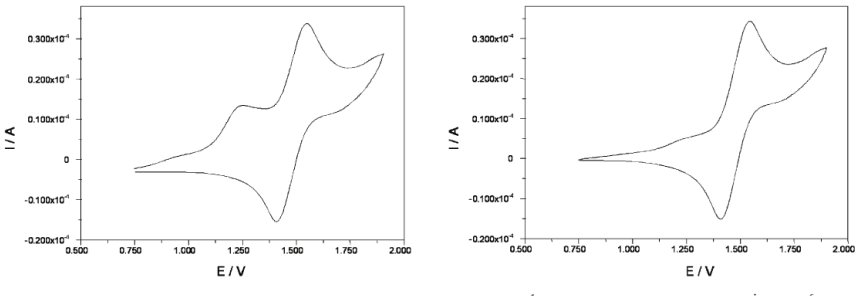


Figure 6. Cyclic voltammograms obtained for $[RuCl_2\{\kappa^1(P)\text{-}2\text{-}Ph_2PC_6H_4CH_2NH^iPr\}(\eta^6\text{-}C_6H_6)]$ (**11aa**) after one (left) and three successive scans (right). Measured at 0.1 V s^{-1} in dichloromethane with a 0.03 M solution of $[^nBu_4N][PF_6]$ as the supporting electrolyte.

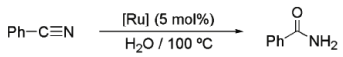
Table 1. Electrochemical Data for Complexes 11aa−13db[a]

complex	$E^{o\prime}$ (V)[b]	i_{pa}/i_{pc}	ΔE_p (mV)	complex	$E^{o\prime}$ (V)[b]	i_{pa}/i_{pc}	ΔE_p (mV)
11aa	1.27	0.8	125	**12ca**	1.07	1.0	95
11ab	1.30	0.8	161	**12cb**	0.94	1.0	165
11ba	1.12	0.8	202	**12da**	0.82	0.8	162
11bb	1.07	0.8	168	**12db**	0.78	0.8	161
11ca	1.18	0.8	156	**13aa**	1.06	1.0	150
11cb	1.09	0.9	147	**13ab**	0.99	1.0	164
11da	0.97	0.9	146	**13ba**	0.95	1.1	162
11db	0.91	0.8	144	**13bb**	0.91	1.0	144
12aa	1.14	1.0	137	**13ca**	0.95	1.0	162
12ab	1.10	1.0	156	**13cb**	0.96	1.2	171
12ba	0.99	1.0	162	**13da**	0.78	1.0	155
12bb	0.95	1.0	168	**13db**	0.80	1.1	232

[a] Measured at 0.1 V s^{-1} in dichloromethane with a 0.03 M solution of $[^nBu_4N][PF_6]$ as the supporting electrolyte. [b] Formal potentials ($E^{o\prime}$) are referenced relative to the potential of the $[Cp_2Fe]/[Cp_2Fe]^+$ couple (E^o = 0.21 V) run under identical conditions ($E^{o\prime} = E^o(Ru^{III}/Ru^{II}) - E^o(Fe^{III}/Fe^{II})$).

(**13ba**) showed the best performances, generating benzamide in >90% yield after only 7 h (entries 8, 14, and 19, respectively). Although those complexes derived from the *ortho*-substituted phosphines $2\text{-}Ph_2PC_6H_4CH_2NHR$ (entries 1−8) are in general less active than their *meta*- (entries 9−16) and *para*-substituted counterparts (entries 17−24),[27] no direct relationships between the structure or electronic nature of these species and their catalytic activity become really evident from the data obtained. Solubility grounds do not explain the reactivities observed since homogeneity of the aqueous phase was in all cases observed.[28a,b]

Table 2. Ruthenium-Catalyzed Hydration of Benzonitrile in Water[a]



entry	catalyst	yield (%)[b]	entry	catalyst	yield (%)[b]
1	**11aa**	65 (96)	19	**13ba**	93 (97)
2	**11ab**	23 (75)	20	**13bb**	83 (95)
3	**11ba**	34 (65)	21	**13ca**	83 (95)
4	**11bb**	34 (77)	22	**13cb**	84 (93)
5	**11ca**	13 (43)	23	**13da**	62 (88)
6	**11cb**	47 (81)	24	**13db**	56 (84)
7	**11da**	61 (85)	25	**14a**	21 (45)
8	**11db**	92 (99)	26	**14b**	11 (45)
9	**12aa**	85 (96)	27	**14c**	10 (21)
10	**12ab**	61 (79)	28	**14d**	24 (48)
11	**12ba**	89 (97)	29	**14a**[c]	61 (85)
12	**12bb**	77 (95)	30	**14a**[d]	35 (55)
13	**12ca**	88 (96)	31	**14b**[c]	28 (62)
14	**12cb**	94 (97)	32	**14b**[d]	52 (77)
15	**12da**	46 (75)	33	**14c**[c]	45 (80)
16	**12db**	76 (98)	34	**14c**[d]	44 (86)
17	**13aa**	72 (87)	35	**14d**[c]	52 (95)
18	**13ab**	44 (70)	36	**14d**[d]	46 (89)

[a] Reactions performed under N_2 atmosphere at 100 °C using 1 mmol of benzonitrile (0.33 M in water). Substrate/Ru ratio: 100/5. [b] Yield after 7 h of heating (yield after 24 h in parentheses). In both cases, yields are reported as uncorrected GC areas. [c] Reactions performed in the presence of 5 mol % of $PhCH_2NH^iPr$. [d] Reactions performed in the presence of 5 mol % of $PhCH_2NH^tBu$.

Interestingly, when the related triphenylphosphine-Ru(II) complexes $[RuCl_2(PPh_3)(\eta^6\text{-arene})]$ (arene = C_6H_6 (**14a**),[19] *p*-cymene (**14b**),[19] $1,3,5\text{-}C_6H_3Me_3$ (**14c**),[29] C_6Me_6 (**14d**)[30]) were used as catalysts under identical reaction conditions, benzamide was formed in remarkably lower yields (21−48% after 24 h; entries 25−28).[28c] This fact clearly evidences that a cooperative effect of the amino-phosphine ligands is taking place. However, since the position of the amino susbtituent in the aromatic ring (*ortho*, *meta*, or *para*) does not exert a marked influence on the catalytic activity, such a cooperative effect of the amino-functionalized ligands **7**−**9a**,**b** seems to be unrelated to the effective approach of the nucleophilic water molecule to the coordinated nitrile, via hydrogen bonding. On the other hand, we have also observed that the effectiveness of $[RuCl_2(PPh_3)(\eta^6\text{-arene})]$ (**14a**−**d**) is greatly improved

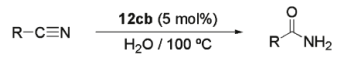
(27) Formation of a stable six-membered chelate ring by intramolecular coordination of the pendant amino group to ruthenium could be responsible for this behavior. In the case of complex $[RuCl_2\{\kappa^1(P)\text{-}2\text{-}Ph_2PC_6H_4CH_2NH^tBu\}(\eta^6\text{-}C_6Me_6)]$ (**11db**), one of the most active catalysts found in this study, such a chelation process is sterically disfavored by the presence of the bulky η^6-coordinated hexamethylbenzene and the *tert*-butyl substituent on the amino-phosphine ligand.

(28) (a) A two-phase system (water/organic products) is observed, the reaction taking place probably at the interface. (b) We note that the addition of surfactants does not improve the catalytic activity of these complexes. On the contrary, it significantly decreases. For example, in the presence of sodium dodecyl sulfate and cetyltrimethylammonium bromide (0.05 M solutions), complex $[RuCl_2\{\kappa^1(P)\text{-}3\text{-}Ph_2PC_6H_4CH_2NH^tBu\}(\eta^6\text{-}1,3,5\text{-}C_6H_3Me_3)]$ (**12cb**) (5 mol %) generates benzamide in only 58% and 60% GC yield, respectively, after 24 h of heating at 100 °C (to be compared with entry 14 in Table 2). (c) Complexes $[RuCl_2(PPh_3)(\eta^6\text{-arene})]$ (**14a**−**d**) are completely insoluble in water at room temperature, but they become partially soluble at 100 °C. Therefore, unlike the case of amino-phosphine derivatives **11aa**−**13db**, the aqueous phase during the catalytic reactions using $[RuCl_2(PPh_3)(\eta^6\text{-arene})]$ (**14a**−**d**) is not completely homogenous, and consequently, solubility issues cannot be completely discarded to explain the different reactivities observed.

(29) Davies, D. L.; Fawcett, J.; Krafczyk, R.; Russell, D. R.; Singh, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2349.

(30) Werner, H.; Kletzin, H. *J. Organomet. Chem.* **1982**, *228*, 289.

Table 3. Catalytic Hydration of Nitriles in Water Using Complex 12cb[a]



entry	substrate	yield after 7 h (%)[b]	yield after 24 h (%)[b]
1	R = Ph	94	97 (84)
2	R = 2-C_6H_4F	48	90 (79)
3	R = 3-C_6H_4Cl	77	99 (87)
4	R = 4-C_6H_4Cl	64	94 (80)
5	R = 3-C_6H_4Br	87	99 (88)
6	R = 3-$C_6H_4NO_2$	89	99 (90)
7	R = 4-$C_6H_4CO_2Et$	50	83 (70)
8	R = 3-C_6H_4OMe	71	98 (86)
9	R = C_6F_5	92	99 (90)
10	R = 3-pyridyl	98	99 (88)
11	R = CH_2-4-C_6H_4Cl	90	99 (91)
12	R = CH_2-2-Thienyl	96	99 (87)
13	R = $(CH_2)_2OPh$	81	89 (74)
14	R = *n*-C_5H_{11}	41	55 (40)
15	R = (*E*)-CH=CHPh	53	80 (72)

[a] Reactions performed under N_2 atmosphere at 100 °C using 1 mmol of the corresponding nitrile (0.33 M in water). Substrate/Ru ratio: 100/5. [b] Yields are reported as uncorrected GC areas (isolated yields are given in parentheses).

when the catalytic reactions are performed in the presence of 5 mol % of *N*-isopropylbenzylamine or *N*-benzyl-*tert*-butylamine (entries 29−36), i.e., in basic media. Consequently, we can conclude that the beneficial effect of the coordinated aminophosphines **7**−**9a**,**b** is more likely related with the activation of water by deprotonation, thus generating in the reaction media the more nucleophilic hydroxyl group.[31]

Using the most active complex [$RuCl_2\{\kappa^1(P)$-3-$Ph_2PC_6H_4CH_2NH^tBu\}(\eta^6$-1,3,5-$C_6H_3Me_3$)] (**12cb**), the generality of this catalytic transformation was also evaluated (see Table 3). Thus, as observed for benzonitrile (entry 1), other aromatic (entries 2−9) and heteroaromatic (entry 10) substrates could be selectively converted into the corresponding amides (83−99% GC yields) after 24 h of heating, regardless of the position and electronic nature of the substituents present in the aromatic ring. Common functional groups (halide, nitro, ester, ether) were tolerated, and no overhydrolysis to carboxylic acids was observed, thus demonstrating the wide scope and synthetic utility of this procedure. Subsequent purification by column chromatography on silica gel provided analytically pure samples of the corresponding amides in 70−88% isolated yields. As shown in entries 11−15, this aqueous process is not restricted to aromatic organonitriles, the hydration of substrates containing alkyl- and alkenyl-CN bonds being also conveniently achieved under the standard reaction conditions. However, we must note that in the case of the aliphatic derivative hexanenitrile (entry 14) only a modest yield of hexanamide could be reached (55% by CG).

Conclusions

In summary, in this work three series of novel arene-ruthenium(II) complexes containing amino-phosphine ligands, namely, [$RuCl_2\{\kappa^1(P)$-2-$Ph_2PC_6H_4CH_2NHR\}(\eta^6$-arene)] (**11aa**−**11db**), [$RuCl_2\{\kappa^1(P)$-3-$Ph_2PC_6H_4CH_2NHR\}(\eta^6$-arene)] (**12aa**−**12db**), and [$RuCl_2\{\kappa^1(P)$-4-$Ph_2PC_6H_4CH_2NHR\}(\eta^6$-arene)] (**13aa**−**13db**), have been synthesized. These readily accessible species are efficient catalysts for the selective conversion of organonitriles into amides under challenging reaction conditions, i.e., pure aqueous medium in the absence of any cocatalyst, being much more active than their corresponding nonfunctionalized triphenylphosphine counterparts [$RuCl_2(PPh_3)(\eta^6$-arene)]. Experimental results seem to indicate that complexes **11aa**−**13db** operate through a "bifunctional catalysis" mechanism in which the ruthenium center acts as a Lewis acid, activating the nitrile molecule, and the amino-phoshine ligand acts as a Brønsted base, the pendant amino group generating the real nucleophilic species of the process, i.e., the OH^- group.

(31) pH measurements on 0.016 M aqueous solutions of complexes **11aa**−**13db** (the same concentration used in the catalytic experiments) confirm this hypothesis. The values obtained, ranging from 7.12 to 7.37, indicate that when dissolved in water **11aa**−**13db** are able to generate a slightly basic media.

Experimental Section

Synthetic procedures were performed under an atmosphere of dry nitrogen using vacuum-line and standard Schlenk techniques. Solvents were dried by standard methods and distilled under nitrogen before use. All reagents were obtained from commercial suppliers and used without further purification with the exception of compounds 2-$Ph_2PC_6H_4CHO$ (**1**),[17a,c] 3-$Ph_2PC_6H_4CHO$ (**2**),[17d] 4-$Ph_2PC_6H_4CHO$ (**3**),[17b] 2-$Ph_2PC_6H_4CH$=N^{i}Pr (**4a**),[16a,c] 2-$Ph_2PC_6H_4CH$=N^{t}Bu (**4b**),[16a,c] 2-$Ph_2PC_6H_4$-CH_2NH^iPr (**7a**),[16d] 2-$Ph_2PC_6H_4CH_2NH^tBu$ (**7b**),[16b,e] [{RuCl(μ-Cl)(η^6-arene)}$_2$] (arene = C_6H_6 (**10a**),[19] *p*-cymene (**10b**),[20] 1,3,5-$C_6H_3Me_3$ (**10c**),[21] C_6Me_6 (**10d**)[20]), and [$RuCl_2(PPh_3)(\eta^6$-arene)] (arene = C_6H_6 (**14a**),[19] *p*-cymene (**14b**),[19] 1,3,5-$C_6H_3Me_3$ (**14c**),[29] C_6Me_6 (**14d**)[30]), which were prepared by following the methods reported in the literature. Infrared spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. The C, H, and N analyses were carried out with a Perkin-Elmer 2400 microanalyzer. NMR spectra were recorded on a Bruker DPX300 instrument at 300 MHz (^{1}H), 121.5 MHz (^{31}P), or 75.4 MHz (^{13}C) using $SiMe_4$ or 85% H_3PO_4 as standard. DEPT experiments have been carried out for all the compounds reported in this paper.

Synthesis of Imino-phosphines 3-$Ph_2PC_6H_4CH$=NR (R = ^{i}Pr (5a), ^{t}Bu (5b)) and 4-$Ph_2PC_6H_4CH$=NR (R = ^{i}Pr (6a), ^{t}Bu (6b)). A solution of the corresponding diphenylphosphinobenzaldehyde (**2**, **3**; 0.50 g, 1.72 mmol) in 20 mL of a MeOH/CH_2Cl_2 mixture (1:1 v/v) was treated, at room temperature, with the appropriate primary amine (17 mmol) for 2 h. Volatiles were then removed under vacuum, yielding phosphino-imines **5**−**6a**, **b** as colorless oils in quantitative yield. **5a:** Anal. Calcd for $C_{22}H_{22}NP$: C, 79.74; H, 6.69; N, 4.23. Found: C, 79.65; H, 6.84; N, 4.37. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −5.4 (s) ppm. ^{1}H NMR ($CDCl_3$): δ 1.27 (d, 6H, $^3J_{HH}$ = 6.0 Hz, CHMe_2), 3.54 (sept, 1H, $^3J_{HH}$ = 6.0 Hz, C*H*Me$_2$), 7.32−7.89 (m, 14H, CH_{arom}), 8.25 (s, 1H, CH=N) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.3 (s, CHMe_2), 61.7 (s, *C*HMe$_2$), 127.0−135.6 (m, CH_{arom} and C_{arom}), 157.9 (s, CH=N) ppm. **5b:** Anal. Calcd for $C_{23}H_{24}NP$: C, 79.97; H, 7.00; N, 4.06. Found: C, 80.15; H, 7.12; N, 4.17. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −5.9 (s) ppm. ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 9H, CMe$_3$), 7.29−7.98 (m, 14H, CH_{arom}), 8.22 (s, 1H, CH=N) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 29.4 (s, C*Me*$_3$), 57.3 (s, *C*Me$_3$), 127.7−138.0 (m, CH_{arom} and C_{arom}), 154.5 (s, CH=N) ppm. **6a:** Anal. Calcd for $C_{22}H_{22}NP$: C, 79.74; H, 6.69; N, 4.23. Found: C, 79.58; H, 6.87; N, 4.40. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −5.4 (s) ppm. ^{1}H NMR ($CDCl_3$): δ 1.37 (br, 6H, CHMe_2), 3.62 (br, 1H, C*H*Me$_2$), 7.39−7.81 (m, 14H, CH_{arom}), 8.36 (s, 1H, CH=N) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.4 (s, CHMe_2), 61.8 (s, *C*HMe$_2$), 128.1−134.1 (m, CH_{arom} and C_{arom}), 157.8 (s, CH=N) ppm. **6b:** Anal. Calcd for $C_{23}H_{24}NP$: C, 79.97; H, 7.00; N, 4.06. Found: C, 80.10; H, 7.19; N, 4.23. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −5.4 (s) ppm. ^{1}H

NMR ($CDCl_3$): δ 1.19 (s, 9H, CMe_3), 7.41−7.83 (m, 14H, CH_{arom}), 8.36 (s, 1H, CH=N) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 29.9 (s, CMe_3), 57.3 (s, CMe_3), 127.9−140.0 (m, CH_{arom} and C_{arom}), 154.7 (s, CH=N) ppm.

Synthesis of Amino-phosphines 3-$Ph_2PC_6H_4CH_2NHR$ (R = ^{i}Pr (8a), ^{t}Bu (8b)) and 4-$Ph_2PC_6H_4CH_2NHR$ (R = ^{i}Pr (9a), ^{t}Bu (9b)). A solution of the corresponding imino-phosphine (**5**−**6a**,**b**; 1.5 mmol) in 20 mL of methanol was treated by $NaBH_4$ (0.208 g, 5.5 mmol) at 0 °C for 45 min. The reaction was then quenched with aqueous NaOH (5 mL, 1 M), the organic layer was extracted with dichloromethane (3 × 15 mL), and the combined phases were dried over $MgSO_4$. Solvent removal under reduced pressure afforded amino-phosphines **8**−**9a**,**b** as pale yellow oils. **8a:** Yield: 0.400 g (80%). Anal. Calcd for $C_{22}H_{24}NP$: C, 79.25; H, 7.26; N, 4.20. Found: C, 79.33; H, 7.39; N, 4.41. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −5.4 (s) ppm. ^1H NMR ($CDCl_3$): δ 1.10 (d, 6H, $^3J_{HH}$ = 6.0 Hz, $CHMe_2$), 2.84 (m, 1H, $CHMe_2$), 3.79 (br, 2H, CH_2), 7.19−7.38 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 22.9 (s, $CHMe_2$), 48.0 (s, $CHMe_2$), 51.4 (s, CH_2), 128.5−132.3 (m, CH_{arom} and C_{arom}) ppm. **8b:** Yield: 0.395 g (76%). Anal. Calcd for $C_{23}H_{26}NP$: C, 79.51; H, 7.54; N, 4.03. Found: C, 79.67; H, 7.59; N, 4.12. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −5.3 (s) ppm. ^1H NMR ($CDCl_3$): δ 1.16 (s, 9H, CMe_3), 3.72 (br, 2H, CH_2), 7.12−7.38 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 29.6 (s, CMe_3), 47.5 (s, CH_2), 51.2 (s, CMe_3), 128.8−134.2 (m, CH_{arom} and C_{arom}) ppm. **9a:** Yield: 0.415 g (83%). Anal. Calcd for $C_{22}H_{24}NP$: C, 79.25; H, 7.26; N, 4.20. Found: C, 79.41; H, 7.15; N, 4.33. $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ −6.2 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.24 (d, 6H, $^3J_{HH}$ = 6.0 Hz, $CHMe_2$), 3.02 (m, 1H, $CHMe_2$), 3.95 (br, 2H, CH_2), 7.47−7.88 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 23.1 (s, $CHMe_2$), 48.4 (s, $CHMe_2$), 51.3 (s, CH_2), 128.4−143.0 (m, CH_{arom} and C_{arom}) ppm. **9b:** Yield: 0.412 g (79%). Anal. Calcd for $C_{23}H_{26}NP$: C, 79.51; H, 7.54; N, 4.03. Found: C, 79.59; H, 7.65; N, 4.17. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −6.1 (s) ppm. ^1H NMR ($CDCl_3$): δ 1.28 (s, 9H, CMe_3), 3.83 (br, 2H, CH_2), 7.36−7.45 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.4 (s, CMe_3), 47.1 (s, CH_2), 50.7 (s, CMe_3), 128.5−143.0 (m, CH_{arom} and C_{arom}) ppm.

Synthesis of Complexes [$RuCl_2\{\kappa^1(P)$-2-$Ph_2PC_6H_4CH_2NHR\}$-(η^6-arene)] (arene = C_6H_6, R = ^{i}Pr (11aa), ^{t}Bu (11ab); arene = *p*-cymene, R = ^{i}Pr (11ba), ^{t}Bu (11bb); arene = 1,3,5-$C_6H_3Me_3$, R = ^{i}Pr (11ca), ^{t}Bu (11cb); arene = C_6Me_6, R = ^{i}Pr (11da), ^{t}Bu (11db)). A solution of the corresponding dimer [{RuCl(μ-Cl)(η^6-arene)}$_2$] (**10a**−**d**; 0.5 mmol) in 40 mL of tetrahydrofuran was treated, at room temperature, with the appropriate amino-phosphine ligand **7a**,**b** (1 mmol) for 2 h (24 h when **10a** is used as starting material). The resulting solution was then evaporated to dryness, thus yielding a microcrystalline orange-red solid, which was washed with a 1:2 mixture of diethyl ether/hexane (3 × 10 mL) and vacuum-dried. **11aa:** Yield: 0.426 g (73%). Anal. Calcd for $RuC_{28}H_{30}Cl_2NP$: C, 57.64; H, 5.18; N, 2.40. Found: C, 57.71; H, 5.22; N, 2.53. IR (Nujol, cm^{-1}): ν 3204 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 28.9 (s) ppm. ^1H NMR (CD_2Cl_2): δ 0.88 (d, 6H, $^3J_{HH}$ = 6.0 Hz, $CHMe_2$), 2.50 (m, 1H, $CHMe_2$), 3.59 (br, 2H, CH_2), 5.47 (s, 6H, C_6H_6), 7.35−7.86 (m, 14H, CH_{arom}) ppm; NH signal not observed. **11ab:** Yield: 0.382 g (64%). Anal. Calcd for $RuC_{29}H_{32}Cl_2NP$: C, 58.29; H, 5.40; N, 2.34. Found: C, 58.20; H, 5.48; N, 2.45. IR (Nujol, cm^{-1}): ν 3211 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 28.3 (s) ppm. ^1H NMR (CD_2Cl_2): δ 0.84 (s, 9H, CMe_3), 3.44 (br, 2H, CH_2), 5.44 (s, 6H, C_6H_6), 7.38−7.94 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 27.8 (s, CMe_3), 45.9 (s, CH_2), 51.2 (s, CMe_3), 89.4 (d, $^2J_{CP}$ = 3.1 Hz, C_6H_6), 128.0−134.4 (m, CH_{arom} and C_{arom}) ppm. **11ba:** Yield: 0.441 g (69%). Anal. Calcd for $RuC_{32}H_{38}Cl_2NP$: C, 60.09; H, 5.99; N, 2.19. Found: C, 59.91; H, 6.12; N, 2.31. IR (Nujol, cm^{-1}): ν 3317 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 27.4 (s) ppm. ^1H NMR (CD_2Cl_2): δ 0.79 (br, 6H, $CHMe_2$), 1.28 (d, 6H, $^3J_{HH}$ = 6.0 Hz, $CHMe_2$), 1.82 (s, 3H, Me of cym), 2.29 (br, 1H, $CHMe_2$), 2.93 (sept, 1H, $^3J_{HH}$ = 6.0 Hz, $CHMe_2$), 3.40 (br, 2H, CH_2), 4.83 and 5.33 (d, 2H each, $^3J_{HH}$ = 6.0 Hz, CH of cym), 7.33−7.91 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 17.8 (s, Me of cym), 21.6 and 21.9 (both s, $CHMe_2$), 30.6 (s, $CHMe_2$ of cym), 49.7 (s, $CHMe_2$), 49.9 (s, CH_2), 86.9 and 88.3 (s, CH of cym), 98.2 and 111.7 (s, C of cym), 127.7−134.1 (m, CH_{arom} and C_{arom}) ppm. **11bb:** Yield: 0.463 g (71%). Anal. Calcd for $RuC_{33}H_{40}Cl_2NP$: C, 60.64; H, 6.17; N, 2.14. Found: C, 60.77; H, 6.09; N, 2.20. IR (Nujol, cm^{-1}): ν 3260 (N−H). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 26.5 (s) ppm. ^1H NMR ($CDCl_3$): δ 0.75 (s, 9H, CMe_3), 1.27 (d, 6H, $^3J_{HH}$ = 7.0 Hz, $CHMe_2$ of cym), 1.84 (s, 3H, Me of cym), 2.89 (sept, 1H, $^3J_{HH}$ = 7.0 Hz, $CHMe_2$ of cym), 3.22 (br, 2H, CH_2), 4.84 and 5.31 (d, 2H each, $^3J_{HH}$ = 4.8 Hz, CH of cym), 7.35−7.95 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 17.8 (s, Me of cym), 21.9 (s, $CHMe_2$ of cym), 28.5 (s, CMe_3), 30.5 (s, $CHMe_2$ of cym), 46.0 (s, CH_2), 50.2 (s, CMe_3), 87.3 and 87.9 (s, CH of cym), 98.0 and 110.9 (s, C of cym), 126.2−137.2 (m, CH_{arom} and C_{arom}) ppm. **11ca:** Yield: 0.400 g (64%). Anal. Calcd for $RuC_{31}H_{36}Cl_2NP$: C, 59.52; H, 5.80; N, 2.24. Found: C, 59.60; H, 5.86; N, 2.32. IR (Nujol, cm^{-1}): ν 3298 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 30.7 (s) ppm. ^1H NMR (CD_2Cl_2): δ 0.69 (d, 6H, $^3J_{HH}$ = 6.0 Hz, $CHMe_2$), 2.02 (s, 9H, $C_6H_3Me_3$), 3.24 (m, 3H, $CHMe_2$ and CH_2), 4.60 (s, 3H, $C_6H_3Me_3$), 7.39−8.30 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 18.3 (s, $C_6H_3Me_3$), 22.4 (s, $CHMe_2$), 49.0 (s, $CHMe_2$), 50.6 (s, CH_2), 84.8 (d, $^2J_{CP}$ = 4.5 Hz, CH of $C_6H_3Me_3$), 104.6 (s, C of $C_6H_3Me_3$), 126.3−145.6 (m, CH_{arom} and C_{arom}) ppm. **11cb:** Yield: 0.396 g (62%). Anal. Calcd for $RuC_{32}H_{38}Cl_2NP$: C, 60.09; H, 5.99; N, 2.19. Found: C, 60.15; H, 5.87; N, 2.22. IR (Nujol, cm^{-1}): ν 3248 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 30.7 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.19 (s, 9H, CMe_3), 2.02 (s, 9H, $C_6H_3Me_3$), 3.16 (br, 2H, CH_2), 4.61 (s, 3H, $C_6H_3Me_3$), 7.39−8.31 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 18.3 (s, $C_6H_3Me_3$), 28.5 (s, CMe_3), 46.2 (s, CH_2), 50.0 (s, CMe_3), 84.8 (d, $^2J_{CP}$ = 3.4 Hz, CH of $C_6H_3Me_3$), 104.7 (d, $^2J_{CP}$ = 3.4 Hz, C of $C_6H_3Me_3$), 125.9−147.0 (m, CH_{arom} and C_{arom}) ppm. **11da:** Yield: 0.594 g (89%). Anal. Calcd for $RuC_{34}H_{42}Cl_2NP$: C, 61.16; H, 6.34; N, 2.10. Found: C, 60.97; H, 6.36; N, 2.19. IR (Nujol, cm^{-1}): ν 3270 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 30.1 (s) ppm. ^1H NMR (CD_2Cl_2): δ 0.68 (br, 6H, $CHMe_2$), 1.75 (s, 18H, C_6Me_6), 3.01 (m, 1H, $CHMe_2$), 3.72 (br, 2H, CH_2), 7.15−7.91 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 14.7 (s, C_6Me_6), 22.6 (s, $CHMe_2$), 48.7 (s, $CHMe_2$), 50.8 (s, CH_2), 96.5 (s, C_6Me_6), 125.6−139.5 (m, CH_{arom} and C_{arom}) ppm. **11db:** Yield: 0.538 g (79%). Anal. Calcd for $RuC_{35}H_{44}Cl_2NP$: C, 61.67; H, 6.51; N, 2.05. Found: C, 61.60; H, 6.64; N, 2.15. IR (Nujol, cm^{-1}): ν 3291 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 30.1 (s) ppm. ^1H NMR (CD_2Cl_2): δ 0.67 (s, 9H, CMe_3), 1.73 (s, 18H, C_6Me_6), 3.26 (br, 2H, CH_2), 7.15−7.85 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 14.8 (s, C_6Me_6), 28.5 (s, CMe_3), 46.1 (s, CH_2), 50.0 (s, CMe_3), 96.5 (d, $^2J_{CP}$ = 3.0 Hz, C_6Me_6), 125.5−147.0 (m, CH_{arom} and C_{arom}) ppm.

Synthesis of Complexes [$RuCl_2\{\kappa^1(P)$-3-$Ph_2PC_6H_4CH_2NHR\}$-(η^6-arene)] (arene = C_6H_6, R = ^{i}Pr (12aa), ^{t}Bu (12ab); arene = *p*-cymene, R = ^{i}Pr (12ba), ^{t}Bu (12bb); arene = 1,3,5-$C_6H_3Me_3$, R = ^{i}Pr (12ca), ^{t}Bu (12cb); arene = C_6Me_6, R = ^{i}Pr (12da), ^{t}Bu (12db)). Complexes **12aa**−**12db**, isolated as orange microcrystalline solids, were prepared as described for **11aa**−**11db** starting from the appropriate [{RuCl(μ-Cl)(η^6-arene)}$_2$] dimer (**10a**−**d**; 0.5 mmol) and amino-phosphine ligand **8a**,**b** (1.2 mmol). **12aa:** Yield: 0.414 g (71%). Anal. Calcd for $RuC_{28}H_{30}Cl_2NP$: C, 57.64; H, 5.18; N, 2.40. Found: C, 57.72; H, 5.09; N, 2.51. IR (Nujol, cm^{-1}): ν 3293 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 28.0 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.05 (d, 6H, $^3J_{HH}$ = 6.0 Hz, $CHMe_2$), 2.77 (sept, 1H, $^3J_{HH}$ = 6.0 Hz, $CHMe_2$), 3.79 (br, 2H, CH_2), 5.42 (s, 6H, C_6H_6), 7.35−7.79 (m, 14H, CH_{arom}) ppm; NH signal not observed.

$^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 22.7 (s, CH*Me*$_2$), 48.1 (s, *C*HMe$_2$), 50.8 (s, CH_2), 89.3 (d, $^2J_{CP}$ = 4.0 Hz, C_6H_6), 128.0−141.1 (m, CH_{arom} and C_{arom}) ppm. **12ab:** Yield: 0.370 g (62%). Anal. Calcd for $RuC_{29}H_{32}Cl_2NP$: C, 58.29; H, 5.40; N, 2.34. Found: C, 58.35; H, 5.29; N, 2.33. IR (Nujol, cm^{-1}): ν 3280 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 28.3 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.14 (s, 9H, CMe_3), 3.75 (br, 2H, CH_2), 5.43 (s, 6H, C_6H_6), 7.35−7.87 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 29.0 (s, *C*Me$_3$), 46.6 (s, CH_2), 50.7 (s, *C*Me$_3$), 89.3 (s, C_6H_6), 128.0−142.3 (m, CH_{arom} and C_{arom}) ppm. **12ba:** Yield: 0.498 g (78%). Anal. Calcd for $RuC_{32}H_{38}Cl_2NP$: C, 60.09; H, 5.99; N, 2.19. Found: C, 60.22; H, 6.08; N, 2.01. IR (Nujol, cm^{-1}): ν 3302 (N−H). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 24.2 (s) ppm. ^1H NMR ($CDCl_3$): δ 1.06 and 1.11 (d, 6H each, $^3J_{HH}$ = 6.0 Hz, CH*Me*$_2$), 1.90 (s, 3H, Me of cym), 2.82 (m, 2H, *C*HMe$_2$), 3.78 (br, 2H, CH_2), 5.04 and 5.22 (d, 2H each, $^3J_{HH}$ = 6.0 Hz, CH of cym), 7.32−7.92 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 17.5 (s, Me of cym), 21.7 and 22.8 (s, CH*Me*$_2$), 30.3 (s, *C*HMe$_2$ of cym), 47.9 (s, *C*HMe$_2$), 51.0 (s, CH_2), 87.3 and 89.0 (s, CH of cym), 96.4 and 110.2 (s, C of cym), 127.8−142.2 (m, CH_{arom} and C_{arom}) ppm. **12bb:** Yield: 0.471 g (72%). Anal. Calcd for $RuC_{33}H_{40}Cl_2NP$: C, 60.64; H, 6.17; N, 2.14. Found: C, 60.51; H, 6.23; N, 2.20. IR (Nujol, cm^{-1}): ν 3302 (N−H). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 24.5 (s) ppm. ^1H NMR ($CDCl_3$): δ 1.12 (d, 6H, $^3J_{HH}$ = 6.0 Hz, CH*Me*$_2$ of cym), 1.17 (s, 9H, CMe_3), 1.90 (s, 3H, Me of cym), 2.87 (sept, 1H, $^3J_{HH}$ = 6.0 Hz, C*H*Me$_2$ of cym), 3.75 (br, 2H, CH_2), 5.03 and 5.23 (d, 2H each, $^3J_{HH}$ = 6.2 Hz, CH of cym), 7.31−7.94 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 17.7 (s, Me of cym), 21.8 (s, CH*Me*$_2$ of cym), 29.0 (s, *C*Me$_3$), 30.4 (s, *C*HMe$_2$ of cym), 46.8 (s, CH_2), 50.6 (s, *C*Me$_3$), 87.5 and 88.9 (s, CH of cym), 96.4 and 110.3 (s, C of cym), 127.7−142.1 (m, CH_{arom} and C_{arom}) ppm. **12ca:** Yield: 0.406 g (65%). Anal. Calcd for $RuC_{31}H_{36}Cl_2NP$: C, 59.52; H, 5.80; N, 2.24. Found: C, 59.44; H, 5.92; N, 2.30. IR (Nujol, cm^{-1}): ν 3306 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 33.1 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.09 (d, 6H, $^3J_{HH}$ = 6.8 Hz, CH*Me*$_2$), 2.03 (s, 9H, C_6H_3*Me*$_3$), 2.82 (m, 1H, C*H*Me$_2$), 3.82 (br, 2H, CH_2), 4.71 (s, 3H, C_6*H*$_3$Me$_3$), 7.40−7.86 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 18.2 (s, C_6H_3*Me*$_3$), 22.6 (s, CH*Me*$_2$), 48.1 (s, *C*HMe$_2$), 50.8 (s, CH_2), 85.4 (d, $^2J_{CP}$ = 4.5 Hz, CH of $C_6H_3Me_3$), 104.5 (d, $^2J_{CP}$ = 2.3 Hz, C of $C_6H_3Me_3$), 127.6−141.0 (m, CH_{arom} and C_{arom}) ppm. **12cb:** Yield: 0.409 g (64%). Anal. Calcd for $RuC_{32}H_{38}Cl_2NP$: C, 60.09; H, 5.99; N, 2.19. Found: C, 59.92; H, 6.06; N, 2.25. IR (Nujol, cm^{-1}): ν 3312 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 33.4 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.19 (s, 9H, CMe_3), 2.02 (s, 9H, C_6H_3*Me*$_3$), 3.80 (br, 2H, CH_2), 4.72 (s, 3H, C_6*H*$_3$Me$_3$), 7.37−7.95 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 18.2 (s, C_6H_3*Me*$_3$), 28.9 (s, *C*Me$_3$), 46.7 (s, CH_2), 50.7 (s, *C*Me$_3$), 85.3 (d, $^2J_{CP}$ = 4.0 Hz, CH of $C_6H_3Me_3$), 104.6 (d, $^2J_{CP}$ = 3.0 Hz, C of $C_6H_3Me_3$), 127.6−141.8 (m, CH_{arom} and C_{arom}) ppm. **12da:** Yield: 0.580 g (87%). Anal. Calcd for $RuC_{34}H_{42}Cl_2NP$: C, 61.16; H, 6.34; N, 2.10. Found: C, 61.31; H, 6.26; N, 2.22. IR (Nujol, cm^{-1}): ν 3270 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 29.8 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.12 (d, 6H, $^3J_{HH}$ = 9.0 Hz, CH*Me*$_2$), 1.77 (s, 18H, C_6Me_6), 2.79 (m, 1H, C*H*Me$_2$), 3.79 (br, 2H, CH_2), 7.40−7.78 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_3OD): δ 12.7 (s, C_6*Me*$_6$), 19.2 (s, CH*Me*$_2$), 45.7 (s, *C*HMe$_2$), 48.3 (s, CH_2), 95.3 (s, C_6Me$_6$), 125.9−133.8 (m, CH_{arom} and C_{arom}) ppm. **12db:** Yield: 0.559 g (82%). Anal. Calcd for $RuC_{35}H_{44}Cl_2NP$: C, 61.67; H, 6.51; N, 2.05. Found: C, 61.56; H, 6.47; N, 2.13. IR (Nujol, cm^{-1}): ν 3230 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 30.3 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.15 (s, 9H, CMe_3), 1.75 (s, 18H, C_6Me_6), 3.73 (br, 2H, CH_2), 7.40−7.82 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 14.8 (s, C_6*Me*$_6$), 28.8 (s, C*Me*$_3$), 46.9 (s, CH_2), 50.6 (s, *C*Me$_3$), 96.7 (d, $^2J_{CP}$ = 3.0 Hz, C_6Me$_6$), 127.5−141.7 (m, CH_{arom} and C_{arom}) ppm.

Synthesis of Complexes [$RuCl_2\{\kappa^1(P)$-4-$Ph_2PC_6H_4CH_2NHR\}(\eta^6$-arene)] (arene = C_6H_6, R = ^{i}Pr (13aa), ^{t}Bu (13ab); arene = *p*-cymene, R = ^{i}Pr (13ba), ^{t}Bu (13bb); arene = 1,3,5-$C_6H_3Me_3$, R = ^{i}Pr (13ca), ^{t}Bu (13cb); arene = C_6Me_6, R = ^{i}Pr (13da), ^{t}Bu (13db)). Complexes **13aa**−**13db**, isolated as orange microcrystalline solids, were prepared as described for **11aa**−**11db** starting from the appropriate [{RuCl(μ-Cl)(η^6-arene)}$_2$] dimer (**10a**−**d**; 0.5 mmol) and amino-phosphine ligand **9a**,**b** (1.2 mmol). **13aa:** Yield: 0.391 g (67%). Anal. Calcd for $RuC_{28}H_{30}Cl_2NP$: C, 57.64; H, 5.18; N, 2.40. Found: C, 57.50; H, 5.31; N, 2.55. IR (Nujol, cm^{-1}): ν 3270 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 26.8 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.21 (br, 6H, CH*Me*$_2$), 2.91 (br, 1H, C*H*Me$_2$), 3.81 (br, 2H, CH_2), 5.43 (s, 6H, C_6H_6), 7.41−7.77 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 28.5 (s, CH*Me*$_2$), 46.5 (s, CH_2), 48.5 (s, *C*HMe$_2$), 89.3 (s, C_6H_6), 126.1−143.5 (m, CH_{arom} and C_{arom}) ppm. **13ab:** Yield: 0.376 g (63%). Anal. Calcd for $RuC_{29}H_{32}Cl_2NP$: C, 58.29; H, 5.40; N, 2.34. Found: C, 58.13; H, 5.51; N, 2.44. IR (Nujol, cm^{-1}): ν 3275 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 26.8 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.22 (s, 9H, CMe_3), 3.83 (br, 2H, CH_2), 5.43 (s, 6H, C_6H_6), 7.40−7.77 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 28.2 (s, C*Me*$_3$), 46.4 (s, CH_2), 52.4 (s, *C*Me$_3$), 89.3 (s, C_6H_6), 128.1−142.5 (m, CH_{arom} and C_{arom}) ppm. **13ba:** Yield: 0.454 g (71%). Anal. Calcd for $RuC_{32}H_{38}Cl_2NP$: C, 60.09; H, 5.99; N, 2.19. Found: C, 60.18; H, 5.91; N, 2.23. IR (Nujol, cm^{-1}): ν 3317 (N−H). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 23.7 (s) ppm. ^1H NMR ($CDCl_3$): δ 1.13 (d, 12H, $^3J_{HH}$ = 6.0 Hz, CH*Me*$_2$), 1.90 (s, 3H, Me of cym), 2.88 (m, 2H, C*H*Me$_2$), 3.83 (br, 2H, CH_2), 5.02 and 5.22 (d, 2H each, $^3J_{HH}$ = 6.0 Hz, CH of cym), 7.35−7.88 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 17.6 (s, Me of cym), 21.8 and 22.5 (s, CH*Me*$_2$), 30.4 (s, *C*HMe$_2$ of cym), 48.4 (s, *C*HMe$_2$), 50.7 (s, CH_2), 87.3 and 89.2 (s, CH of cym), 96.3 and 110.2 (s, C of cym), 127.6−143.0 (m, CH_{arom} and C_{arom}) ppm. **13bb:** Yield: 0.490 g (75%). Anal. Calcd for $RuC_{33}H_{40}Cl_2NP$: C, 60.64; H, 6.17; N, 2.14. Found: C, 60.80; H, 6.02; N, 2.25. IR (Nujol, cm^{-1}): ν 3317 (N−H). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 23.7 (s) ppm. ^1H NMR ($CDCl_3$): δ 1.13 (d, 6H, $^3J_{HH}$ = 6.7 Hz, CH*Me*$_2$ of cym), 1.20 (s, 9H, CMe_3), 1.89 (s, 3H, Me of cym), 2.88 (sept, 1H, $^3J_{HH}$ = 6.7 Hz, C*H*Me$_2$ of cym), 3.76 (br, 2H, CH_2), 5.01 and 5.21 (d, 2H each, $^3J_{HH}$ = 5.4 Hz, CH of cym), 7.30−7.87 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 17.5 (s, Me of cym), 21.7 (s, CH*Me*$_2$ of cym), 28.8 (s, C*Me*$_3$), 30.3 (s, *C*HMe$_2$ of cym), 46.6 (s, CH_2), 50.6 (s, *C*Me$_3$), 87.3 and 89.1 (s, CH of cym), 96.2 and 110.3 (s, C of cym), 127.6−144.0 (m, CH_{arom} and C_{arom}) ppm. **13ca:** Yield: 0.419 g (67%). Anal. Calcd for $RuC_{31}H_{36}Cl_2NP$: C, 59.52; H, 5.80; N, 2.24. Found: C, 59.61; H, 5.72; N, 2.11. IR (Nujol, cm^{-1}): ν 3301 (N−H). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 31.1 (s) ppm. ^1H NMR ($CDCl_3$): δ 1.13 (d, 6H, $^3J_{HH}$ = 6.0 Hz, CH*Me*$_2$), 2.03 (s, 9H, C_6H_3*Me*$_3$), 2.89 (sept, 1H, $^3J_{HH}$ = 6.0 Hz, C*H*Me$_2$), 3.82 (br, 2H, CH_2), 4.67 (s, 3H, C_6*H*$_3$Me$_3$), 7.36−7.79 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 18.2 (s, C_6H_3*Me*$_3$), 22.8 (s, CH*Me*$_2$), 48.5 (s, *C*HMe$_2$), 51.0 (s, CH_2), 85.5 (d, $^2J_{CP}$ = 5.0 Hz, CH of $C_6H_3Me_3$), 104.3 (s, C of $C_6H_3Me_3$), 127.3−143.9 (m, CH_{arom} and C_{arom}) ppm. **13cb:** Yield: 0.428 g (67%). Anal. Calcd for $RuC_{32}H_{38}Cl_2NP$: C, 60.09; H, 5.99; N, 2.19. Found: C, 59.89; H, 6.13; N, 2.21. IR (Nujol, cm^{-1}): ν 3294 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 32.1 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.19 (s, 9H, CMe_3), 2.02 (s, 9H, C_6H_3*Me*$_3$), 3.79 (br, 2H, CH_2), 4.68 (s, 3H, C_6*H*$_3$Me$_3$), 7.41−7.76 (m, 14H, CH_{arom}) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 18.3 (s, C_6H_3*Me*$_3$), 28.9 (s, C*Me*$_3$), 46.6 (s, CH_2), 50.6 (s, *C*Me$_3$), 85.6 (s, CH of $C_6H_3Me_3$), 104.4 (s, C of $C_6H_3Me_3$), 127.4−144.7 (m, CH_{arom} and C_{arom}) ppm. **13da:** Yield: 0.561 g (84%). Anal. Calcd for $RuC_{34}H_{42}Cl_2NP$: C, 61.16; H, 6.34; N, 2.10. Found: C, 61.29; H, 6.46; N, 2.01. IR (Nujol, cm^{-1}): ν 3290 (N−H). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 28.8 (s) ppm. ^1H NMR ($CDCl_3$): δ 1.12 (d, 6H, $^3J_{HH}$ = 6.0 Hz, CH*Me*$_2$), 1.76 (s, 18H, C_6Me_6), 2.88 (m, 1H,

Table 4. Crystal Data and Structure Refinement Details for Compounds 11bb·HCl, 12bb, and 13bb

	11bb·HCl	12bb	13bb
chemical formula	$RuC_{33}H_{41}Cl_3NP$	$RuC_{33}H_{40}Cl_2NP$	$RuC_{33}H_{40}Cl_2NP$
fw	690.06	653.60	653.60
T, K	293(2)	293(2)	293(2)
wavelength, Å	1.5418	1.5418	1.5418
cryst syst	monoclinic	triclinic	monoclinic
space group	$P2_1/n$	$P\bar{1}$	$P2_1/n$
cryst size, mm	0.101 × 0.057 × 0.028	0.086 × 0.062 × 0.025	0.125 × 0.099 × 0.031
a, Å	18.1728(2)	9.8513(3)	11.6372(1)
b, Å	10.3861(1)	10.3852(3)	19.7352(2)
c, Å	18.3489(3)	15.9639(4)	13.9921(1)
α, deg	90	89.619(2)	90
β, deg	111.663(2)	76.419(2)	106.732(1)
γ, deg	90	79.882(2)	90
Z	4	2	4
V, Å^3	3218.65(7)	1561.85(8)	3077.41(5)
ρ_{calcd}, g cm^{-3}	1.424	1.390	1.411
μ, mm^{-1}	6.868	6.278	6.372
F(000)	1424	676	1352
θ range, deg	2.92 to 73.92	2.85 to 74.01	3.99 to 73.81
index ranges	$-22 \le h \le 22$	$-12 \le h \le 12$	$-14 \le h \le 14$
	$-12 \le k \le 12$	$-12 \le k \le 12$	$-23 \le k \le 15$
	$-22 \le l \le 17$	$-18 \le l \le 19$	$-17 \le l \le 16$
completeness to θ_{max}	96.9%	99.4%	96.9%
no. of data collected	18786	18252	17444
no. of unique data	6320 (R_{int} = 0.0234)	6304 (R_{int} = 0.0254)	6042 (R_{int} = 0.0279)
no. of params/restraints	516/0	417/3	353/0
refinement method	full-matrix least-squares on F^2		
goodness of fit on F^2	1.083	1.033	1.063
weight function (a, b)	0.0535, 1.922	0.0638, 0.7391	0.0577, 1.1784
R1[a] [$I > 2\sigma(I)$]	0.0327	0.0354	0.0348
wR2[a] [$I > 2\sigma(I)$]	0.0923	0.0957	0.0880
R1 (all data)	0.0363	0.0392	0.0417
wR2 (all data)	0.0945	0.0992	0.0961
largest diff peak and hole, e Å^{-3}	1.263 and −0.779	0.787 and −0.648	0.809 and −0.379

[a] $R1 = \sum(|F_o| - |F_c|)/\sum|F_o|$; $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$.

C*H*Me$_2$), 3.81 (br, 2H, CH$_2$), 7.39−7.79 (m, 14H, CH$_{arom}$) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 14.8 (s, C$_6$*Me$_6$*), 22.1 (s, CH*Me$_2$*), 48.4 (s, CH$_2$), 50.5 (s, *C*HMe$_2$), 96.7 (d, $^2J_{CP}$ = 3.8 Hz, *C*$_6$Me$_6$), 127.4−135.2 (m, CH$_{arom}$ and C$_{arom}$) ppm. **13db:** Yield: 0.552 g (81%). Anal. Calcd for $RuC_{35}H_{44}Cl_2NP$: C, 61.67; H, 6.51; N, 2.05. Found: C, 61.78; H, 6.55; N, 1.97. IR (Nujol, cm^{-1}): ν 3174 (N−H). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 29.2 (s) ppm. ^1H NMR (CD_2Cl_2): δ 1.21 (s, 9H, CMe$_3$), 1.77 (s, 18H, C$_6$Me$_6$), 3.80 (br, 2H, CH$_2$), 7.43−7.18 (m, 14H, CH$_{arom}$) ppm; NH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 14.9 (s, C$_6$*Me$_6$*), 28.8 (s, C*Me$_3$*), 46.6 (s, CH$_2$), 50.9 (s, *C*Me$_3$), 96.7 (s, *C*$_6$Me$_6$), 127.5−144.2 (m, CH$_{arom}$ and C$_{arom}$) ppm.

Electrochemistry. CV measurements (25 °C) were carried out with a three-electrode system. The working electrode was a platinum disk electrode, the counter electrode was a platinum spiral, and the reference electrode was an aqueous saturated calomel electrode separated from the solution by a porous septum. Current and voltage parameters were controlled using a PAR system M273. In a typical experiment, 0.15 mmol of the complex was dissolved under a nitrogen atmosphere in 10 mL of freshly distilled and deoxygenated dichloromethane containing 1.15 g of pure [^{n}Bu$_4$N][PF$_6$] (0.3 mmol) as electrolyte. Formal CV potentials ($E^{o\prime}$) given in Table 1 are referenced relative to the potential of the $[Cp_2Fe]/[Cp_2Fe]^+$ couple (E^o = 0.21 V) run under identical conditions ($E^{o\prime} = E^o(Ru^{III}/Ru^{II}) - E^o(Fe^{III}/Fe^{II})$).[24]

General Procedure for the Catalytic Hydration Reactions. Under nitrogen atmosphere, the corresponding nitrile (1 mmol), water (3 mL), and the appropriate ruthenium catalyst (5 mol % of Ru) were introduced into a sealed tube, and the reaction mixture was stirred at 100 °C for the indicated time (see Tables 2 and 3). The course of the reaction was monitored by regularly taking samples of 20 μL, which after extraction with CH_2Cl_2 (3 mL) were analyzed by GC. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using diethyl ether as eluent. The identity of the resulting amides was assessed by comparison of their ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data with those reported in the literature and by their fragmentation in GC/MSD.

X-ray Crystal Structure Determination of Complexes 11bb·HCl, 12bb, and 13bb. Crystals suitable for X-ray diffraction analysis were obtained by slow diffusion of *n*-pentane into saturated solutions of the appropriate complex in dichloromethane. The most relevant crystal and refinement data are collected in Table 4. For all crystals, data collection was performed on an Oxford Diffraction Xcalibur Nova single-crystal diffractometer, using Cu Kα radiation (λ = 1.5418 Å). Images were collected at a 65 mm fixed crystal−detector distance, using the oscillation method, with 1° oscillation and variable exposure time per image (3−40 s). Data collection strategy was calculated with the program CrysAlis Pro CCD.[32] Data reduction and cell refinement were performed with the program CrysAlis Pro RED.[32] An empirical absorption correction was applied using the SCALE3 ABSPACK algorithm as implemented in the program CrysAlis Pro RED.[32] The software package WINGX[33] was used for space group determination, structure solution, and refinement. The structures of complexes **11bb·HCl** and **13bb** were solved by direct methods using SIR2004.[34] For **12bb** the structure was solved by Patterson interpretation and phase expansion using DIRDIF.[35]

(32) *CrysAlisPro CCD, CrysAlisPro RED*; Oxford Diffraction Ltd.: Abingdon, Oxfordshire, UK, 2008.

(33) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.

Isotropic least-squares refinement on F^2 using SHELXL97[36] was performed. During the final stages of the refinements, all the positional parameters and the anisotropic temperature factors of all the non-H atoms were refined. For **11bb**·HCl and **12bb** the coordinates of H atoms were found from different Fourier maps and included in a refinement with isotropic parameters (except those of the CH_3 groups of **12bb**, which were geometrically located and their coordinates refined riding on their parent atoms). For **13bb**, the H atoms were geometrically located and their coordinates were refined riding on their parent atoms (except H_{N1}, which was found from different Fourier maps and included in a refinement with isotropic parameters). The function minimized was $[\sum w(F_o^2 - F_c^2)/\sum w(F_o^2)]^{1/2}$ where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ (a and b values are given in Table 4) with $\sigma(F_o^2)$ from counting statistics and $P = (\max(F_o^2,0) + 2F_c^2)/3$. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[37] Geometrical calculations were made with PARST.[38] The crystallographic plots were made with PLATON.[39]

Acknowledgment. Financial support from the Spanish MICINN (Projects CTQ2006-08485/BQU and CSD2007-00006) and the Gobierno del Principado de Asturias (FICYT Project IB08-036) is acknowledged.

Supporting Information Available: CIF file giving crystallographic data for compounds **11bb**·HCl, **12bb**, and **13bb**. This material is available free of charge via the Internet at http://pubs.acs.org.

(34) Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **2005**, *38*, 381.
(35) Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; García-Granda, S.; Gould, R. O.; Smits, J. M. M.; Smykalla, C. *The DIRDIF Program System*; Technical Report of the Crystallographic Laboratory; University of Nijmegen: Nijmegen, The Netherlands, 1999.
(36) Sheldrick, G. M. *SHELXL97, Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.
(37) *International Tables for X-Ray Crystallography*; Kynoch Press: Birminghan, U.K., 1974; Vol. *IV* (Present distributor: Kluwer Academic Publishers; Dordrecht, The Netherlands).
(38) Nardelli, M. *Comput. Chem.* **1983**, *7*, 95.
(39) Spek, A. L. *PLATON: A Multipurpose Crystallographic Tool*; University of Utrecht: Utrecht, The Netherlands, 2007.

Tetrahedron Letters 52 (2011) 4218–4220

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ibuprofenamide: a convenient method of synthesis by catalytic hydration of 2-(4-isobutylphenyl)propionitrile in pure aqueous medium

Rocío García-Álvarez, Javier Francos, Pascale Crochet*, Victorio Cadierno*

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica 'Enrique Moles' (Unidad Asociada al CSIC), Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain

ARTICLE INFO

Article history:
Received 3 May 2011
Revised 31 May 2011
Accepted 7 June 2011
Available online 13 June 2011

Keywords:
Non-steroidal anti-inflammatory drugs
Ibuprofenamide
Nitrile hydration
Microwave irradiation
Ruthenium

ABSTRACT

An efficient and practical synthesis of the non-steroidal anti-inflammatory drug (NSAID) ibuprofenamide by catalytic hydration of 2-(4-isobutylphenyl)propionitrile is described. The readily accessible arene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ is used as the catalyst, pure water as the solvent, and microwave irradiation as the heating source.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first choice of drugs in the treatment of pain, degenerative joint diseases and rheumatic disorders. The clinical effects of NSAIDs are based on the inhibition of the enzyme cyclooxygenase (COX), which catalyzes the formation of prostaglandins (PGs).[1] Production of PGs is induced at sites of inflammation, where they are involved in the propagation of inflammation, pain, and fever. Inhibition of PGs production alleviates these pathologic effects, but it also interferes with the normal physiologic role of these molecules, that is, cytoprotection of gastric mucosa, hemostasis, renal function, gestation, and parturition.[2] Consequently, long-term therapy with NSAIDs is frequently limited by their adverse effects, particularly those caused by gastrointestinal bleeding, ulceration and perforation.[3]

Ibuprofen, chemically 2-(4-isobutylphenyl)propionic acid (**1**), is a well-known NSAID widely prescribed for the treatment of musculoskeletal disorders, inflammation, fever, primary dysmenorrhea and also in the management of mild pain.[1–3] Similar to other prototypical NSAIDs (aspirin, indomethacin, etc.), ibuprofen suffers from the limitation of gastrointestinal toxicity caused by the presence of a carboxylic acid moiety in its structure.[3]

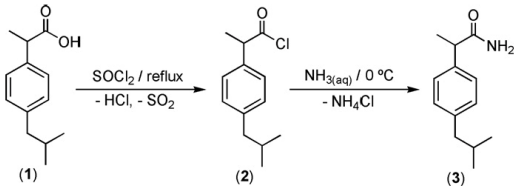
A common strategy in pharmaceutical research is the use of well-established drugs as lead compounds to design new drug candidates with improved therapeutic properties (the 'prodrug approach'). Accordingly, in order to minimize its negative effects, considerable synthetic efforts have been made to mask the carboxylic acid group of ibuprofen. In this sense, a large number of amides able to *in vivo* deliver its parent acid **1** in a controlled manner by hydrolysis of the $-C(=O)NR^1R^2$ function have been developed, some of them showing improved analgesic activity and lower ulcerogenic effects.[4,5] The simplest member of this family, that is, ibuprofenamide (**3**), presents by itself a very good anti-inflammatory activity,[4a,j] and it has been used as an advanced intermediate in the preparation of several N-substituted derivatives with reduced ulcerogenic action.[4e–g,k,m] Repertaxin, a non-competitive allosteric blocker of interleukin-8 (CXCL8/IL-8) receptors (CXCR1/R2) belonging to the class of 2-phenylpropionyl methanesulfonamides, is also produced starting from **3**.[6]

The conventional method to prepare ibuprofenamide (**3**) involves a two-step sequence consisting in the conversion of ibuprofen (**1**) to the acid chloride **2**, by action of harmful thionyl chloride, followed by treatment with aqueous or gaseous ammonia (Scheme 1).[4a,e–g,j,k,m] Herein, an alternative, efficient, and practical synthetic approach to this valuable intermediate, via catalytic hydration of 2-(4-isobutylphenyl)propionitrile (**4**), is presented (Scheme 2).[7]

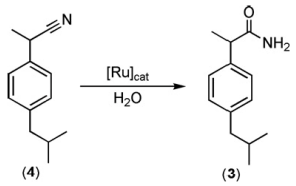
Hydration of nitriles is one of the most appealing and greener routes presently available for the large-scale production of amides. Traditionally, these hydration processes have been catalyzed by strong acids and bases under harsh conditions, methods which are not compatible with many sensitive functional groups and usually cause over-hydrolysis of the amides into the corresponding carboxylic acids.[8] It is now well-established that all these limitations can be circumvented by using enzymes[9] and metal

* Corresponding authors.
E-mail addresses: crochetpascale@uniovi.es (P. Crochet), vcm@uniovi.es (V. Cadierno).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.06.026



Scheme 1. Classical synthesis of ibuprofenamide (**3**).



Scheme 2. Catalytic hydration of 2-(4-isobutylphenyl)propionitrile (**4**).

catalysts,[10] several protocols for the selective formation of the amides being presently available for practical applications. However, despite these recent advances, no efficient preparations of **3** by catalytic hydration of **4** have been reported to date.[11,12]

In the course of our recent studies on metal-catalyzed nitrile hydration reactions,[13] we have found that the arene-ruthenium(II) complex **5** and the bis(allyl)-ruthenium(IV) derivatives **6–7** are extremely efficient and selective catalysts for this transformation (Fig. 1), the presence of hydrosoluble P-donor ligands in these complexes allows us to run the catalytic reactions in pure aqueous medium at neutral pH.[13a,b] With all these precedents in mind, the ability of complexes **5–7** to promote the hydration of 2-(4-isobutylphenyl)propionitrile (**4**) into ibuprofenamide (**3**) under these challenging reaction conditions has been explored as an alternative method of synthesis of this relevant compound.

In a typical experiment, the corresponding ruthenium precursor **5–7** (5 mol % of Ru) was added to a 0.33 M aqueous solution of 2-(4-isobutylphenyl)propionitrile (**4**) and the mixture heated in an oil-bath at 100 °C. The course of the reaction was monitored by regular sampling and analysis by gas chromatography (GC). The results obtained are summarized in Table 1.

As expected from our previous works,[13a,b] complexes **5–7** were able to provide ibuprofenamide **3** as the unique reaction product after 24 h of heating (ibuprofen was not detected by GC/MSD in the crude reaction mixtures). However, only a good conversion (91% GC yield) could be attained with the mononuclear Ru(II) complex **5** (entry 1), the ruthenium(IV) species **6** and **7** being poorly effective under the reaction conditions employed (22–64% GC yield; entries 2–3). With the aim of finding a more efficient catalyst for this relevant transformation other mononuclear $[RuCl_2(\eta^6\text{-}C_6Me_6)(PR_3)]$ derivatives were checked,[14] and to our delight we discovered that the readily accessible tris(dimethylamino)phosphine-based complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**)[15] (5 mol %) is able to generate the desired amide **3** in a remarkable 97% GC yield after only 7 h of heating at 100 °C (entry 4 in Table 1).[16a] Subsequent purification by column chromatography on silica gel provided analytically pure ibuprofenamide in 87% isolated yield (copies of the ^1H and $^{13}C\{^1H\}$ NMR and GC/MSD spectra of this sample are given as Supplementary material).

The combined use of microwaves (MWs), as a nonclassical low-energy-consuming heating source, and water, as an environmentally friendly solvent, to perform organic reactions has recently

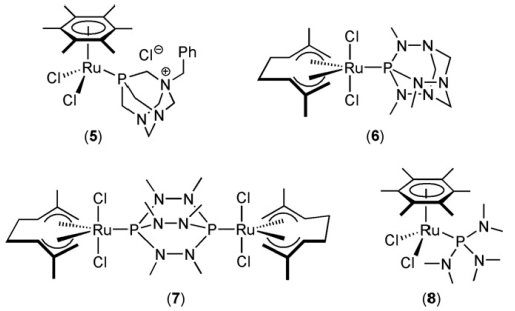


Figure 1. Structure of the ruthenium catalysts employed in this work.

Table 1
Ru-catalyzed hydration of 2-(4-isobutylphenyl)propionitrile (**4**) under thermal conditions[a]

Entry	Catalyst	Time (h)	Yield (%)[b]	TOF (h^{-1})[c]
1	**5**	24	91 (80)	0.8
2	**6**	24	22	0.2
3	**7**	24	64	0.5
4	**8**	7	97 (87)	2.8

[a] Reactions performed under N_2 atmosphere at 100 °C using 1 mmol of **4** (0.33 M in water). Substrate/Ru ratio:100/5.
[b] Yield of ibuprofenamide (**3**) determined by GC. Isolated yields after appropriate chromatographic work-up are given in brackets.
[c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the indicated time.

Table 2
Hydration of 2-(4-isobutylphenyl)propionitrile (**4**) catalyzed by complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**) under MW irradiation[a]

Entry	Ru (mol %)	Time (h)	Yield (%)[b]	TOF (h^{-1})[c]
1	5	0.33	>99	60.0
2	2.5	1	>99 (91)	39.6

[a] Reactions were performed under N_2 atmosphere using 1 mmol of **4** (0.33 M in water). A CEM Discover® S-Class microwave was used (150 W, 150 °C).
[b] Yield of ibuprofenamide (**3**) determined by GC. Isolated yield after appropriate chromatographic work-up is given in brackets.
[c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the indicated time.

emerged as a promising new field of research within the 'Green Chemistry' context.[17] In this sense, as shown in Table 2, the catalytic hydration of **4** by means of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**) can be conveniently performed in pure water under MW-irradiation, the working conditions employed (150 W/150 °C) allowing to reduce drastically the reaction time. Thus, in the presence of 5 mol % of **8**, quantitative formation of ibuprofenamide was observed after only 20 min of irradiation (entry 1). More interestingly, the use of MWs also allowed the reduction of the catalyst loading without compromising the efficiency of the hydration process. Thus, using only 2.5 mol % of **8**, ibuprofenamide was generated in >99% GC yield after 1 h and could be isolated in analytically pure form with an excellent 91% yield (entry 2).[16b] However, we must note that all attempts made to recycle **8** by selective extraction of ibuprofenamide from the aqueous phase failed.

In summary, an effective and practical synthesis of ibuprofenamide, a very valuable raw material for the design of novel NSAIDs, has been developed by catalytic hydration of 2-(4-isobutylphenyl)propionitrile using the readily accessible arene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**). To the best

of our knowledge this is the first efficient and selective protocol described in the literature for this transformation.[11,12] Moreover, the process is truly sustainable since, in addition to its atom-economy, it proceeds in a pure aqueous medium and is compatible with the use of low-energy-consuming MW-irradiation as the heating source. Further investigations into the application of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**) to the catalytic hydration of other challenging organonitriles are now in progress in our laboratories, and will be the subject of future contributions.

Acknowledgments

Financial support from the Spanish MICINN (Projects CTQ2006-08485/BQU, CTQ2010-14796/BQU and CSD2007-00006) is gratefully acknowledged. J.F. thanks MEC of Spain and the European Social Fund (FPU program) for the award of a Ph.D. grant.

Supplementary data

Supplementary data (Copies of the $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectra of complex **8**. Copies of the ^1H and $^{13}C\{^1H\}$ NMR and GC/MSD spectra of ibuprofenamide (**3**) isolated from entry 4 in Table 1. GC conditions employed and GC profiles of the catalytic reactions) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.026.

References and notes

1. (a) Vane, J. R. *Nature* **1971**, *231*, 232–235; (b) Busson, N. *J. Int. Med. Res.* **1986**, *14*, 53–62.
2. See, for example: (a) Smith, W. L.; Marnett, D. L.; DeWitt, D. L. *Pharmacol. Ther.* **1991**, *49*, 153–179; (b) Vane, J. R.; Bakhle, Y. S.; Botting, R. M. *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 97–120; (c) Simmons, D. L.; Botting, R. M.; Robertson, P. M.; Madsen, M. L.; Vane, J. R. *Proc. Natl. Acad. Sci.* **1999**, *96*, 3275–3280; (d) Narumiya, S.; Fitzgerald, G. A. *J. Clin. Invest.* **2001**, *108*, 25–30.
3. See, for example: (a) Allison, M. C.; Howatson, A. G.; Torrance, C. J.; Lee, F. D.; Russell, R. I. *N. Engl. J. Med.* **1992**, *327*, 749–754; (b) Rainsford, K. D.; Quadir, M. *Inflammopharmacology* **1995**, *3*, 169–190; (c) García-Rodríguez, L. A. *Arch. Int. Med.* **1998**, *158*, 33–39; (d) Wolfe, M. M.; Lichtenstein, D. R.; Singh, G. *N. Engl. J. Med.* **1999**, *340*, 1888–1899; (e) Rainsford, K. D. *J. Physiol. (Paris)* **2001**, *95*, 11–19.
4. See, for example: (a) Spickett, R. G. W.; Vega, A.; Prieto, J.; Moragues, J.; Marquez, M.; Roberts, D. J. *Eur. J. Med. Chem.* **1976**, *11*, 7–11; (b) Muteshwar, G.; Kohli, D. V.; Uppadhyay, R. K. *Indian J. Pharm. Sci.* **1990**, *52*, 91–93; (c) Shanbhag, V. R.; Crider, A. M.; Gokhale, R.; Harpalani, A.; Dick, R. M. *J. Pharm. Sci.* **1992**, *81*, 149–154; (d) Robert, J. M. H.; Robert-Piessard, S.; Duflos, M.; Le Baut, G.; Khettab, E. N.; Grimaud, N.; Petit, J. Y.; Welin, L. *Eur. J. Med. Chem.* **1994**, *29*, 841–854; (e) Rajasekaran, A.; Sivakumar, P.; Jayakar, B. *Indian J. Pharm. Sci.* **1999**, *61*, 158–161; (f) Doshi, A.; Samant, S. D.; Deshpande, S. G. *Indian J. Pharm. Sci.* **2002**, *64*, 440–444; (g) Doshi, A.; Deshpande, S. G. *Indian J. Pharm. Sci.* **2002**, *64*, 445–448; (h) Cocco, M. T.; Congiu, C.; Onnis, V.; Morelli, M.; Cauli, O. *Eur. J. Med. Chem.* **2003**, *38*, 513–518; (i) Aureli, L.; Cruciani, G.; Cesta, M. C.; Anacardio, R.; De Simone, L.; Moriconi, A. *J. Med. Chem.* **2005**, *48*, 2469–2479; (j) Allegretti, M.; Bertini, R.; Cesta, M. C.; Bizzarri, C.; Di Bitondo, R.; Di Cioccio, V.; Galliera, E.; Berdini, V.; Topai, A.; Zampella, G.; Russo, V.; Di Bello, N.; Nano, G.; Nicolini, L.; Locati, M.; Fantucci, P.; Florio, S.; Colotta, F. *J. Med. Chem.* **2005**, *48*, 4312–4331; (k) Guo, C. B.; Cai, Z. F.; Guo, Z. R.; Feng, Z. Q.; Chu, F. M.; Cheng, G. F. *Chinese Chem. Lett.* **2006**, *17*, 325–328; (l) Allegretti, M.; Bertini, R.; Beccari, A.; Moriconi, A.; Aramini, A.; Bizzarri, C.; Colotta, F. PCT Int. Appl. WO2006063999, 2006.; (m) Doshi, A.; Deshpande, S. G. *Indian J. Pharm. Sci.* **2007**, *69*, 824–827; (n) Metha, N.; Aggarwal, S.; Thareja, S.; Malla, P.; Misra, M.; Bhardwaj, T. R.; Kumar, M. *Int. J. ChemTech Res.* **2010**, *2*, 233–238; (o) Metha, N.; Thareja, S.; Aggarwal, S.; Malla, P.; Bhardwaj, T. R.; Kumar, M. *Der Pharma Chemica* **2010**, *2*, 397–403.
5. Esters are also prodrugs of ibuprofen under active investigation. See, for example: (a) Khan, M. S. Y.; Akhter, M. *Eur. J. Med. Chem.* **2005**, *40*, 371–376; (b) Davaran, S.; Rashidi, M. R.; Hanaee, J.; Hamidi, A. A.; Hashemi, M. *Drug Delivery* **2006**, *13*, 383–387; (c) Duan, Y.; Yu, J.; Liu, S.; Ji, M. *Med. Chem.* **2009**, *5*, 577–582; (d) Ghosh, B.; Gb, P.; Mishra, R.; Parcha, V. *Int. J. Pharm. Pharm. Sci.* **2010**, *2*, 79–85.
6. (a) Bertini, R.; Bizzarri, C.; Sabbatini, V.; Porzio, S.; Caselli, G.; Allegretti, M.; Cesta, M. C.; Gandolfi, C. A.; Mantovanini, M.; Colotta, F. PCT Int. Appl. WO2000024710, 2000.; (b) Bertini, R.; Allegretti, M.; Bizzarri, C.; Moriconi, A.; Locati, M.; Zampella, G.; Cervellera, M. N.; Di Cioccio, V.; Cesta, M. C.; Galliera, E.; Martinez, F. O.; Di Bitondo, R.; Troiani, G.; Sabbatini, V.; D'Anniballe, G.; Anacardio, R.; Cutrin, J. C.; Cavalieri, B.; Mainiero, F.; Strippoli, R.; Villa, P.; Di Girolamo, M.; Martin, F.; Gentile, M.; Santoni, A.; Corda, D.; Poli, G.; Mantovani, A.; Ghezzi, P.; Colotta, F. *Proc. Natl. Acad. Sci.* **2004**, *101*, 11791–11796.
7. Nitrile **4** is a commercially available compound (ABCR GmbH & Co. KG) that can be generated by catalytic hydrocyanation of the corresponding vinylarene: (a) Nugent, W. A.; McKinney, R. J. *J. Org. Chem.* **1985**, *50*, 5370–5372; (b) Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869–9882.
8. See, for example: (a) *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970; (b) Bailey, P. D.; Mills, T. J.; Pettecrew, R.; Price, R. A. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. 5, pp 201–294; (c) *Methoden Org. Chem. (Houben Weyl)*; Dopp, D., Dopp, H., Eds.; Thieme: Stuttgart, 1985; Vol. E5(2), pp 1024–1031.
9. For recent reviews covering the use of enzymes in catalytic nitrile hydrations, see: (a) Kobayashi, M.; Shimizu, S. *Curr. Opin. Chem. Biol.* **2000**, *4*, 95–102; (b) Endo, I.; Nojori, M.; Tsujimura, M.; Nakasako, M.; Nagashima, S.; Yohda, M.; Odaka, M. *J. Inorg. Biochem.* **2001**, *83*, 247–253; (c) Mylerová, V.; Martínková, L. *Curr. Org. Chem.* **2003**, *7*, 1279–1295; (d) Kovacs, J. A. *Chem. Rev.* **2004**, *104*, 825–848; (e) De Santis, G.; Di Cosimo, R. In *Biocatalysis for the Pharmaceutical Industry: Discovery, Development and Manufacturing*; Tao, J., Lin, G.-Q., Liese, A., Eds.; Wiley-VCH: Weinheim, 2009; pp 153–181.
10. For reviews covering the field of metal-mediated and metal-catalyzed nitrile hydrations, see: (a) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771–1802; (b) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *358*, 1–21; (c) Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* **2011**, *255*, 949–974.
11. The use of nitrile hydratases proved ineffective due to the preferential formation of ibuprofen by hydrolysis of **3**: (a) Beard, T.; Cohen, M. A.; Parratt, J. S.; Turner, N. J.; Crosby, J.; Moilliet, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1085–1104; (b) Effenberger, F.; Graef, B. W. *J. Biotechnol.* **1998**, *60*, 165–174; (c) Fallon, R. D.; Stieglitz, B.; Turner, I. *Appl. Microbiol. Biotechnol.* **1997**, *47*, 156–161; (d) Rzeznicka, K.; Schätzle, S.; Böttcher, D.; Klein, J.; Bornscheuer, U. T. *Appl. Microbiol. Biotechnol.* **2010**, *85*, 1417–1425.
12. Formation of ibuprofenamide by phase transfer catalyzed oxidation of **4** with basic hydrogen peroxide has been described (up to 70% conversion with 90% selectivity): Yadav, G. D.; Ceasar, J. L. *Org. Process Res. Dev.* **2008**, *12*, 740–747.
13. (a) Cadierno, V.; Francos, J.; Gimeno, J. *Chem. Eur. J.* **2008**, *14*, 6601–6605; (b) Cadierno, V.; Díez, J.; Francos, J.; Gimeno, J. *Chem. Eur. J.* **2010**, *16*, 9808–9817; (c) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno, V. *Organometallics* **2010**, *29*, 3955–3965; (d) García-Garrido, S. E.; Francos, J.; Cadierno, V.; Basset, J. M.; Polshettiwar, V. *ChemSusChem* **2011**, *4*, 104–111.
14. Known compounds such as $[RuCl_2(\eta^6\text{-}C_6Me_6)(PR_3)]$ (PR_3 = PMe_3, PPh_3, P^iPr_3, TPPMS, PTA, $P(OMe)_3$, $P(OPh)_3$) were completely ineffective (up to 10% conversion after 24 h at 100 °C).
15. Preparation of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**): A solution of dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$ (0.130 g, 0.194 mmol) in dichloromethane (20 mL) was treated with $P(NMe_2)_3$ (0.352 mL, 1.94 mmol) at room temperature for 3 h. The solution was then evaporated to dryness and the resulting oily residue washed with a 1:2 mixture of diethyl ether/hexane (4 × 10 mL), thus yielding an orange solid which was vacuum-dried. Yield: 0.133 g, 71% (Found: C, 43.33; H, 7.40; N, 8.60%. $C_{18}H_{36}N_3Cl_2PRu$ requires C, 43.46; H, 7.29; N, 8.45%). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162.1 MHz) δ 114.9 (s) ppm. ^1H NMR ($CDCl_3$, 400.5 MHz) δ 2.68 (d, 18H, $^3J_{PH}$ = 8.0 Hz, NMe), 1.96 (s, 18H, C_6Me_6) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 100.6 MHz) δ 90.1 (s, C_6Me_6), 35.2 (br, NMe), 16.0 (s, C_6Me_6) ppm. Copies of the spectra can be found in the Supplementary material.
16. (a) Catalytic hydration of 2-(4-isobutylphenyl)propionitrile (4) using complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**) under classical thermal conditions: Under nitrogen atmosphere, 2-(4-isobutylphenyl)propionitrile (0.187 g, 1 mmol), water (3 mL), and $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (24.8 mg, 0.05 mmol; 5 mol % of Ru) were introduced into a sealed tube and the reaction mixture stirred at 100 °C for 7 h. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by flash chromatography over silica gel using diethyl ether as eluent to afford 0.178 g of analytically pure ibuprofenamide (**3**) as a white solid (87% yield). The identity of **3** was assessed by comparison of its ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data with those reported in the literature and by their fragmentation in GC/MSD;
(b) Catalytic hydration of 2-(4-isobutylphenyl)propionitrile (**4**) using complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**8**) under MW-irradiation: Under nitrogen atmosphere, a pressure-resistant septum-sealed glass microwave reactor vial was charged with 2-(4-isobutylphenyl)propionitrile (0.187 g, 1 mmol), water (3 mL), $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (12.4 mg, 0.025 mmol; 2.5 mol % of Ru) and a magnetic stirring bar. The vial was then placed inside the cavity of a CEM Discover® S-Class microwave synthesizer and power was held at 150 W until the desired temperature was reached (150 °C). Microwave power was automatically regulated for the remainder of the experiment to maintain the temperature (monitored by a built-in infrared sensor; P_{max} = 25 psi). Work-up as described above led to 0.187 g of analytically pure ibuprofenamide (91% yield).
17. For reviews and a recent book on this topic, see: (a) Dallinger, D.; Kappe, O. C. *Chem. Rev.* **2007**, *107*, 2563–2591; (b) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546–1557; (c) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629–639; (d) *Aqueous Microwave Assisted Chemistry*; Polshettiwar, V., Varma, R. S., Eds.; RSC Publishing: Cambridge, 2010.

ORGANOMETALLICS

ARTICLE

pubs.acs.org/Organometallics

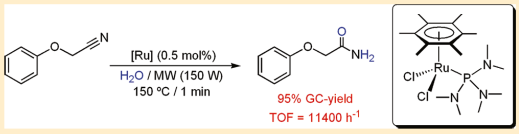
Arene–Ruthenium(II) Complexes Containing Inexpensive Tris(dimethylamino)phosphine: Highly Efficient Catalysts for the Selective Hydration of Nitriles into Amides†

Rocío García-Álvarez, Josefina Díez, Pascale Crochet,* and Victorio Cadierno*

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles" (Unidad Asociada al CSIC), Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain

Supporting Information

ABSTRACT: The catalytic hydration of nitriles into amides, in water under neutral conditions, has been studied using a series of arene–ruthenium(II) derivatives containing the commercially available and inexpensive ligand tris(dimethylamino)phosphine. Among them, best results were obtained with the complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$, which selectively provided the desired amides in excellent yields and short times (TOF values up to 11 400 h^{-1}). The process was operative with both aromatic, heteroaromatic, aliphatic, and α,β-unsaturated organonitriles and showed a high functional group tolerance. The stability of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ in water was evaluated, observing its progressive decomposition into the less-active dimethylamine–ruthenium(II) complex $[RuCl_2(\eta^6\text{-}C_6Me_6)(NHMe_2)]$ by hydrolysis of the coordinated $P(NMe_2)_3$ ligand. The X-ray crystal structure determination of the toluene complex $[RuCl_2(\eta^6\text{-}C_6H_5Me)\{P(NMe_2)_3\}]$ is also included.

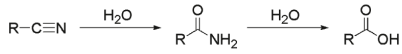


INTRODUCTION

The amide bond is one of the most important functional groups in contemporary chemistry since amides are versatile synthetic intermediates used in the manufacture of several pharmacological products, polymers, detergents, lubricants, and drug stabilizers, as well as key structural motifs present in numerous natural products.[1] Accordingly, the development of atom-efficient catalytic methods for amide formation is currently an extremely active area of research.[2] In this context, one of the simplest methods of synthesizing primary amides is the catalytic hydration of nitriles (Scheme 1). Conventionally, these reactions have been catalyzed by strong acids and bases using high-temperature regimes.[1,3] However, under these conditions, the corresponding carboxylic acids are usually formed as a byproduct due to the competitive overhydrolysis of the amides. Also, many sensitive functional groups do not endure such harsh conditions, which consequently decreases the selectivity of the synthetic protocol.

More selective methods for the conversion of nitriles into amides are based on the use of metalloenzymes (nitrile hydratases),[4] heterogeneous catalysts,[5] and transition-metal complexes.[6] In fact, some nitrile hydratases and metal oxides have already been employed in the industrial production of relevant amides, such as acrylamide, nicotinamide, and 5-cyanovaleramide.[7] In a laboratory scale, a variety of transition-metal complexes (mainly of groups 8–12) have been investigated,[6] with the Murahashi's ruthenium dihydride $[RuH_2(PPh_3)_4]$,[8] the Parkins's platinum hydride $[PtH(PMe_2OH)\{(PMe_2O)_2H\}]$,[9] the acetylacetonate complex *cis*-$[Ru(acac)_2(PPh_2py)_2]$,[10] and the Rh(I)-based system $[\{Rh(\mu\text{-}OMe)(cod)\}_2]/PCy_3$ (cod = 1,5-cyclooctadiene),[11] showing remarkable activities and selectivities under mild conditions.

Scheme 1. Nitrile Hydration and Amide Hydrolysis Reactions



All the above-mentioned catalysts operate in organic media in the presence of only small amounts of water. That is why, in order to develop more environmentally benign and safer procedures, during the last years, our group has focused on the search of homogeneous catalysts able to perform the selective hydration of nitriles into amides employing directly water as a solvent.[12,13] Note that, in line with the increasing academic and industrial interest in fulfilling the principles of "Green Chemistry",[14] the development of organic transformations in aqueous media has become one of the major cornerstones in modern chemistry,[15] since water is the most convenient solvent that one can imagine in terms of cost, availability, safety, and environmental impact.[16] In addition, its use may be particularly advantageous when water itself participates as one of the reactants of the process. In this context, our studies have brought to light the arene–ruthenium(II) complex **A** and the bis(allyl)–ruthenium(IV) derivatives **B** and **C** (Figure 1) as the most efficient catalysts described to date for the selective hydration of nitriles into amides in pure aqueous media.[12a,b] Remarkably, all of them operate without the assistance of any acidic or basic additive, showing also a wide scope with respect to nature of the substrates and high tolerance toward common functional groups. However, TOF values

Received: July 20, 2011
Published: September 28, 2011

reached with these catalysts in water (up to 127 h^{-1}) are still modest compared to those reported for homogeneous systems operating in organic media (e.g., up to 20 900 h^{-1} using *cis*-[Ru(acac)$_2$-(PPh$_2$py)$_2$]).[10] In addition, the requirement of elaborated "cage-like" phosphine ligands to ensure their solubility in water may also be a drawback for future applications.

In our search for more efficient systems, we have now found that arene–ruthenium(II) complexes containing the commercially available and inexpensive ligand tris(dimethylamino)phosphine (hexamethylphosphorous triamide, HMPT) are convenient and more competitive alternatives to compounds **A**–**C** for the selective hydration of nitriles to amides in pure aqueous medium at neutral pH (**D** in Figure 2). In particular, when the hexamethylbenzene complex [RuCl$_2$(η^6-C$_6$Me$_6$){P(NMe$_2$)$_3$}] is used, turnover frequencies (TOFs) up to 11 400 h^{-1} could be reached, the highest reported to date in the literature under these challenging reaction conditions. Results from this study are presented herein.[17]

RESULTS AND DISCUSSION

Synthesis and Characterization of Complexes [RuCl$_2$-(η^6-arene){P(NMe$_2$)$_3$}]. Treatment of the dimeric precursors

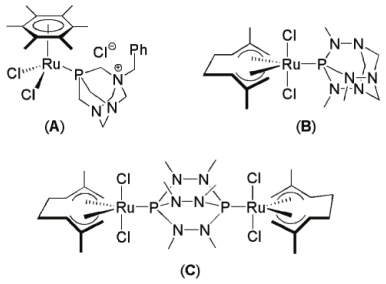


Figure 1. Structure of the ruthenium complexes **A**–**C**.

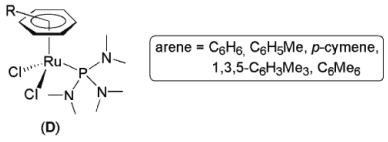
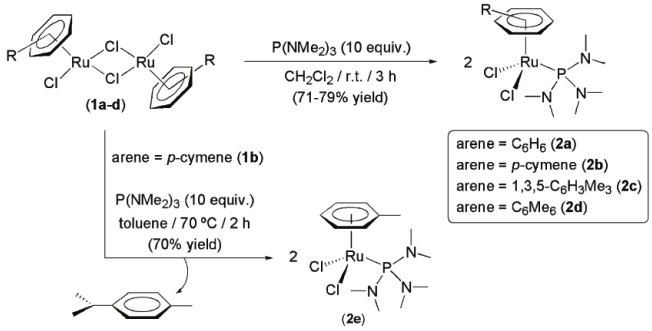


Figure 2. Structure of the arene–ruthenium(II) complexes **D**.

[{RuCl(μ-Cl)(η^6-arene)}$_2$] (arene = C$_6$H$_6$ (**1a**),[18] *p*-cymene (**1b**),[19] 1,3,5-C$_6$H$_3$Me$_3$ (**1c**),[20] C$_6$Me$_6$ (**1d**)[19]) with 10 equiv of tris(dimethylamino)phosphine, in dichloromethane at room temperature for 3 h, produced the mononuclear derivatives [RuCl$_2$(η^6-arene){P(NMe$_2$)$_3$}] (**2a**–**2d**) through a classical bridge-splitting reaction (Scheme 2).[21,22] Interestingly, when the synthesis of complex [RuCl$_2$(η^6-*p*-cymene){P(NMe$_2$)$_3$}] (**2b**) was attempted by heating a toluene solution of [{RuCl(μ-Cl)-(η^6-*p*-cymene)}$_2$] (**1b**) with P(NMe$_2$)$_3$ (10 equiv) at 70 °C, formation of [RuCl$_2$(η^6-C$_6$H$_5$Me){P(NMe$_2$)$_3$}] (**2e**) was observed. In this reaction, the coordinated *p*-cymene ligand was unexpectedly replaced by toluene.[23] Note that, although arene substitution reactions in ruthenium complexes are classical,[24] they usually occur at temperatures above 100 °C and involve, in most cases, the displacement of an electron-poor arene by a richer one.[25,26] In fact, to the best of our knowledge, formation of minor amounts of [Ru(=PMes)(IMes)(η^6-C$_6$H$_5$Me)] (Mes = mesityl; IMes = 1,3-dimesityl-imidazol-2-ylidene) in the reaction of [RuCl$_2$(PH$_2$Mes)(η^6-*p*-cymene)] with an excess of IMes in toluene is the only example quoted in the literature of the replacement of a ruthenium-coordinated *p*-cymene ligand by the poorer toluene donor.[27] The strongly basic properties of P(NMe$_2$)$_3$ may be responsible of this unexpected result.

Complexes **2a**–**2e**, isolated as air-stable red-orange solids in 70–79% yield, are soluble in polar solvents, such as dichloromethane, chloroform, THF, alcohols, and even water (see below), partially soluble in diethyl ether, and insoluble in *n*-alkanes. Their characterization was straightforward following the analytical and spectroscopic data obtained (details are given in the Experimental Section). In particular, the $^{31}P\{^1H\}$ NMR spectra of all these derivatives exhibit a singlet resonance at 106.8–114.9 ppm, slightly shielded with respect to that of free tris(dimethylamino)phosphine (δ 122.7 ppm), while their ^1H and $^{13}C\{^1H\}$ NMR spectra show the expected signals for the η^6-coordinated arene groups and the P(NMe$_2$)$_3$ ligand. For the latter, characteristic N–Me doublet resonances were observed at δ_H 2.68–2.75 ppm ($^3J_{PH}$ = 8.0–9.2 Hz) and δ_C 35.2–39.7 ($^2J_{PC}$ = 3.0–5.0 Hz) ppm. In addition, the structure of the toluene complex [RuCl$_2$(η^6-C$_6$H$_5$Me){P(NMe$_2$)$_3$}] (**2e**) could be unambiguously confirmed by means of an X-ray diffraction analysis. X-ray quality crystals were obtained by slow diffusion of *n*-pentane into a saturated solution of **2e** in dichloromethane. An ORTEP view of the molecule, along with selected structural parameters, is shown in Figure 3. The metal exhibits the usual pseudooctahedral three-legged piano-stool geometry with the

Scheme 2. Synthesis of Mononuclear Ru(II) Complexes [RuCl$_2$(η^6-arene){P(NMe$_2$)$_3$}] (2a–2e)



dx.doi.org/10.1021/om2006563 |*Organometallics* 2011, 30, 5442–5451

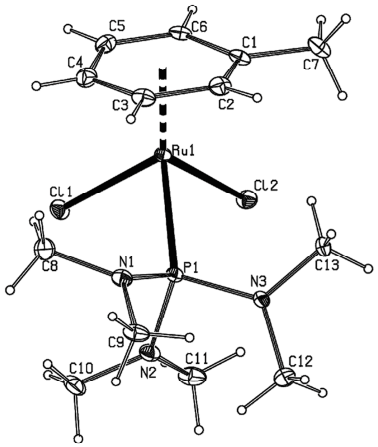


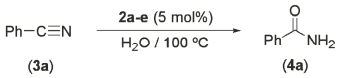
Figure 3. ORTEP-type view of the structure of complex **2e** showing the crystallographic labeling scheme. Thermal ellipsoids are drawn at the 10% probability level. Selected bond distances (Å) and angles (deg): Ru−C* = 1.7097(5); Ru−Cl(1) = 2.4090(18); Ru−Cl(2) = 2.4052 (17); Ru−P(1) = 2.3611(15); P(1)−N(1) = 1.666(7); P(1)−N(2) = 1.673(7); P(1)−N(3) = 1.658(6); C*−Ru−Cl(1) = 124.10(5); C*−Ru−Cl(2) = 124.96(5); C*−Ru−P(1) = 133.66(5); Cl(1)−Ru−Cl(2) = 88.71(7); Cl(1) Ru P(1) = 85.38(6); Cl(2) Ru P(1) = 87.28(6); Ru P(1)−N(1) = 109.7(2); Ru−P(1)−N(2) = 120.6(2); Ru−P(1)−N(3) = 115.4(2); N(1)−P(1)−N(2) = 103.3(3); N(1)−P(1)−N(3) = 107.5(3); N(2)−P(1)−N(3) = 98.9(3). C* denotes the centroid of the toluene ring (C(1), C(2), C(3), C(4), C(5), and C(6)).

phosphorus atom of the $P(NMe_2)_3$ unit and the two chloride ligands as the legs. The interligand angles Cl(1)−Ru−P(1) (85.38(6)°), Cl(2)−Ru−P(1) (87.28(6)°), and Cl(1)−Ru−Cl(2) (88.71(7)°), and those between the centroid of the toluene ring C* and the legs (124.10(5)−133.66(5)°), showed typical values for $[RuCl_2(\eta^6\text{-arene})(PR_3)]$ species.[24] The angle sums around N(1), N(2), and N(3) are 356.3, 356.5, and 359.9°, respectively, indicating a trigonal planar geometry at all three nitrogen centers. This fact, previously observed in the solid-state structure of the related Ru(II) complex $[RuI_2(\eta^6\text{-}p\text{-cymene})\{P(NMe_2)_3\}]$,[22] contrasts with the geometry found for the free $P(NMe_2)_3$ ligand, which shows that two of the nitrogen atoms are planar and sp^2-hybridized, and the third one is pyramidal sp^3-hybridized.[28] Apparently, rehybridization at nitrogen upon coordination is a hallmark of $P(NMe_2)_3$ since similar observations have also been made with other metal fragments.[29] As expected, the Ru−P bond length of **2e** (2.3611(15) Å) is almost identical to that found in $[RuI_2(\eta^6\text{-}p\text{-cymene})\{P(NMe_2)_3\}]$ (2.3657(11) Å).[22]

Catalytic Hydration of Nitriles in Aqueous Medium. Initially, the catalytic potential of complexes $[RuCl_2(\eta^6\text{-arene})\{P(NMe_2)_3\}]$ (**2a**−**2e**) was investigated using benzonitrile (**3a**) as a model substrate. In a typical experiment, the corresponding ruthenium catalyst (5 mol %) was added to a 0.33 M aqueous solution of **3a** and the mixture heated in an oil bath at 100 °C. The course of the reaction was monitored by regular sampling and analysis by gas chromatography (GC).

As shown in Table 1, to our delight, all the complexes synthesized were found to be active catalysts, providing benzamide (**4a**) as the unique reaction product in ≥98% GC yield after 1−5 h of heating (entries 1−5). As previously observed with

Table 1. Hydration of Benzonitrile (3a) into Benzamide (4a) Catalyzed by Complexes $[RuCl_2(\eta^6\text{-arene})\{P(NMe_2)_3\}]$ (2a−2e) in Water[a]



entry	catalyst	time (h)	yield[b]	TOF[c] (h^{-1})
1	$[RuCl_2(\eta^6\text{-}C_6H_6)\{P(NMe_2)_3\}]$ (**2a**)	3	>99%	7
2	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(NMe_2)_3\}]$ (**2b**)	5	98%	4
3	$[RuCl_2(\eta^6\text{-}1,3,5\text{-}C_6H_3Me_3)\{P(NMe_2)_3\}]$ (**2c**)	5	99%	4
4	$[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**2d**)	1	>99%	20
5	$[RuCl_2(\eta^6\text{-}C_6H_5Me)\{P(NMe_2)_3\}]$ (**2e**)	4	99%	5
6[d]	$[RuCl_2(\eta^6\text{-}C_6H_6)\{P(NMe_2)_3\}]$ (**2a**)	3	25%	2
7[d]	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(NMe_2)_3\}]$ (**2b**)	5	47%	2
8[d]	$[RuCl_2(\eta^6\text{-}1,3,5\text{-}C_6H_3Me_3)\{P(NMe_2)_3\}]$ (**2c**)	5	40%	2
9[d]	$[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**2d**)	1	85%	17
10[d]	$[RuCl_2(\eta^6\text{-}C_6H_5Me)\{P(NMe_2)_3\}]$ (**2e**)	4	29%	1

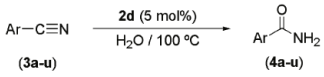
[a] Reactions performed under a N_2 atmosphere at 100 °C using 1 mmol of benzonitrile (0.33 M in water). Substrate/Ru ratio: 100/5. [b] Yields determined by GC (uncorrected GC areas). [c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case. [d] Reactions performed in the presence of 200 equiv of the corresponding free arene (respective to Ru).

related arene−ruthenium(II) complexes,[12a,13o] in no case were traces of benzoic acid detected by GC in the crude reaction mixtures. Within this family of complexes, best results in terms of activity were obtained with $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**2d**), that is, that containing the more sterically demanding and electron-rich arene hexamethylbenzene, which was able to generate benzamide quantitatively in only 1 h (TOF = 20 h^{-1}; entry 5). However, from the data obtained, no direct relationships between the steric and/or electronic nature of the auxiliary arene ligand and the catalytic activity observed became apparent. It is also important to note that, when the same reactions were performed in the presence of 200 equiv of the corresponding free arene (i.e., benzene, *p*-cymene, mesitylene, hexamethylbenzene, or toluene), the performances shown by these catalysts were, in general, drastically reduced (entries 6−10 vs 1−5). Only complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**2d**) had a similar effectiveness under these new reaction conditions (TOF of 17 vs 20 h^{-1}; entry 9 vs 4). These observations seem to indicate that the activation of precatalysts **2a**−**2c** and **2e** may operate through the dissociation of the arene ligand. In contrast, such a displacement does not take place with the more electron-rich ligand hexamethylbenzene. Hence, coordination of the substrate onto complex **2d** requires the dissociation of one Ru−Cl bond. In accord with this, we have observed that compound $[RuCl(NCMe)(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}][PF_6]$, in which one chloride has been replaced by an acetonitrile ligand, is also a very effective catalyst for nitrile hydrations.[30]

The scope of this aqueous transformation was next explored using the most active catalyst $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**2d**).[31] First, we focused on a wide array of functionalized benzonitriles, performing the catalytic reactions routinely at 100 °C with a ruthenium loading of 5 mol % (entries 2−19 in Table 2). Thus, as observed for **3a** (entry 1), benzonitriles **3b**−**3n** (entries 2−14) with electron-withdrawing groups afforded the corresponding amides **4b**−**4n** in excellent yields (≥95% by

dx.doi.org/10.1021/om2006563 |*Organometallics* 2011, 30, 5442–5451

Table 2. Hydration of the Aromatic Nitriles 3a—3u into Amides 4a—4u Catalyzed by Complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (2d) in Water[a]

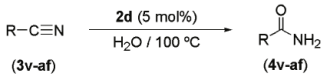


(3a-u) (4a-u)

entry	substrate	time	yield[b]	TOF[c] (h^{-1})
1	Ar = Ph (**3a**)	1 h	>99% (87%)	20
2	Ar = 2-C_6H_4F (**3b**)	1.5 h	97% (82%)	13
3	Ar = 3-C_6H_4F (**3c**)	45 min	98% (86%)	26
4	Ar = 4-C_6H_4F (**3d**)	1 h	98% (84%)	20
5	Ar = 2-C_6H_4Cl (**3e**)	1.5 h	95% (82%)	10
6	Ar = 3-C_6H_4Cl (**3f**)	15 min	>99% (90%)	79
7	Ar = 4-C_6H_4Cl (**3g**)	15 min	98% (87%)	78
8	Ar = 2-C_6H_4Br (**3h**)	45 min	98% (85%)	26
9	Ar = 3-C_6H_4Br (**3i**)	5 min	98% (89%)	235
10	Ar = 4-C_6H_4Br (**3j**)	30 min	96% (81%)	38
11	Ar = C_6F_5 (**3k**)	5 min	>99% (91%)	238
12	Ar = 3-$C_6H_4NO_2$ (**3l**)	30 min	>99% (88%)	40
13	Ar = 4-$C_6H_4C(=O)Me$ (**3m**)	1.5 h	97% (82%)	13
14	Ar = 4-$C_6H_4C(=O)OEt$ (**3n**)	30 min	98% (80%)	39
15	Ar = 2-C_6H_4OMe (**3o**)	5 h	81% (70%)	3
16	Ar = 3-C_6H_4OMe (**3p**)	1.5 h	99% (85%)	13
17	Ar = 4-C_6H_4OMe (**3q**)	2.5 h	94% (79%)	8
18	Ar = piperonyl (**3r**)	3 h	99% (87%)	7
19	Ar = 2-C_6H_4OH (**3s**)	2 h	97% (84%)	10
20	Ar = 3-pyridyl (**3t**)	1 h	98% (88%)	20
21	Ar = 2-thienyl (**3u**)	15 min	98% (86%)	78

[a] Reactions performed under a N_2 atmosphere at 100 °C using 1 mmol of the corresponding nitrile (0.33 M in water). Substrate/Ru ratio: 100/5. [b] Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate chromatographic workup are given in brackets. [c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case.

Table 3. Hydration of Nitriles 3v—3af into Amides 4v—4af Catalyzed by Complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (2d) in Water[a]



(3v-af) (4v-af)

entry	substrate	time	yield[b]	TOF[c] (h^{-1})
1	R = Me (**3v**)	2 h	99% (91%)	10
2	R = *n*-C_5H_{11} (**3w**)	4 h	97% (84%)	5
3[d]	R = 5-norbornen-2-yl (**3x**)	5 h	97% (82%)	4
4	R = $(CH_2)_3Ph$ (**3y**)	5 h	89% (77%)	4
5	R = CH_2OPh (**3z**)	2 min	>99% (90%)	594
6	R = $(CH_2)_2OPh$ (**3aa**)	1.5 h	94% (81%)	13
7	R = CH_2-4-C_6H_4Cl (**3ab**)	10 min	96% (85%)	115
8	R = CH_2-2-pyridyl (**3ac**)	2.5 h	91% (79%)	7
9	R = CH_2-2-thienyl (**3ad**)	45 min	99% (89%)	26
10	R = (*E*)-CH=CHPh (**3ae**)	1 h	96% (83%)	19
11	R = (*E*)-CH=CH-4-C_6H_4Cl (**3af**)	1 h	88% (71%)	18

[a] Reactions performed under a N_2 atmosphere at 100 °C using 1 mmol of the corresponding nitrile (0.33 M in water). Substrate/Ru ratio: 100/5. [b] Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate chromatographic workup are given in brackets. [c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case. [d] Both the starting nitrile **3x** and the final amide **4x** were a mixture of the corresponding endo and exo isomers (ca. 3:2 ratio).

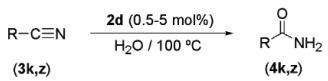
GC) and short reaction times (from 5 min to 1.5 h). Significant TOF values of 235 and 238 h^{-1} were reached in the hydration of 3-bromobenzonitrile (**3i**) and pentafluorobenzonitrile (**3k**), respectively, which are ca. 12 times higher than those previously achieved with the related hexamethylbenzene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (**A** in Figure 1).[12a] In general, due probably to steric factors, ortho-substituted substrates showed a lower reactivity compared to their meta- or para-substituted counterparts (entry 2 vs 3—4, entry 5 vs 6—7, and entry 8 vs 9—10). Benzonitriles **3o**—**3s**, containing electron-donating groups, were equally hydrated using complex **2d** (entries 15—19). However, slightly longer reaction times were, in these cases, required to attain similar conversions (1.5—5 h; TOF values up to 13 h^{-1}). It should be noted that the present catalytic system tolerates different functional groups, such as aromatic fluoro, chloro, bromo, nitro, and alcohol functionalities, as well as methyl ketone, ethyl ester, and methyl ether. In addition, heteroaromatic nitriles, such as 3-cyanopyridine (**3t**) and thiophene-2-carbonitrile (**3u**), were also found to participate in this reaction, delivering selectively the desired amides **4t**—**4u** in 98% GC yield (entries 20—21). Solvent removal and chromatographic workup on silica gel provided analytically pure samples of amides **4a**—**4u** (70—91% isolated yields), whose identity was assessed by comparison of their ^1H and $^{13}C\{^1H\}$ NMR data with those previously described in the literature and by their fragmentation in GC/MSD.

Complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**2d**) was also effective in the hydration of a variety of nitriles containing alkyl—CN bonds, thus confirming the wide scope of this catalytic transformation (see Table 3). Again, reactions proceeded to completion in the absence of any additive. Thus, under the standard reaction conditions (5 mol % of Ru, 100 °C), substrates **3v**—**3ad** were cleanly transformed into amides **4v**—**4ad**, which could be isolated in 77—91% yield after appropriate chromatographic workup (entries 1—9). As shown in entry 5, hydration of phenoxyacetonitrile (**3z**) was quantitative in only 2 min, leading to a respectable TOF value of 594 h^{-1}. For the rest of the substrates employed, variable reaction times were required to attain good conversions (≥89%), which, in no case, exceeded 5 h. Remarkably, hydration of the α,β-unsaturated nitriles cinnamonitrile (**3ae**, entry 10) and 4-chlorocinnamonitrile (**3af**, entry 11) also proceeded cleanly using our protocol, providing the desired cinnamamide (**4ae**) and 4-chlorocinnamamide (**4af**) in high yields after only 1 h. Neither hydration of the C=C bond nor competitive polymerization processes were observed in these reactions.

Interestingly, the catalytic activity of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**2d**) remains high at lower ruthenium loadings (details are given in Table 4). For example, using only 0.5 mol % of **2d**, hydration of pentafluorobenzonitrile (**3k**) and phenoxyacetonitrile (**3z**) proceeded in excellent 93—95% GC yields in less than 3 h (TOF = 63 and 392 h^{-1}, respectively; entries 5 and 11). On the other hand, the combined use of microwaves (MWs), as a nonclassical low-energy-consuming heating source, and water, as an environmentally friendly solvent,

dx.doi.org/10.1021/om2006563 |Organometallics 2011, 30, 5442–5451

Table 4. Hydration of Nitriles 3k and 3z into Amides 4k and 4z Catalyzed by Complex [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (2d) in Water at Different Ruthenium Loadings[a]



entry	substrate	% Ru (mol %)	time	yield[b]	TOF[c] (h^{-1})
1	R = C_6F_5 (**3k**)	5	5 min	>99%	238
2	R = C_6F_5 (**3k**)	3	15 min	>99%	132
3	R = C_6F_5 (**3k**)	2	30 min	99%	99
4	R = C_6F_5 (**3k**)	1	1.5 h	99%	66
5	R = C_6F_5 (**3k**)	0.5	3 h	95%	63
6[d]	R = C_6F_5 (**3k**)	0.5	30 min	93%	372
7	R = CH_2OPh (**3z**)	5	2 min	>99%	594
8	R = CH_2OPh (**3z**)	3	3 min	>99%	660
9	R = CH_2OPh (**3z**)	2	5 min	>99%	594
10	R = CH_2OPh (**3z**)	1	15 min	>99%	396
11	R = CH_2OPh (**3z**)	0.5	30 min	98%	392
12[d]	R = CH_2OPh (**3z**)	0.5	1 min	95%	11 400

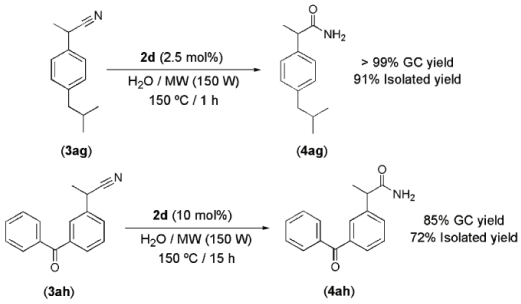
[a] Reactions performed under a N_2 atmosphere at 100 °C using 1 mmol of the corresponding nitrile (0.33 M in water). [b] Yields determined by GC (uncorrected GC areas). [c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case. [d] Reaction was carried out in a CEM Discover S-Class microwave oven (150 W, 150 °C).

to perform organic reactions has recently emerged as a promising new field of research within the "Green Chemistry" context.[32] In this sense, as shown in entries 6 and 12 (Table 4), the hydration reactions of nitriles **3k** and **3z** with 0.5 mol % of complex **2d** could be conveniently performed under MW irradiation, the working conditions employed (150 W/150 °C) allowing reducing considerably the reaction times. Significantly, an impressive TOF value of 11 400 h^{-1}, the highest reported to date for this catalytic transformation in water and close to the benchmarks set in organic media,[10] was reached in the hydration of phenoxyacetonitrile (**3z**) into phenoxyacetamide (**4z**) under these MW conditions (entry 12).

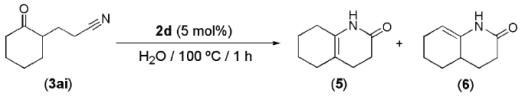
The outstanding performance of complex **2d** was further exploited in the catalytic synthesis of the nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofenamide (**4ag**) and ketoprofenamide (**4ah**) by hydration of commercially available 2-(4-isobutylphenyl)propionitrile (**3ag**) and 2-(3-benzoylphenyl)-propionitrile (**3ah**), respectively (Scheme 3).[17,33] Note that no efficient preparations of these compounds, widely employed as advanced intermediates in the preparation of several ibuprofen- and ketoprofen-prodrugs as well as other pharmacologically active compounds,[34] by catalytic hydration of nitriles **3ag** and **3ah** have been reported to date.[35−37] Thus, we have found that, in the presence of 2.5 mol % of **2d**, quantitative formation of ibuprofenamide (**4ag**) takes place after only 1 h of MW irradiation (150 W, 150 °C), allowing its isolation in analytically pure form with an excellent 91% yield. In the case of nitrile **3ah**, the hydration process was also operative but a longer reaction time (15 h of MW irradiation) and a higher catalyst loading (10 mol %) were necessary to obtain the desired ketoprofenamide (**4ah**) in good yield (72%).

Complex [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**2d**) proved also effective for the conversion of δ-ketonitriles into ene-lactams,

Scheme 3. Catalytic Synthesis of Ibuprofenamide (4ag) and Ketoprofenamide (4ah)



Scheme 4. Catalytic Synthesis of ene-Lactams 5 and 6 from δ-Ketonitrile 3ai



98% GC yield; 87% Isolated yield (*ca.* **5**:**6** ratio = 3:1)

via a tandem hydration/cyclocondensation sequence.[8] Thus, as shown in Scheme 4, treatment of a suspension of commercially available 2-(2-cyanoethyl)cyclohexanone (**3ai**) in water with 5 mol % of **2d** led to a ca. 3:1 mixture of isomeric 3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (**5**) and 3,4,4a,5,6,7-hexahydro-2(1*H*)-quinolinone (**6**) in high yield (87%) after 1 h of conventional thermal heating at 100 °C. Such a tandem process promoted by [$RuH_2(PPh_3)_4$] in an organic medium was already described by Murahashi,[8b] but, to the best of our knowledge, no previous examples in pure aqueous medium have appeared in the literature.

Finally, we must note that the only limitation encountered during our studies concerns the use of dinitriles, for example, 1,4-dicyanobenzene, adiponitrile, or fumaronitrile, which, under the standard reaction conditions, gave rise to unidentified highly insoluble materials.

Stability of Complexes [$RuCl_2(\eta^6$-arene)$\{P(NMe_2)_3\}$] in Water. Interestingly, despite the remarkable solubility (ca. 20 mg/mL) and catalytic activity shown by complex [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**2d**) in water, its stability in this medium proved low. In fact, as assessed by $^{31}P\{^1H\}$ NMR spectroscopy, it completely decomposes at room temperature (48 h) into a mixture of several unidentified phosphorus-containing compounds. At 100 °C, formation of the same decomposition products was observed in only 4 h. Inspection by ^1H NMR spectroscopy of these crude reaction mixtures showed, however, the major formation of a single ruthenium complex, which, by recrystallization from dichloromethane/hexanes, could be isolated in pure form (51% yield) and identified as [$RuCl_2(\eta^6\text{-}C_6Me_6)(NHMe_2)$] (**7d**) (Scheme 5).

Formation of the dimethylamino derivative **7d** from complex **2d** most probably involves the initial release of Me_2NH by hydrolytic cleavage of the P−N bonds of the coordinated tris(dimethylamino)phosphine ligand, which subsequently displaces the resulting $P(OH)_x(NMe_2)_{3-x}$ ($x = 1, 2, 3$) species from

Scheme 5. Formation of Complexes 7b–7d by Decomposition of 2b–2d

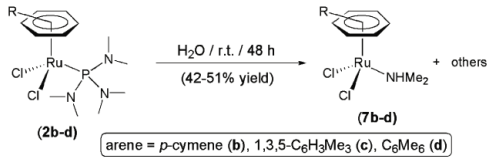
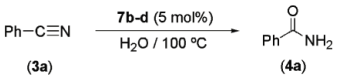


Table 5. Hydration of Benzonitrile (3a) into Benzamide (4a) Catalyzed by Complexes $[RuCl_2(\eta^6\text{-arene})(NHMe_2)]$ (7b–7d) in Water[a]



entry	catalyst	time (h)	yield[b]	TOF[c] (h^{-1})
1	$[RuCl_2(\eta^6\text{-}p\text{-cymene})(NHMe_2)]$ (**7b**)	24	53%	<1
2	$[RuCl_2(\eta^6\text{-}1,3,5\text{-}C_6H_3Me_3)(NHMe_2)]$ (**7c**)	24	65%	1
3	$[RuCl_2(\eta^6\text{-}C_6Me_6)(NHMe_2)]$ (**7d**)	24	71%	1

[a] Reactions performed under a N_2 atmosphere at 100 °C using 1 mmol of benzonitrile (0.33 M in water). Substrate/Ru ratio: 100/5. [b] Yields determined by GC (uncorrected GC areas). [c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case.

the ruthenium center.[38,39] Note that such a decomposition pathway seems to be general since the related species $[RuCl_2(\eta^6\text{-}p\text{-cymene})(NHMe_2)]$ (**7b**)[40] and $[RuCl_2(\eta^6\text{-}1,3,5\text{-}C_6H_3Me_3)(NHMe_2)]$ (**7c**) could also be isolated (42–45% yield) when aqueous solutions of complexes **2b–2c** were stirred at room temperature for 48 h (Scheme 5). Compounds **7b–7d**, which can be more conveniently prepared (84–87% isolated yields) by bubbling gaseous dimethylamine through a solution of dimers $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})\}_2]$ (**1b–1d**) in tetrahydrofuran, were characterized by standard spectroscopic techniques as well as elemental analyses (details are given in the Experimental Section). Key spectroscopic features are as follows: (i) (IR) a typical ν(N-H) absorption band at 3231–3251 cm^{-1}, (ii) (^1H NMR) a broad singlet at 2.51–2.70 ppm and a doublet resonance at ca. 2.8 ppm ($^3J_{HH}$ = 4.0–6.8 Hz) assigned to the NH and methyl protons, respectively, of the coordinated $NHMe_2$ ligand, and (iii) ($^{13}C\{^1H\}$ NMR) a characteristic low-field singlet resonance in the range of 43.2–46.2 ppm for the $NHMe_2$ carbons.

The easy decomposition of complexes **2b–2d** into the dimethylamino derivatives **7b–7d** in an aqueous medium raised the question on the real nature of the catalytically active species in the nitrile hydration reactions discussed above. Thus, to determine the role played by **7b–7d** in the catalytic events, the hydration of benzonitrile (**3a**) promoted by these species (5 mol %) was studied under the same reaction conditions previously employed with complexes **2b–2d** (Table 1). As shown in Table 5, although active in the hydration process, remarkably lower activities as compared with **2b–2d** were observed (TOF values up to 1 h^{-1} vs 4–20 h^{-1}). Consequently, formation of these dimethylamino derivatives seems to be not responsible for the high performances showed by complexes $[RuCl_2(\eta^6\text{-arene})\{P(NMe_2)_3\}]$ (**2a–2d**).

CONCLUSION

In summary, a practical and efficient protocol for selective hydrations of nitriles into amides under challenging reaction conditions, that is, in an aqueous medium at neutral pH, has been developed. The reaction is promoted by arene–ruthenium(II) catalysts containing the commercially available and inexpensive tris(dimethylamino)phosphine ligand. In particular, impressive TOF values of up to 11 400 h^{-1} were reached with the hexamethylbenzene derivative $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**2d**). This represents the highest activity reported to date for this catalytic transformation in water and is close to the benchmarks set in organic media.[10] The wide scope and high tolerance toward functional groups showed by the ruthenium catalyst **2d** make this process an attractive synthetic approach to amides. The only drawback of this new methodology is the impossibility to recycle **2d** due to its progressive decomposition into less-active species by hydrolysis of the coordinated $P(NMe_2)_3$ ligand.

EXPERIMENTAL SECTION

Synthetic procedures were performed under an atmosphere of dry nitrogen using vacuum-line and standard Schlenk techniques. Solvents were dried by standard methods and distilled under nitrogen before use. All reagents were obtained from commercial suppliers and used without further purification with the exception of compounds $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})\}_2]$ (arene = C_6H_6 (**1a**),[18] *p*-cymene (**1b**),[19] $1,3,5\text{-}C_6H_3Me_3$ (**1c**),[20] C_6Me_6 (**1d**)[19]), which were prepared by following the methods reported in the literature. Infrared spectra were recorded on a PerkinElmer 1720-XFT spectrometer. The C, H, and N analyses were carried out with a PerkinElmer 2400 microanalyzer. NMR spectra were recorded on Bruker DPX300 or AV400 instruments. Chemical shifts are given in parts per million, relative to internal tetramethylsilane (^1H and ^{13}C), and external 85% aqueous H_3PO_4 solutions (^{31}P). DEPT experiments have been carried out for all the compounds reported in this paper.

Synthesis of Complexes $[RuCl_2(\eta^6\text{-arene})\{P(NMe_2)_3\}]$ (arene = C_6H_6 (2a), *p*-cymene (2b), $1,3,5\text{-}C_6H_3Me_3$ (2c), C_6Me_6 (2d)). A solution of the corresponding dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})\}_2]$ (**1a–1d**; 0.194 mmol) in 20 mL of dichloromethane was treated with $P(NMe_2)_3$ (0.352 mL, 1.94 mmol) at room temperature for 3 h. The solution was then evaporated to dryness and the resulting oily residue washed with a 1:2 mixture of diethyl ether/hexanes (4 × 10 mL), thus yielding an orange-red solid that was vacuum-dried. (**2a**):[21] Yield: 0.120 g (75%). Anal. Calcd for $C_{12}H_{24}N_3Cl_2PRu$: C, 34.87; H, 5.85; N, 10.17. Found: C, 34.99; H, 6.01; N, 10.03. IR (Nujol, cm^{-1}): ν 3072 (w), 3058 (w), 2787 (w), 1523 (w), 1495 (w), 1459 (s), 1437 (m), 1377 (m), 1269 (m), 1194 (w), 1179 (s), 1137 (w), 1058 (m), 954 (m). $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 106.8 (s) ppm. ^1H NMR ($CDCl_3$) δ 5.67 (s, 6H, C_6H_6), 2.75 (d, 18H, $^3J_{PH}$ = 9.2 Hz, NMe) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 88.8 (d, $^2J_{PC}$ = 4.0 Hz, C_6H_6), 38.9 (d, $^2J_{PC}$ = 5.0 Hz, NMe) ppm. (**2b**):[22] Yield: 0.134 g (74%). Anal. Calcd for $C_{16}H_{32}N_3Cl_2PRu$: C, 40.94; H, 6.87; N, 8.95. Found: C, 40.75; H, 6.98; N, 9.20. IR (Nujol, cm^{-1}): ν 3064 (w), 3038 (w), 2794 (w), 1543 (w), 1506 (w), 1465 (s), 1404 (w), 1386 (w), 1375 (m), 1275 (s), 1184 (s), 1139 (w), 1088 (w), 1059 (m), 1034 (w), 962 (m). $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 109.8 (s) ppm. ^1H NMR ($CDCl_3$) δ 5.38 (d, 2H, $^3J_{HH}$ = 6.0 Hz, CH of cym), 4.80 (d, 2H, $^3J_{HH}$ = 6.0 Hz, CH of cym), 3.21 (sept, 1H, $^3J_{HH}$ = 7.0 Hz, $CHMe_2$), 2.68 (d, 18H, $^3J_{PH}$ = 9.0 Hz, NMe), 1.85 (s, 3H, Me of cym), 1.34 (d, 6H, $^3J_{HH}$ = 7.0 Hz, $CHMe_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 111.3 (d, $^2J_{PC}$ = 7.0 Hz, C of cym), 97.7 (s, C of cym), 88.6 (d, $^2J_{PC}$ = 6.0 Hz, CH of cym), 85.9 (s, CH of cym), 39.3 (d, $^2J_{PC}$ = 5.0 Hz, NMe), 30.5 (s, $CHMe_2$), 22.0 (s, $CHMe_2$), 17.8 (s, Me of cym) ppm. (**2c**): Yield: 0.141 g (79%). Anal. Calcd for $C_{15}H_{30}N_3Cl_2PRu$: C, 39.56; H, 6.64; N, 9.23. Found: C, 39.77; H, 6.50; N, 9.51. IR (Nujol, cm^{-1}): ν 3080 (w), 3042 (w), 2793 (w), 1538 (w),

dx.doi.org/10.1021/om2006563 |Organometallics 2011, 30, 5442–5451

1525 (m), 1462 (s), 1377 (m), 1276 (s), 1185 (s), 1139 (w), 1065 (m), 1032 (m), 964 (m). $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 113.9 (s) ppm. ^1H NMR ($CDCl_3$) δ 4.84 (s, 3H, $C_6H_3Me_3$), 2.72 (d, 18H, $^3J_{PH}$ = 9.0 Hz, NMe), 2.16 (s, 9H, $C_6H_3Me_3$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 106.1 (d, $^2J_{PC}$ = 3.0 Hz, C of $C_6H_3Me_3$), 83.7 (d, $^2J_{PC}$ = 5.0 Hz, CH of $C_6H_3Me_3$), 39.7 (d, $^2J_{PC}$ = 5.0 Hz, NMe), 18.3 (s, $C_6H_3Me_3$) ppm. (**2d**): Yield: 0.133 g (71%). Anal. Calcd for $C_{18}H_{36}N_3Cl_2PRu$: C, 43.46; H, 7.29; N, 8.45. Found: C, 43.33; H, 7.40; N, 8.60. IR (Nujol, cm^{-1}): ν 2786 (w), 1460 (s), 1378 (s), 1272 (m), 1194 (m), 1171 (m), 1137 (w), 1065 (m), 960 (m). $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 114.9 (s) ppm. ^1H NMR ($CDCl_3$) δ 2.68 (d, 18H, $^3J_{PH}$ = 8.0 Hz, NMe), 1.96 (s, 18H, C_6Me_6) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 90.1 (s, C_6Me_6), 35.2 (br, NMe), 16.0 (s, C_6Me_6) ppm.

Synthesis of Complex [$RuCl_2(\eta^6$-$C_6H_5Me)\{P(NMe_2)_3\}$] (2e). A solution of dimer [$\{RuCl(\mu$-$Cl)(\eta^6$-*p*-cymene$)\}_2$] (**1b**; 0.120 g, 0.196 mmol) in 20 mL of toluene was treated with $P(NMe_2)_3$ (0.356 mL, 1.96 mmol) at 70 °C for 2 h. The solvent was then removed under vacuum, the crude product extracted with dichloromethane (ca. 20 mL), and the extract filtered over Kieselguhr. Concentration of the resulting solution (ca. 2 mL), followed by the addition of hexanes (ca. 30 mL), precipitated an orange solid, which was washed with a 1:2 mixture of diethyl ether/hexanes (4 × 10 mL) and vacuum-dried. Yield: 0.117 g (70%). Anal. Calcd for $C_{13}H_{26}N_3Cl_2PRu$: C, 36.54; H, 6.13; N, 9.83. Found: C, 36.88; H, 6.01; N, 9.96. IR (Nujol, cm^{-1}): ν 3072 (w), 3041 (w), 2791 (w), 1539 (w), 1481 (m), 1452 (s), 1420 (m), 1374 (m), 1277 (s), 1188 (s), 1150 (w), 1063 (m), 989 (w), 963 (m). $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 108.4 (s) ppm. ^1H NMR ($CDCl_3$) δ 5.52 (m, 2H, C_6H_5Me), 5.36 (d, 2H, $^3J_{HH}$ = 6.0 Hz, C_6H_5Me), 5.27 (t, 1H, $^3J_{HH}$ = 6.0 Hz, C_6H_5Me), 2.75 (d, 18H, $^3J_{PH}$ = 9.0 Hz, NMe), 2.30 (s, 3H, C_6H_5Me) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 110.7 (d, $^2J_{PC}$ = 9.0 Hz, C of C_6H_5Me), 89.1 (d, $^2J_{PC}$ = 9.0 Hz, CH of C_6H_5Me), 87.6 (s, CH of C_6H_5Me), 78.8 (s, CH of C_6H_5Me), 39.2 (d, $^2J_{PC}$ = 3.0 Hz, NMe), 18.6 (s, C_6H_5Me) ppm.

Reactivity of Complexes [$RuCl_2(\eta^6$-arene$)\{P(NMe_2)_3\}$] (arene = *p*-cymene (2b), 1,3,5-$C_6H_3Me_3$ (2c), C_6Me_6 (2d)) toward Water. A solution of the appropriate complex [$RuCl_2(\eta^6$-arene$)\{P(NMe_2)_3\}$] (**2b**−**2d**, 0.2 mmol) in 40 mL of water was stirred at room temperature for 48 h. The resulting solution was then evaporated to dryness, and the brown solid residue was washed with hexanes (3 × 10 mL) and recrystallized from dichloromethane/hexanes to give complexes [$RuCl_2(\eta^6$-arene$)(NHMe_2)$] (**7b**−**7d**) as yellow crystals. (**7b**):[40] Yield: 0.032 g (45%). Anal. Calcd for $C_{12}H_{21}Cl_2NRu$: C, 41.03; H, 6.03; N, 3.99. Found: C, 41.20; H, 6.19; N, 3.80. IR (Nujol, cm^{-1}): ν 3231 (m, N-H), 3042 (w), 2728 (w), 1718 (w), 1462 (s), 1377 (m), 1259 (w), 1111 (w), 1088 (w), 1045 (m), 1021 (w), 971 (w). ^1H NMR ($CDCl_3$) δ 5.33 (d, 2H, $^3J_{HH}$ = 5.9 Hz, CH of cym), 5.29 (d, 2H, $^3J_{HH}$ = 5.9 Hz, CH of cym), 3.05 (sept, 1H, $^3J_{HH}$ = 6.8 Hz, $CHMe_2$), 2.91 (d, 6H, $^3J_{PH}$ = 6.4 Hz, NMe), 2.51 (br, 1H, NH), 2.25 (s, 3H, Me of cym), 1.32 (d, 6H, $^3J_{HH}$ = 6.8 Hz, $CHMe_2$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 104.7 (s, C of cym), 93.1 (s, C of cym), 83.0 (s, CH of cym), 78.1 (s, CH of cym), 46.2 (s, NMe), 30.9 (s, $CHMe_2$), 22.0 (s, $CHMe_2$), 18.4 (s, Me of cym) ppm. (**7c**): Yield: 0.028 g (42%). Anal. Calcd for $C_{11}H_{19}Cl_2NRu$: C, 39.17; H, 5.68; N, 4.15. Found: C, 38.89; H, 5.60; N, 4.31. IR (Nujol, cm^{-1}): ν 3240 (m, N-H), 3039 (w), 2790 (w), 1716 (w), 1522 (m), 1459 (s), 1418 (w), 1377 (s), 1365 (m), 1289 (w), 1251 (w), 1127 (w), 1051 (w), 1033 (m), 1020 (m), 982 (w). ^1H NMR ($CDCl_3$) δ 4.99 (s, 3H, $C_6H_3Me_3$), 2.88 (d, 6H, $^3J_{HH}$ = 6.0 Hz, NMe), 2.70 (br, 1H, NH), 2.29 (s, 9H, $C_6H_3Me_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 97.9 (s, C of $C_6H_3Me_3$), 78.3 (s, CH of $C_6H_3Me_3$), 44.7 (s, NMe), 19.0 (s, $C_6H_3Me_3$) ppm. (**7d**): Yield: 0.039 g (51%). Anal. Calcd for $C_{14}H_{25}Cl_2NRu$: C, 44.33; H, 6.64; N, 3.69. Found: C, 44.50; H, 6.53; N, 3.84. IR (Nujol, cm^{-1}): ν 3251 (m, N-H), 2723 (w), 1716 (w), 1464 (s), 1377 (m), 1252 (w), 1132 (w), 1061 (m), 1031 (m), 960 (w). ^1H NMR ($CDCl_3$) δ 2.71 (d, 6H, $^3J_{HH}$ = 4.0 Hz, NMe), 2.55 (br, 1H, NH), 2.13 (s, 18H, C_6Me_6) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 90.2 (s, C_6Me_6), 43.2 (s, NMe), 16.2 (s, C_6Me_6) ppm.

Synthesis of Complexes [$RuCl_2(\eta^6$-arene$)(NHMe_2)$] (arene = *p*-cymene (7b), 1,3,5-$C_6H_3Me_3$ (7c), C_6Me_6 (7d)) from Dimers [$\{RuCl(\mu$-$Cl)(\eta^6$-arene$)\}_2$] (1b−1d). Dimethylamine was bubbled through a solution of the corresponding dimer [$\{RuCl(\mu$-$Cl)(\eta^6$-arene$)\}_2$] (**1b**−**1d**; 0.1 mmol) in 50 mL of tetrahydrofuran at rt for 1.5 h. Concentration of the resulting solution (ca. 2 mL), followed by the addition of hexanes (ca. 30 mL), precipitated a yellow solid, which was washed with a 1:2 mixture of diethyl ether/hexanes (3 × 10 mL) and vacuum-dried. (**7b**): Yield: 0.061 g (87%). (**7c**): Yield: 0.060 g (89%). (**7d**): Yield: 0.064 g (84%).

General Procedure for the Catalytic Hydration Reactions under Conventional Thermal Heating. Under a nitrogen atmosphere, the corresponding nitrile (1 mmol), water (3 mL), and the appropriate ruthenium catalyst, **2a**−**2e** or **7b**−**7d** (0.5−10 mol % of Ru), were introduced into a sealed tube and the reaction mixture stirred at 100 °C for the indicated time (see Tables 1−5 and Scheme 4). The course of the reaction was monitored by regularly taking samples of ca. 20 μL, which, after extraction with CH_2Cl_2 (3 mL), were analyzed by GC. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using diethyl ether as the eluent. The identity of the resulting amides was assessed by comparison of their ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data with those reported in the literature and by their fragmentation in GC/MSD.

Table 6. Crystal Data and Structure Refinement Details for Compound 2e

chemical formula	$C_{13}H_{26}N_3Cl_2PRu$
fw	427.31
T (K)	293(2)
wavelength (Å)	1.5418
cryst syst	monoclinic
space group	$P2_1/c$
cryst size, mm	0.166 × 0.09 × 0.047
a, Å	7.2695(5)
b, Å	11.3844(9)
c, Å	21.116(2)
α, deg	90
β, deg	90.432(7)
γ, deg	90
Z	4
V, Å^3	1747.5(2)
ρ_{calcd}, g cm^{-3}	1.624
μ, mm^{-1}	10.888
$F(000)$	872
θ range, deg	4.19−73.94
index ranges	$-8 \le h \le 5$
	$-14 \le k \le 13$
	$-24 \le l \le 26$
completeness to θ_{max}	95.3%
no. of data collected	5990
no. of unique data	3366 (R_{int} = 0.0650)
no. of params/restraints	188/0
refinement method	full-matrix least-squares on F^2
goodness of fit on F^2	1.061
R1[a] [$I > 2\sigma(I)$]	0.0699
wR2[a] [$I > 2\sigma(I)$]	0.1854
R1 (all data)	0.0819
wR2 (all data)	0.1966
largest diff peak and hole, e Å^{-3}	2.669 and −2.081

[a] $R1 = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$; $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

dx.doi.org/10.1021/om2006563 |*Organometallics* 2011, 30, 5442–5451

General Procedure for the Catalytic Hydration Reactions under MW Irradiation. Under a nitrogen atmosphere, a pressure-resistant septum-sealed glass microwave reactor vial was charged with the corresponding nitrile (1 mmol), water (3 mL), complex **2d** (0.025 mmol; 0.5−10 mol % of Ru), and a magnetic stirring bar. The vial was then placed inside the cavity of a CEM Discover S-Class microwave synthesizer, and the power was held at 150 W until the desired temperature was reached (150 °C). Microwave power was automatically regulated for the remainder of the experiment to maintain the temperature (monitored by a built-in infrared sensor; P_{max} = 25 psi; see Table 4 and Scheme 3). Workup as described above allowed the isolation of the resulting amides in pure form.

X-ray Crystal Structure Determination of Complex 2e. Crystals suitable for X-ray diffraction analysis were obtained by slow diffusion of *n*-pentane into a saturated solution of complex [$RuCl_2$-(η^6-C_6H_5Me){$P(NMe_2)_3$}] (**2e**) in dichloromethane. The most relevant crystal and refinement data are collected in Table 6. Data collection was performed on a Oxford Diffraction Xcalibur Nova single-crystal diffractometer, using Cu−Kα radiation (λ = 1.5418 Å). Images were collected at a 63 mm fixed crystal-detector distance, using the oscillation method, with 1° oscillation and variable exposure time per image (7−35 s). Data collection strategy was calculated with the program CrysAlis^{Pro} CCD.[41] Data reduction and cell refinement was performed with the program CrysAlis^{Pro} RED.[41] An empirical absorption correction was applied using the SCALE3 ABSPACK algorithm as implemented in the program CrysAlis^{Pro} RED.[41] The software package WINGX[42] was used for space group determination, structure solution, and refinement. The structure was solved by Patterson interpretation and phase expansion using DIRDIF.[43]

Isotropic least-squares refinement on F^2 using SHELXL97[44] was performed. During the final stages of the refinements, all the positional parameters and the anisotropic temperature factors of all the non-H atoms were refined. The H atoms were geometrically located, and their coordinates were refined riding on their parent atoms with isotropic displacement parameters set to 1.2 times the U_{eq} of the atoms to which they are attached (1.5 for methyl groups). The function minimized was $[\Sigma w(F_o^2 - F_c^2)/\Sigma w(F_o^2)]^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ (a = 0.1320 and b = 0.000) with $\sigma(F_o^2)$ from counting statistics and $P = (\max(F_o^2,0) + 2F_c^2)/3$. The maximum residual electron density is located near heavier atoms. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[45] Geometrical calculations were made with PARST.[46] The crystallographic plots were made with PLATON.[47]

■ ASSOCIATED CONTENT

Supporting Information. CIF file giving crystallographic data for compound **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: crochetpascale@uniovi.es (P.C.), vcm@uniovi.es (V.C.).

■ ACKNOWLEDGMENT

This work was supported by the Spanish Ministry of Science and Innovation (MICINN; projects CTQ2010-14796/BQU and CSD2007-00006).

■ DEDICATION

†Dedicated to Prof. Christian Bruneau on the occasion of his 60th birthday.

■ REFERENCES

(1) See, for example: (a) Zabicky, J., Ed. *The Chemistry of Amides*; Wiley: New York, 1970. (b) Greenberg, A., Breneman, C. M., Liebman, J. F., Eds. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Wiley: New York, 2000. (c) Deopura, B. L., Gupta, B., Joshi, M., Alagirusami, R., Eds. *Polyesters and Polyamides*; CRC Press: Boca Raton, FL, 2008. (d) Johansson, I. *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley: New York, 2004; Vol. 2, pp 442−463.

(2) For a recent general review on metal-catalyzed approaches to amide bond formation, see: Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405.

(3) See, for example: (a) Bailey, P. D.; Mills, T. J.; Pettecrew, R.; Price, R. A. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, U.K., 2005; Vol. 5, pp 201−294. (b) Dopp, D., Dopp, H., Eds. *Methoden der Organischen Chemie (Houben Weyl)*; Thieme Verlag: Stuttgart, Germany, 1985; Vol. E5(2), pp 1024−1031.

(4) For selected reviews covering the use of enzymes in catalytic nitrile hydrations, see: (a) Kobayashi, M.; Shimizu, S. *Curr. Opin. Chem. Biol.* **2000**, *4*, 95. (b) Endo, I.; Nojori, M.; Tsujimura, M.; Nakasako, M.; Nagashima, S.; Yohda, M.; Odaka, M. *J. Inorg. Biochem.* **2001**, *83*, 247. (c) Mylerová, V.; Martínková, L. *Curr. Org. Chem.* **2003**, *7*, 1279. (d) Kovacs, J. A. *Chem. Rev.* **2004**, *104*, 825. (e) De Santis, G.; Di Cosimo, R. In *Biocatalysis for the Pharmaceutical Industry: Discovery, Development and Manufacturing*; Tao, J., Lin, G.-Q., Liese, A., Eds.; Wiley-VCH: Weinheim, Germany, 2009; pp 153−181. (f) Prasad, S.; Bhalla, T. C. *Biotechnol. Adv.* **2010**, *28*, 725.

(5) For recent examples, see: (a) Yamaguchi, K.; Matsushita, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1576. (b) Bazi, F.; El Badaoui, H.; Tamani, S.; Sokori, S.; Solhy, A.; Macquarrie, D. J.; Sebti, S. *Appl. Catal., A* **2006**, *301*, 211. (c) Polshettiwar, V.; Varma, R. S. *Chem.—Eur. J.* **2009**, *15*, 1582. (d) Mitsudome, T.; Mikami, Y.; Mori, H.; Arita, S.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.* **2009**, 3258. (e) Ishizuka, A.; Nakazaki, Y.; Oshiki, T. *Chem. Lett.* **2009**, *38*, 360. (f) Yamaguchi, K.; Mizuno, N. *Synlett* **2010**, 2365. (g) Kim, A. Y.; Bae, H. S.; Park, S.; Park, S.; Park, K. H. *Catal. Lett.* **2011**, *141*, 685. (h) García-Garrido, S. E.; Francos, J.; Cadierno, V.; Basset, J.-M.; Polshettiwar, V. *ChemSusChem* **2011**, *4*, 104.

(6) For reviews covering the field of metal-mediated and metal-catalyzed nitrile hydrations, see: (a) Parkins, A. W. *Platinum Met. Rev.* **1996**, *40*, 169. (b) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771. (c) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *358*, 1. (d) Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* **2011**, *255*, 949.

(7) See, for example: (a) Yamada, H.; Kobayashi, M. *Biosci., Biotechnol., Biochem.* **1996**, *60*, 1391. (b) van Pelt, S.; van Rantwijk, F.; Sheldon, R. A. *Focus on Catalysis Applications* (supplement to *Chimica Oggi/Chemistry Today*); Teknoscienze Srl: Milano, Italy, **2008**; Vol. 26, pp 2−4. (c) Sanchez, S.; Demain, A. L. *Org. Process Res. Dev.* **2011**, *15*, 224. (d) Li, B.; Su, J.; Tao, J. *Org. Process Res. Dev.* **2011**, *15*, 291.

(8) (a) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521. (b) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* **1993**, *49*, 8805. (c) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225.

(9) (a) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657. (b) Akisanya, J.; Parkins, A. W.; Steed, J. W. *Org. Process Res. Dev.* **1998**, *2*, 274. (c) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A: Chem.* **2000**, *160*, 249. (d) Jiang, X.-B.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Org. Chem.* **2004**, *69*, 2327.

(10) Oshiki, T.; Yamashita, H.; Sawada, K.; Utsunomiya, M.; Takahashi, K.; Takai, K. *Organometallics* **2005**, *24*, 6287.

(11) Goto, A.; Endo, K.; Saito, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3607.

(12) (a) Cadierno, V.; Francos, J.; Gimeno, J. *Chem.—Eur. J.* **2008**, *14*, 6601. (b) Cadierno, V.; Díez, J.; Francos, J.; Gimeno, J. *Chem.—Eur. J.* **2010**, *16*, 9808. (c) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno, V. *Organometallics* **2010**, *29*, 3955.

(13) For related work from other groups, see: (a) Chin, C. S.; Kim, S. Y.; Joo, K.-S.; Won, G.; Chong, D. *Bull. Korean Chem. Soc.* **1999**,

20, 535. (b) Djoman, M. C. K.-B.; Ajjou, A. N. *Tetrahedron Lett.* **2000**, *41*, 4845. (c) Kopylovich, M. N.; Kukushkin, V. Y.; Haukka, M.; Fraústo da Silva, J. J. R.; Pombeiro, A. J. L. *Inorg. Chem.* **2002**, *41*, 4798. (d) Breno, K. L.; Pluth, M. D.; Tyler, D. R. *Organometallics* **2003**, *22*, 1203. (e) Fung, W. K.; Huang, X.; Man, M. L.; Ng, S. M.; Hung, M. Y.; Lin, Z.; Lau, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11539. (f) Breno, K. L.; Pluth, M. D.; Landorf, C. W.; Tyler, D. R. *Organometallics* **2004**, *23*, 1738. (g) Crestani, M. G.; Arévalo, A.; García, J. J. *Adv. Synth. Catal.* **2006**, *348*, 732. (h) Crisóstomo, C.; Crestani, M. G.; García, J. J. *J. Mol. Catal. A: Chem.* **2007**, *266*, 139. (i) Ahmed, T. J.; Zakharov, L. N.; Tyler, D. R. *Organometallics* **2007**, *26*, 5179. (j) Ashraf, S. M.; Berger, L; Nazarov, A. A.; Hartinger, C. G.; Koroteev, M. P.; Nifantév, E. E.; Keppler, B. K. *Chem. Biodiversity* **2008**, *5*, 1640. (k) Ashraf, S. M.; Kandioller, W.; Mendoza-Ferri, M.-G.; Nazarov, A. A.; Hartinger, C. G.; Keppler, B. K. *Chem. Biodiversity* **2008**, *5*, 2060. (l) Crestani, M. G.; Steffen, A.; Kenwright, A. M.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Organometallics* **2009**, *28*, 2904. (m) Crestani, M. G.; García, J. J. *J. Mol. Catal. A: Chem.* **2009**, *299*, 26. (n) Crisóstomo, C.; Crestani, M. G.; García, J. J. *Inorg. Chim. Acta* **2010**, *363*, 1092. (o) Cavarzan, A.; Scarso, A.; Struckul, G. *Green Chem.* **2010**, *12*, 790.

(14) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, U.K., 1998. (b) Anastas, P. T.; Williamson, T. C. *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processes*; Oxford University Press: New York, 1998. (c) Matlack, A. S. *Introduction to Green Chemistry*; Marcel Dekker: New York, 2001. (d) Lancaster, M. In *Handbook of Green Chemistry and Technology*; Clark, J. H., Macquarrie, D. J., Eds.; Blackwell Publishing: Abingdon, U.K., 2002. (e) Lancaster, M. *Green Chemistry: An Introductory Text*; RSC: London, 2002. (f) Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T. *Science* **2002**, *297*, 807. (g) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686. (h) Sheldon, R. A.; Arends, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, 2007.

(15) For leading references in this field, see: (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (b) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741. (c) Li, C.-J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (d) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (e) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (f) Andrade, C. K. Z.; Alves, L. M. *Curr. Org. Chem.* **2005**, *9*, 195. (g) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68. (h) Herrerías, C. I.; Yao, X.; Li, Z.; Li, C. J. *Chem. Rev.* **2007**, *107*, 2546. (i) Lindström, U. M., Ed. *Organic Reactions in Water*; Blackwell Publishing: Oxford, U.K., 2007. (j) Li, C.-J.; Chan, T. H. *Comprehensive Organic Reactions in Aqueous Media*; Wiley-VCH: Weinheim, Germany, 2007. (k) Skouta, R. *Green Chem. Lett. Rev.* **2009**, *2*, 121.(l) Anastas, P. T., Li, C.-J., Eds. *Handbook of Green Chemistry*; Wiley-VCH: Weinheim, Germany, 2010; Vol. 5.

(16) See, for example: (a) Nelson, W. M. *Green Solvents for Chemistry: Perspectives and Practice*; Oxford University Press: New York, 2003. (b) Clark, J. H.; Taverner, S. J. *Org. Process Res. Dev.* **2007**, *11*, 149. (c) Kerton, F. M. *Alternative Solvents for Green Chemistry*; RSC Publishing: Cambridge, U.K., 2009.

(17) Application of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ to the catalytic synthesis of the nonsteroidal anti-inflammatory drug ibuprofenamide by hydration of 2-(4-isobutylphenyl)propionitrile has been communicated in a preliminary report: García-Álvarez, R.; Francos, J.; Crochet, P.; Cadierno, V. *Tetrahedron Lett.* **2011**, *52*, 4218.

(18) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233.

(19) Bennett, M. A.; Huang, T.-N.; Matheson, T. W.; Smith, A. K. *Inorg. Synth.* **1982**, *21*, 74.

(20) Hull, J. W.; Gladfelter, W. L. *Organometallics* **1984**, *3*, 605.

(21) Preparation of complex **2a** by heating a benzene solution of **1a** with an excess of $P(NMe_2)_3$ has been previously described in the literature. The only spectroscopic data given for **2a** in the article were ^{1}H NMR resonances: Werner, H.; Werner, R. *Chem. Ber.* **1982**, *115*, 3766.

(22) Synthesis of complex **2b**, by reacting dimer **1b** with a large excess of $P(NMe_2)_3$ (33 equiv) in dichloromethane for 24 h, has also been previously described: Boshaala, A. M. A.; Simpson, S. J.; Autschbach, J.; Zheng, S. *Inorg. Chem.* **2008**, *47*, 9279.

(23) As one could expect, this arene substitution process is easier starting from the benzene dimer. Thus, complex **2e** was quantitatively formed after heating for 2 h the dimer **1a** with 10 equiv of $P(NMe_2)_3$ in toluene at only 50 °C. Such displacement was not observed with the more electron-rich arenes, and the reaction of **1c** or **1d** with 10 equiv of $P(NMe_2)_3$ in toluene at 70 °C only gave rise to the formation of **2c** or **2d**, respectively, in which the original arene remains coordinated.

(24) For reviews on the chemistry of $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})\}_2]$ dimers, see: (a) Le Bozec, H.; Touchard, D.; Dixneuf, P. H. *Adv. Organomet. Chem.* **1989**, *29*, 163. (b) Bennett, M. A. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, U.K., 1995; Vol. 7, pp 549−602. (c) Bennett, M. A. *Coord. Chem. Rev.* **1997**, *166*, 225. (d) Pigge, F. C.; Coniglio, J. J. *Curr. Org. Chem.* **2001**, *5*, 757. (e) Kündig, E. P. *Top. Organomet. Chem.* **2004**, *7*, 3. (f) Gimeno, J.; Cadierno, V.; Crochet, P. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Oxford, U.K., 2007; Vol. 6, pp 465−550. (g) Therrien, B. *Coord. Chem. Rev.* **2009**, *253*, 493.

(25) In the case of intramolecular processes, that is, formation of tethered-arene complexes, the reactions can proceed under milder reaction conditions. See, for example: (a) Cadierno, V.; Díez, J.; García-Álvarez, J.; Gimeno, J. *Chem. Commun.* **2004**, 1820. (b) Arquier, D.; Vendier, L.; Miqueu, K.; Sotiropoulos, J.-M.; Bastin, S.; Igau, A. *Organometallics* **2009**, *28*, 4945 and references cited therein.

(26) Formation of toluene−ruthenium(II) complexes $[RuCl_2(\eta^6\text{-}C_6H_5Me)(PR_3)]$ usually involves the cleavage of the known dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6H_5Me)\}_2]$ by phosphines or the substitution of a ruthenium-coordinated benzene ligand by toluene. See, for example: (a) Redwine, K. D.; Hansen, H. D.; Bowley, S.; Isbell, J.; Sanchez, M.; Vodak, D.; Nelson, J. H. *Synth. React. Inorg. Met.-Org. Chem.* **2000**, *30*, 379. (b) Nelson, J. H.; Ghebreyessus, K. Y. *Organometallics* **2000**, *19*, 3387. (c) Nelson, J. H.; Ghebreyessus, K. Y. *Synth. React. Inorg. Met.-Org. Chem.* **2003**, *33*, 1329. (d) Chaplin, A. B.; Dyson, P. J. *Organometallics* **2007**, *26*, 2447. (e) Wang, L.; Zhuo, X.-G.; Li, R. X. *Acta Crystallogr., Sect. E* **2008**, *E64*, m429. See also reference 18.

(27) Aktas, H.; Slootweg, J. C.; Schakel, M.; Ehlers, A. W.; Lutz, M.; Spek, A. L.; Lammertsma, K. *J. Am. Chem. Soc.* **2009**, *131*, 6666.

(28) Mitzel, N. W.; Smart, B. A.; Dreihäupl, K.-H.; Rankin, D. W. H.; Schmidbaur, H. *J. Am. Chem. Soc.* **1996**, *118*, 12673.

(29) See, for example: (a) Wang, K.; Emge, T. J.; Goldman, A. S. *Organometallics* **1994**, *13*, 2135. (b) Brunet, J.-J.; Diallo, O.; Donnadieu, B.; Roblou, E. *Organometallics* **2002**, *21*, 3388. (c) Blagg, R. J.; Adams, C. J.; Charmant, J. P. H.; Connelly, N. G.; Haddow, M. F.; Hamilton, A.; Knight, J.; Orpen, A. G.; Ridgway, B. M. *Dalton Trans.* **2009**, 8724.

(30) Complex $[RuCl(NCMe)(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}][PF_6]$ was prepared by treatment of **2d** with $NaPF_6$ in acetonitrile at room temperature for 2 h. Spectroscopic data: $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 115.9 (s) ppm. ^{1}H NMR ($CDCl_3$) δ 2.66 (d, 18H, $^3J_{PH}$ = 9 Hz, NMe), 2.17 (s, 3H, NCMe), 2.05 (s, 18H, C_6Me_6). IR (Nujol, cm $^{-1}$): ν 2360 (C≡N). Complex $[RuCl(NCMe)(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}][PF_6]$ has shown to promote efficiently the hydration of NCMe, yielding to 97% of acetamide after 1 h (1 mol of NCMe, 5 mol % of Ru, 3 mL of water, 100 °C). Similar activity was obtained with catalyst **2d** (see Table 3, entry 1).

(31) Complex **2d** has also proven to promote the hydration of nitriles in different organic solvents in the presence of a small quantity of water, albeit with lower catalytic activities than in pure aqueous medium. For example, benzonitrile was completely transformed into benzamide after 2 h when toluene was used as a solvent, whereas 40% and 75% conversions were reached after 24 h in 1,4-dioxane and 1,2-dimethoxyethane, respectively (5 mol % of **2d**, 100 °C, 3 mL of the corresponding solvent, 4 equiv of water).

(32) For reviews and a recent book on this topic, see: (a) Dallinger, D.; Kappe, O. C. *Chem. Rev.* **2007**, *107*, 2563. (b) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546. (c) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629. (d) Polshettiwar, V., Varma, R. S.,

Eds. *Aqueous Microwave-Assisted Chemistry*; RSC: Cambridge, U.K., 2010.

(33) Details on the anti-inflammatory properties of compounds **4ag** and **4ah** can be found in: (a) Spickett, R. G. W.; Vega, A.; Prieto, J.; Moragues, J.; Marquez, M.; Roberts, D. J. *Eur. J. Med. Chem.* **1976**, *11*, 7. (b) Allegretti, M.; Bertini, R.; Cesta, M. C.; Bizzarri, C.; Di Bitondo, R.; Di Cioccio, V.; Galliera, E.; Berdini, V.; Topai, A.; Zampella, G.; Russo, V.; Di Bello, N.; Nano, G.; Nicolini, L.; Locati, M.; Fantucci, P.; Florio, S.; Colotta, F. *J. Med. Chem.* **2005**, *48*, 4312.

(34) See, for example: (a) Rajasekaran, A.; Sivakumar, P.; Jayakar, B. *Indian J. Pharm. Sci.* **1999**, *61*, 158. (b) Bertini, R.; Bizzarri, C.; Sabbatini, V.; Porzio, S.; Caselli, G.; Allegretti, M.; Cesta, M. C.; Gandolfi, C. A.; Mantovanini, M.; Colotta, F. *PCT International Patent Application* WO2000024710, 2000. (c) Nakatsuka, M.; Nakatani, S.; Okada, S.-I.; Tsuboi, K.; Nishikaku, F. *PCT International Patent Application* WO2001005774, 2001. (d) Doshi, A.; Samant, S. D.; Deshpande, S. G. *Indian J. Pharm. Sci.* **2002**, *64*, 440. (e) Doshi, A.; Deshpande, S. G. *Indian J. Pharm. Sci.* **2002**, *64*, 445. (f) Bertini, R.; Allegretti, M.; Bizzarri, C.; Moriconi, A.; Locati, M.; Zampella, G.; Cervellera, M. N.; Di Cioccio, V.; Cesta, M. C.; Galliera, E.; Martínez, F. O.; Di Bitondo, R.; Troiani, G.; Sabbatini, V.; D'Anniballe, G.; Anacardio, R.; Cutrin, J. C.; Cavalieri, B.; Mainiero, F.; Strippoli, R.; Villa, P.; Di Girolamo, M.; Martin, F.; Gentile, M.; Santoni, A.; Corda, D.; Poli, G.; Mantovani, A.; Ghezzi, P.; Colotta, F. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11791. (g) Allegretti, M.; Cesta, M. C.; Nano, G.; Bertini, R.; Bizzarri, C.; Colotta, F. *PCT International Patent Application* WO2005028425, 2005. (h) Guo, C. B.; Cai, Z. F.; Guo, Z. R.; Feng, Z. Q.; Chu, F. M.; Cheng, G. F. *Chin. Chem. Lett.* **2006**, *17*, 325. (i) Doshi, A.; Deshpande, S. G. *Indian J. Pharm. Sci.* **2007**, *69*, 824. (j) Marjanović, M.; Zorc, B.; Pejnović, L.; Zovko, M.; Kralj, M. *Chem. Biol. Drug Des.* **2007**, *69*, 222.

(35) The use of nitrile hydratases proved ineffective due to the preferential formation of the corresponding carboxylic acids (ibuprofen or ketoprofen) by hydrolysis of **4ag** and **4ah**. See, for example: (a) Beard, T.; Cohen, M. A.; Parratt, J. S.; Turner, N. J.; Crosby, J.; Moilliet, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1085. (b) Fallon, R. D.; Stieglitz, B.; Turner, I. *Appl. Microbiol. Biotechnol.* **1997**, *47*, 156. (c) Effenberger, F.; Graef, B. W. *J. Biotechnol.* **1998**, *60*, 165. (d) Bauer, R.; Knackmuss, H.-J.; Stolz, A. *Appl. Microbiol. Biotechnol.* **1998**, *49*, 89. (e) Rzeznicka, K.; Schätzle, S.; Böttcher, D.; Klein, J.; Bornscheuer, U. T. *Appl. Microbiol. Biotechnol.* **2010**, *85*, 1417.

(36) Formation of ibuprofenamide **4ag** by phase transfer catalyzed oxidation of nitrile **3ag** with basic hydrogen peroxide has been described (up to 70% conversion with 90% selectivity was reached): Yadav, G. D.; Ceasar, J. L. *Org. Process Res. Dev.* **2008**, *12*, 740.

(37) The conventional methods of synthesis of **4ag** and **4ah** involve the conversion of the carboxylic acids ibuprofen and ketoprofen to the corresponding acid chlorides, by action of harmful thionyl chloride, followed by treatment with aqueous or gaseous ammonia. See refs 33 and 34 and: Allegretti, M.; Bertini, R.; Beccari, A.; Moriconi, A.; Aramini, A.; Bizzarri, C.; Colotta, F. *PCT International Patent Application* WO2006063999, 2006.

(38) Cleavage of P—N bonds of free and coordinated dialkylaminophosphines by protic reagents (haloacids, alcohols, water, etc.) are well-documented. See, for example, reference 22 and: (a) Burgada, R. *Bull. Soc. Chim. Fr.* **1972**, 4161. (b) Montemayor, R. G.; Parry, R. W. *Inorg. Chem.* **1973**, *12*, 2482. (c) Kraihanzel, C. S. *J. Organomet. Chem.* **1974**, *73*, 137. (d) Febvay, J.; Casabianca, F.; Riess, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 7985. (e) Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699. (f) Dyer, P. W.; Fawcett, J.; Hanton, M. J.; Kemmitt, R. D. W.; Padda, R.; Singh, N. *Dalton Trans.* **2003**, 104. (g) Miklášová, N.; Julínek, O.; Mešková, M.; Setnička, V.; Urbanová, M.; Putala, M. *Tetrahedron Lett.* **2010**, *51*, 1966.

(39) Decomposition of the free ligand $P(NMe_2)_3$ into several uncharacterized compounds was also observed with time in aqueous solution by $^{31}P\{^1H\}$ NMR spectroscopy.

(40) Complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})(NHMe_2)]$ (**7b**) has been previously described in the literature: DellAmico, D. B.; Calderazzo, F.; Labella, L.; Marchetti, F.; Sbrana, E. *J. Organomet. Chem.* **2002**, *651*, 52.

(41) *CrysAlis^{Pro}CCD* and *CrysAlis^{Pro}RED*; Oxford Diffraction Ltd.: Oxford, UK, 2008.

(42) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.

(43) Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; García-Granda, S.; Gould, R. O.; Smits, J. M. M.; Smykalla, C. *The DIRDIF Program System*; Technical Report of the Crystallographic Laboratory; University of Nijmegen: Nijmegen, The Netherlands, 1999.

(44) Sheldrick, G. M. *SHELXL97: Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.

(45) *International Tables for X-Ray Crystallography*; Kynoch Press: Birminghan, U.K., 1974; Vol. IV (present distributor: Kluwer Academic Publishers: Dordrecht, The Netherlands).

(46) Nardelli, M. *Comput. Chem.* **1983**, *7*, 95.

(47) Spek, A. L. *PLATON: A Multipurpose Crystallographic Tool*; University of Utrecht: Utrecht, The Netherlands, 2007.

CAPÍTULO 1

1.4.- CONCLUSIONES

De los resultados descritos en el presente *Capítulo 1* pueden extraerse las siguientes conclusiones:

- ✓ Se ha evaluado la capacidad de las piridil-fosfinas PPh_2py, PPh_2(py-4-NMe_2) y PPh_2(py-6-*terc*-amil), las amino-aril-fosfinas 2-$Ph_2PC_6H_4CH_2NHR$, 3-$Ph_2PC_6H_4CH_2NHR$ y 4-$Ph_2PC_6H_4CH_2NHR$, y la amino-fosfina $P(NMe_2)_3$, para actuar como ligandos cooperativos en procesos de hidratación de nitrilos empleando especies de tipo [$RuCl_2(\eta^6$-areno)(PR_3)] como catalizadores, en agua y a pH neutro.

- ✓ En el caso de las piridil-fosfinas su efecto cooperativo resultó ser despreciable. De hecho, los catalizadores resultantes mostraron una actividad muy baja debido a la alta tendencia de los ligandos a quelatarse, bloqueando así la esfera de coordinación del metal.

- ✓ Por el contrario, las amino-aril-fosfinas ejercen un efecto cooperativo significativo, activando la molécula de agua por desprotonación, *i.e.* actúan como bases de Brønsted internas. No obstante, la actividad catalítica de los complejos Ru(II)-areno sintetizados con estos ligandos fue tan sólo moderada.

- ✓ Los mejores resultados se obtuvieron con la amino-fosfina $P(NMe_2)_3$, capaz de activar las moléculas de agua de forma efectiva a través de enlaces de hidrógeno. En particular, el derivado [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) ha mostrado una actividad catalítica remarcable, llegando a alcanzarse con él valores de TOF de hasta 11400h^{-1}, los más altos descritos hasta la fecha para reacciones de hidratación de nitrilos que transcurren en un medio puramente acuoso. Es destacar también la alta generalidad y selectividad

mostrada por **1.41d**, que tolera la presencia de una gran variedad de grupos funcionales en los sustratos.

Capítulo 2

Procesos de formación de amidas primarias a partir de aldoximas y aldehídos catalizados por rutenio en medio acuoso

CAPÍTULO 2

2.1.- ANTECEDENTES Y OBJETIVOS

Antecedentes

Como se ha comentado en la *Introducción* del capítulo anterior, la utilización de catalizadores metálicos ha permitido en años recientes el desarrollo de nuevas rutas sintéticas para la formación de amidas empleando materiales de partida distintos de los ácidos carboxílicos y sus derivados. En el caso particular de las amidas primarias ($RC(=O)NH_2$), además de las reacciones de hidratación de nitrilos discutidas previamente, se han descrito procesos catalíticos que permiten acceder a este tipo de derivados a partir de sustratos tales como aldoximas, aldehídos, alcoholes y aminas primarias, azidas o halogenuros de arilo/alquenilo (Figura 2.1).[1]

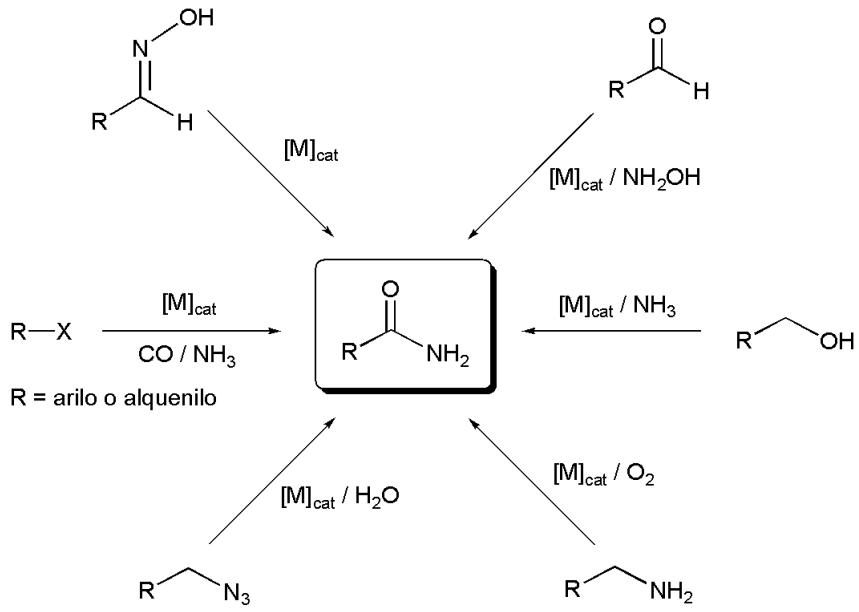
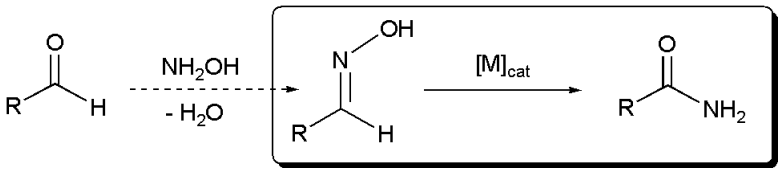


Figura 2.1: Diferentes procesos catalíticos para la generación de amidas primarias.

De entre todos estos procesos, el reordenamiento catalítico de aldoximas (Esquema 2.1) es particularmente atractivo ya que *(i)* transcurre con una economía total de átomos, y *(ii)* hace uso de materias primas muy

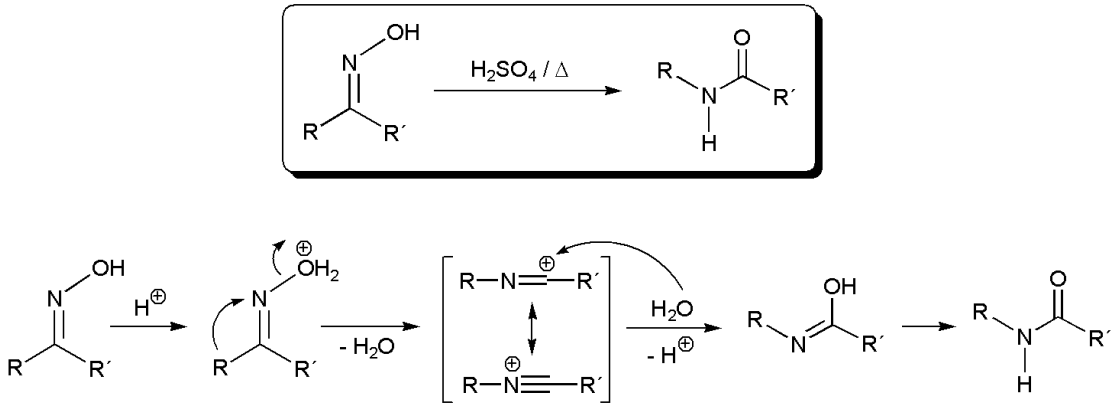
[1] Revisiones bibliográficas cubriendo este campo: (a) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405; (b) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471; (c) R. García-Álvarez, P. Crochet, V. Cadierno, *Green Chem.* **2013**, *15*, 46.

accesibles como son las aldoximas, compuestos que se generan fácilmente por condensación de un aldehído con hidroxilamina.[2]



Esquema 2.1: El reordenamiento catalítico de aldoximas en amidas primarias.

Dicho proceso catalítico está íntimamente relacionado con el conocido como "reordenamiento de Beckmann", en el que una cetoxima (R y R´ ≠ H) es transformada en una amida secundaria por acción de un ácido fuerte, generalmente ácido sulfúrico, a alta temperatura (Esquema 2.2).[3,4] No obstante, debemos hacer notar que el tratamiento de aldoximas con ácidos no suele conducir a la formación de las amidas primarias esperadas, generándose en su lugar los correspondientes nitrilos a través de un simple proceso de deshidratación.[4] Esto es debido a la marcada tendencia que presenta el átomo de hidrógeno para actuar como grupo saliente. De hecho, son muy pocos los ejemplos descritos en la bibliografía sobre la formación de amidas primarias a partir de aldoximas empleando reactivos ácidos.[5]



Esquema 2.2: El reordenamiento de Beckmann y su mecanismo.

---

[2] Ver, por ejemplo: *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids* (eds. Z. Rappoport, J. F. Liebman), John Wiley & Sons, Chichester, **2009**.
[3] E. Beckmann, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988.
[4] Revisiones bibliográficas sobre el reordenamiento Beckmann de cetoximas: (a) R. E. Gawley, *Org. React.* **1988**, *35*, 1; (b) R. R. Kumar, K. A. Vanithan, M. Balasubramanian, en *Name Reactions for Homologations - Part 2* (ed. J. J. Li), John Wiley & Sons, Hoboken, **2009**, pp. 274-292.
[5] (a) E. C. Horning, V. L. Stromberg, *J. Am. Chem. Soc.* **1952**, *74*, 5151; (b) D. S. Hoffenberg, C. R. Hauser, *J. Org. Chem.* **1955**, *20*, 1496.

Aunque la utilización de sales metálicas para promover el reordenamiento de aldoximas ha sido documentada de forma esporádica desde los años sesenta,[6] no es hasta el año 2003 en que esta reacción comienza a ser considerada como una herramienta sintética con utilidad práctica para la generación de amidas primarias. En ese año, S. Chang y colaboradores describen como el catalizador de Wilkinson, *i.e.* $[RhCl(PPh_3)_3]$, es capaz de llevar a cabo por primera vez esta transformación de forma eficiente y selectiva, bajo condiciones de reacción no demasiado drásticas.[7] Así, empleando una carga de catalizador del 5 mol% y tolueno o DMF como disolvente, dichos autores obtuvieron las amidas esperadas con buenos rendimientos (74-94%) tras 2-5 horas de calentamiento a 150 ºC. Un buen número de aldoximas aromáticas, heteroaromáticas y α,β-insaturadas pudieron ser transformadas en sus correspondientes amidas, demostrando la generalidad de este protocolo.

Con posterioridad a este trabajo, se han descrito diferentes complejos metálicos de rodio (ej. [RhCl(NHC)(cod)] (NHC = carbeno *N*-heterocíclico; cod = 1,5-ciclooctadieno),[8] iridio (ej. $[\{IrCp^*Cl(\mu\text{-}Cl\}_2]$ (Cp* = pentametil-ciclopentadienilo),[9] rutenio (ej. $[RuCl_2(dmso)_4]$ (dmso = dimetilsulfóxido) o $[RuH_2(CO)(PPh_3)_3]$)[10] y oro (ej. [AuCl(NHC)]),[11] así como una serie de ácidos de Lewis (ej. $In(NO_3)_3$, $ZnCl_2$, $Cu(OAc)_2$ o $NiCl_2{\cdot}6H_2O$),[12] activos en el proceso. En la mayoría de estos estudios se emplearon tolueno o xileno como disolvente y temperaturas de trabajo comprendidas en el intervalo 80-160 ºC.

---

[6] Ver, por ejemplo: (a) L. Field, P. B. Hughmark, S. H. Shumaker, W. S. Marshall, *J. Am. Chem. Soc.* **1961**, *83*, 1983; (b) A. J. Leusink, T. G. Meerbeek, J. G. Noltes, *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 123; (c) A. J. Leusink, T. G. Meerbeek, J. G. Noltes, *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 142; (d) T. Setsuda, *Jpn. Kokai Tokkyo Koho* JP 52128302, **1977**; (e) S. Komiya, H. Shimazu, T. Tamashima, *Jpn. Kokai Tokkyo Koho* JP 2003342245, **2003**.

[7] S. Park, Y. Choi, H. Han, S. H. Yang, S. Chang, *Chem. Commun.* **2003**, 1936.

[8] N. Kim, J. Lee, H.-Y. Lee, S. Chang, *Adv. Synth. Catal.* **2009**, *351*, 1807.

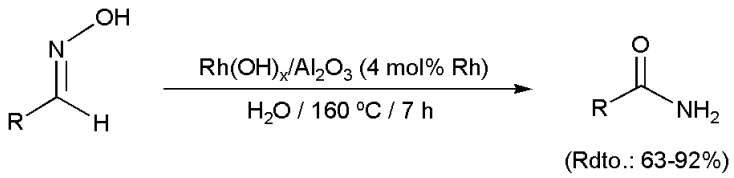
[9] N. A. Owston, A. J. Parker, J. M. J. Williams, *Org. Lett.* **2007**, *9*, 73.

[10] (a) N. A. Owston, A. J. Parker, J. M. J. Williams, *Org. Lett.* **2007**, *9*, 3599; (b) D. Gnanamgari, R. H. Crabtree, *Organometallics* **2009**, *28*, 922; (c) J. F. Hull, S. T. Hilton, R. H. Crabtree, *Inorg. Chim. Acta* **2010**, *363*, 1243; (d) P. Kumar, A. K. Singh, R. Pandey, D. S. Pandey, *J. Organomet. Chem.* **2011**, *696*, 3454.

[11] R. S. Ramón, J. Bosson, S. Díez-González, N. Marion, S. P. Nolan, *J. Org. Chem.* **2010**, *75*, 1197.

[12] (a) C. L. Allen, C. Burel, J. M. J. Williams, *Tetrahedron Lett.* **2010**, *51*, 2724; (b) C. L. Allen, S. Davulcu, J. M. J. Williams, *Org. Lett.* **2010**, *12*, 5096; (c) S. K. Sharma, S. D. Bishopp, C. L. Allen, R. Lawrence, M. J. Bamford, A. A. Lapkin, P. Plucinski, R. J. Watson, J. M. J. Williams, *Tetrahedron Lett.* **2011**, *52*, 4252.

Sin embargo, a pesar del interés creciente en el uso de agua como disolvente en síntesis orgánica,[13] hasta la fecha se ha prestado poca atención al estudio de este reordenamiento en medio acuoso. De hecho, el único precedente conocido fue publicado por N. Mizuno y colaboradores en 2007 empleando hidróxido de rodio soportado en alúmina ($Rh(OH)_x/Al_2O_3$) como catalizador (Esquema 2.3).[14] Las reacciones, llevadas a cabo en agua pura y con una carga de metal del 4 mol%, condujeron a las amidas deseadas con altos rendimientos tras 7 h de calentamiento a 160 ºC, pudiendo además recuperarse fácilmente el sistema catalítico por filtración, y reutilizarse sin pérdidas significativas de actividad.



R = grupos arilo, heteroarilo o alquenilo (16 ejemplos)

Esquema 2.3: Reordenamiento catalítico de aldoximas en agua catalizado por $Rh(OH)_x/Al_2O_3$.

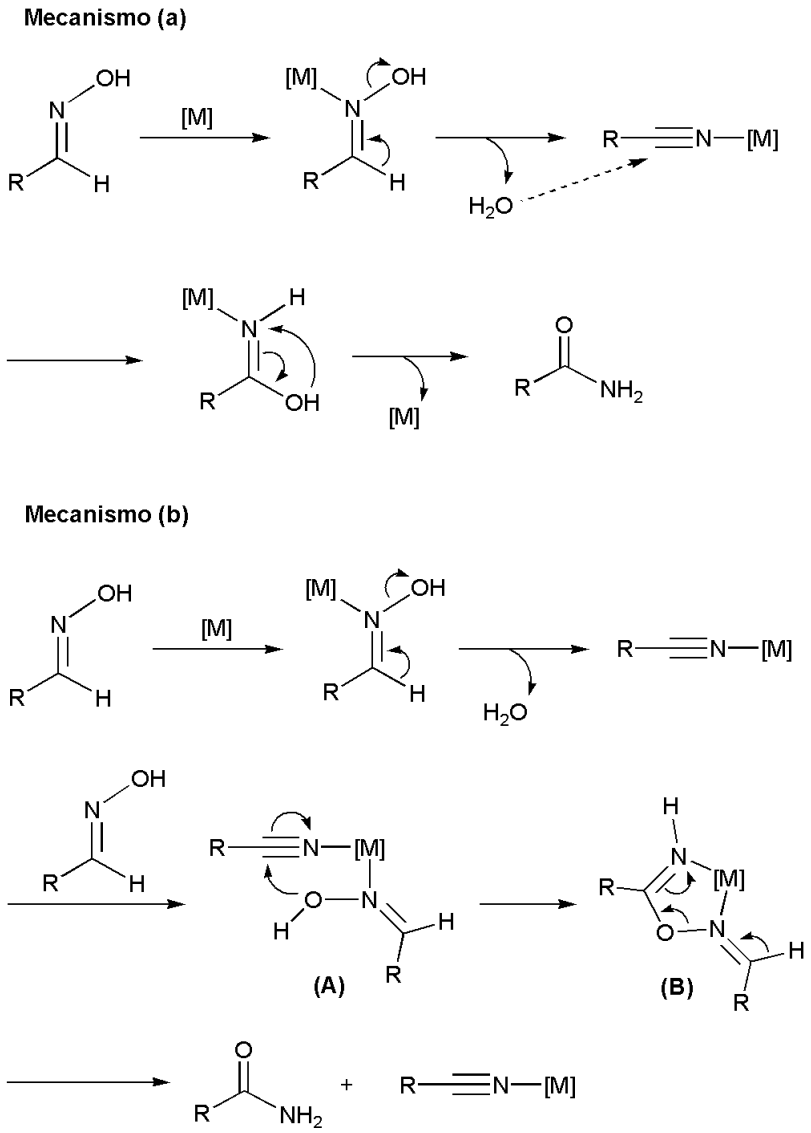
En lo que respecta al mecanismo por el que transcurre esta transformación catalítica, la propuesta comúnmente aceptada involucra dos etapas de reacción independientes. En la primera de ellas, el catalizador metálico actúa como un ácido de Lewis deshidratando la aldoxima.[15] De esta forma se genera un nitrilo, que se convierte posteriormente en la amida final a través de un proceso de hidratación

[13] (a) C. J. Li, T. H. Chan, en *Comprehensive Organic Reactions in Aqueous Media*, John Wiley & Sons, New Jersey, **2007**; (b) *Organic Reactions in Water: Principles, Strategies and Applications* (ed. U. M. Lindstrom), Blackwell Publishing Ltd., Oxford, **2007**; (c) *Handbook of Green Chemistry (vol. 5)* (eds. P. T. Anastas, C.-J. Li), Wiley-VCH, Weinheim, **2010**; (d) *Water in Organic Synthesis* (ed. S. Kobayashi), Thieme-Verlag, Stuttgart, **2012**; (e) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications* (eds. B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **1998**; (f) F. Joó, en *Aqueous Organometallic Catalysis*, Kluver, Dordrecht, **2001**; (g) *Metal-Catalyzed Reactions in Water* (eds. P. H. Dixneuf, V. Cadierno), Wiley-VCH, Weinheim, **2013**.

[14] (a) H. Fujiwara, Y. Ogasawara, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2007**, *46*, 5202; (b) H. Fujiwara, Y. Ogasawara, M. Kotani, K. Yamaguchi, N. Mizuno, *Chem. Asian J.* **2008**, *3*, 1715.

[15] La deshidratación de aldoximas catalizada por complejos de metales de transición es un proceso bien conocido. Ejemplos recientes se pueden encontrar en: (a) H. S. Kim, S. Kim, J. N. Kim, *Tetrahedron Lett.* **2009**, *50*, 1717; (b) N. Jiang, A. J. Ragauskas, *Tetrahedron Lett.* **2010**, *51*, 4479; (c) Y.-T. Li, B. S. Liao, H.-P. Chen, S.-T. Liu, *Synthesis* **2011**, 2639.

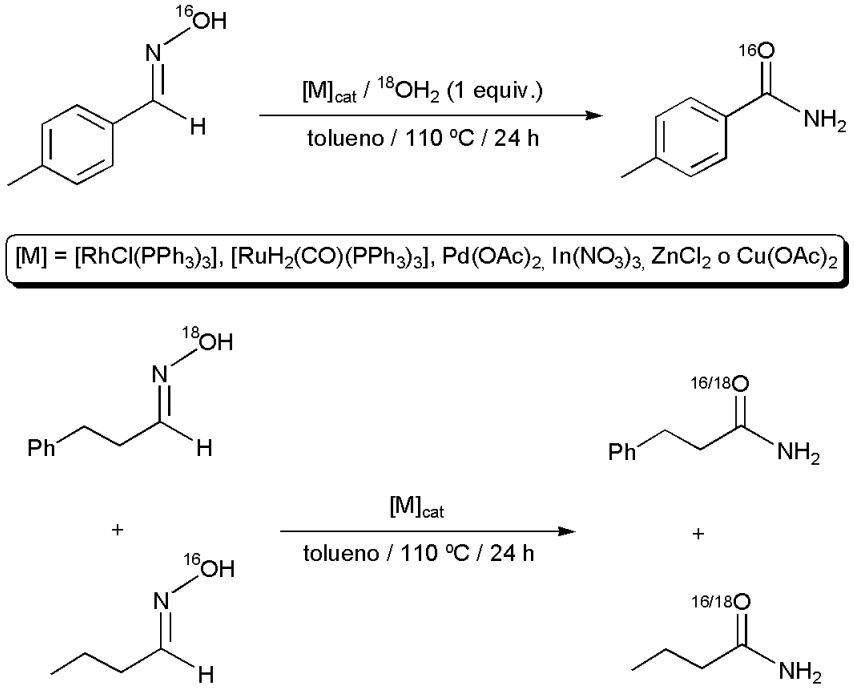
clásico del triple enlace C≡N (mecanismo (a) en el Esquema 2.4). La operatividad de este mecanismo ha venido por lo general avalada por el hecho de que, en la mayoría de los casos, se observa la formación de los correspondientes nitrilos como productos secundarios de reacción.



Esquema 2.4: Mecanismos propuestos para el reordenamiento catalítico de aldoximas.

No obstante, estudios mecanísticos recientes llevados a cabo por J. M. J. Williams y colaboradores empleando los catalizadores $[RhCl(PPh_3)_3]$, $[RuH_2(CO)(PPh_3)_3]$, $Pd(OAc)_2$, $In(NO_3)_3$, $ZnCl_2$ y $Cu(OAc)_2$ han puesto de manifiesto que, en la etapa final de hidratación de la especie nitrilo intermedia, es en realidad una segunda molécula de aldoxima, y no la molécula de agua liberada en la primera etapa, quien actúa como agente

hidratante (mecanismo (b) en el Esquema 2.4).[16,17] Así, la coordinación simultánea del nitrilo y la segunda molécula de aldoxima al centro metálico generaría un intermedio **A**, que evolucionaría por ataque intramolecular del átomo de oxígeno de la aldoxima al átomo de carbono del nitrilo formando un metalaciclo de cinco miembros **B**. Una reorganización posterior de dicho metalaciclo liberaría la amida final.



Esquema 2.5: Estudios de marcaje isotópico llevados a cabo por Williams y col.

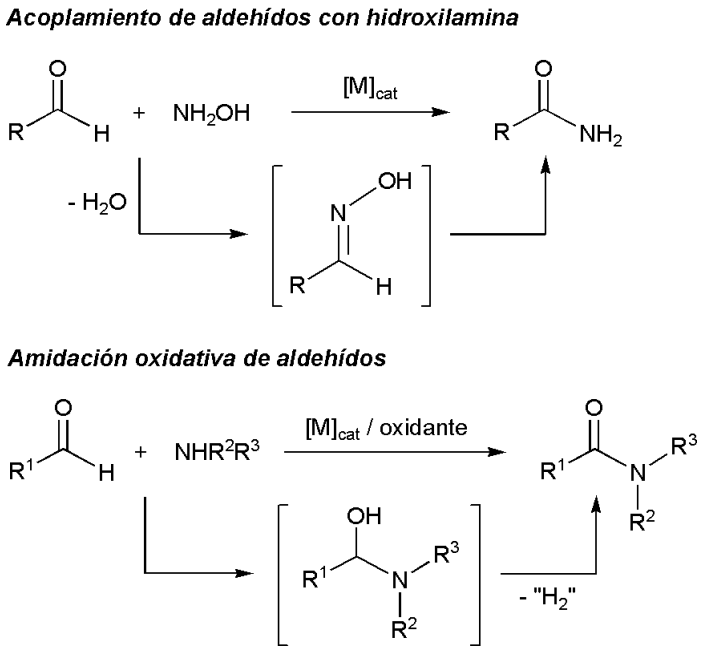
Las evidencias experimentales obtenidas por J. M. J. Williams y colaboradores para proponer este mecanismo alternativo fueron las siguientes (ver Esquema 2.5): Al llevar a cabo el reordenamiento de la 4-metilbenzaldoxima en presencia de un equivalente de agua marcada isotópicamente con ^{18}O, con ninguno de los catalizadores empleados se observó la incorporación de ^{18}O en el producto final de reacción, *i.e.* la 4-metilbenzamida. Sin embargo, al llevar a cabo el reordenamiento de la 3-fenilpropionaldoxima marcada con ^{18}O en presencia de un equivalente de

[16] C. L. Allen, R. Lawrence, L. Emmett, J. M. J. Williams, *Adv. Synth. Catal.* **2011**, *353*, 3262.

[17] Hidrataciones catalíticas de nitrilos en amidas empleando aldoximas como fuente de agua han sido descritas en: (a) E. S. Kim, J. N. Kim, *Tetrahedron Lett.* **2009**, *50*, 2973; (b) J. Lee, M. Kim, S. Chang, H.-Y. Lee, *Org. Lett.* **2009**, *11*, 5598; (c) E. S. Kim, J. N. Kim, *Tetrahedron Lett.* **2010**, *51*, 1598; (d) E. S. Kim, Y. M. Kim, J. N. Kim, *Bull. Korean Chem. Soc.* **2010**, *31*, 700; (e) Á. Kiss, Z. Hell, *Tetrahedron Lett.* **2011**, *52*, 6021; (f) X.-Y. Ma, Y. He, Y.-L. Hu, M. Lu, *Tetrahedron Lett.* **2012**, *53*, 449; (g) X. Ma, Y. He, P. Wang, M. Lu, *Appl. Organomet. Chem.* **2012**, *26*, 377.

butiraldoxima no marcada, con todos los catalizadores empleados se produjo la incorporación de ^{18}O tanto en la 3-fenilpropionamida como en la butiramida finales. En su conjunto, estos resultados sólo pueden explicarse a través del ataque nucleofílico de una segunda molécula de aldoxima sobre el nitrilo coordinado, ya que si fuese al agua quien actuase como nucleófilo en el primer experimento debería de haberse incorporado ^{18}O en el producto final.

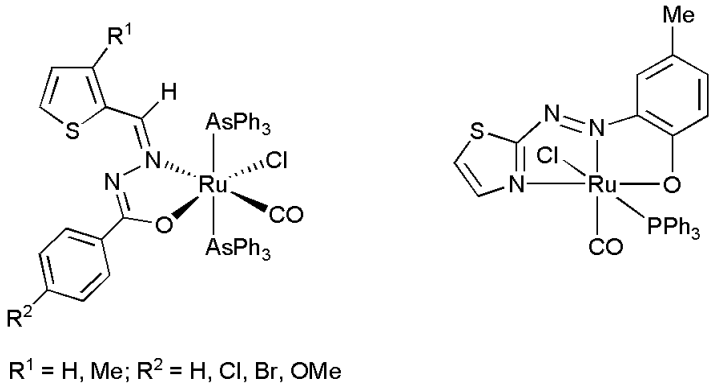
Por otro lado, como se ha comentado anteriormente, las aldoximas se preparan generalmente por condensación de aldehídos con hidroxilamina. No es de extrañar por tanto que, durante los últimos años, se hayan dedicado esfuerzos importantes al desarrollo de procesos *one-pot* que permitan la formación de amidas primarias por acoplamiento directo de aldehídos y derivados de la hidroxilamina, *vía* reordenamiento de la correspondiente aldoxima que se generaría *in situ* (Esquema 2.6). Estos protocolos presentan un elevado interés dada la amplia disponibilidad comercial de los aldehídos, siendo además complementarios a las reacciones de amidación oxidativa de aldehídos, comúnmente aplicadas en la preparación de amidas secundarias y terciarias (Esquema 2.6).[18]



Esquema 2.6: Procesos catalíticos para la formación de amidas a partir de aldehídos.

[18] Para una revisión bibliográfica sobre las reacciones de amidación oxidativa de aldehídos, ver: K. Ekoue-Kovi, C. Wolf, *Chem. Eur. J.* **2008**, *14*, 6302.

Sistemas activos en el reordenamiento catalítico de aldoximas, tales como $Pd(OAc)_2$,[19] $In(NO_3)_3$,[12a] $ZnCl_2$,[12a] $[RuCl_2(dmso)_4]$[10b] y $[RuCl_2(PPh_3)(terpy)]$ (terpy = 2,2′:6′,2″-terpiridina),[10c] han sido ensayados con éxito en este proceso de acoplamiento. Se han descrito igualmente metodologías eficientes basadas en el empleo de $CuSO_4 \cdot 5H_2O$,[20] cloruro de sílica (gel de sílice tratada con $SOCl_2$)[21] o los derivados octaédricos de rutenio(II) recogidos en la Figura 2.2.[22] Todos estos sistemas operan en medio orgánico (tolueno o acetonitrilo), a alta temperatura (90-130 ºC), y empleando la sal comercial $NH_2OH \cdot HCl$ en presencia de una base (para neutralizar el HCl desprendido en el proceso de formación de la aldoxima intermedia).



R^1 = H, Me; R^2 = H, Cl, Br, OMe

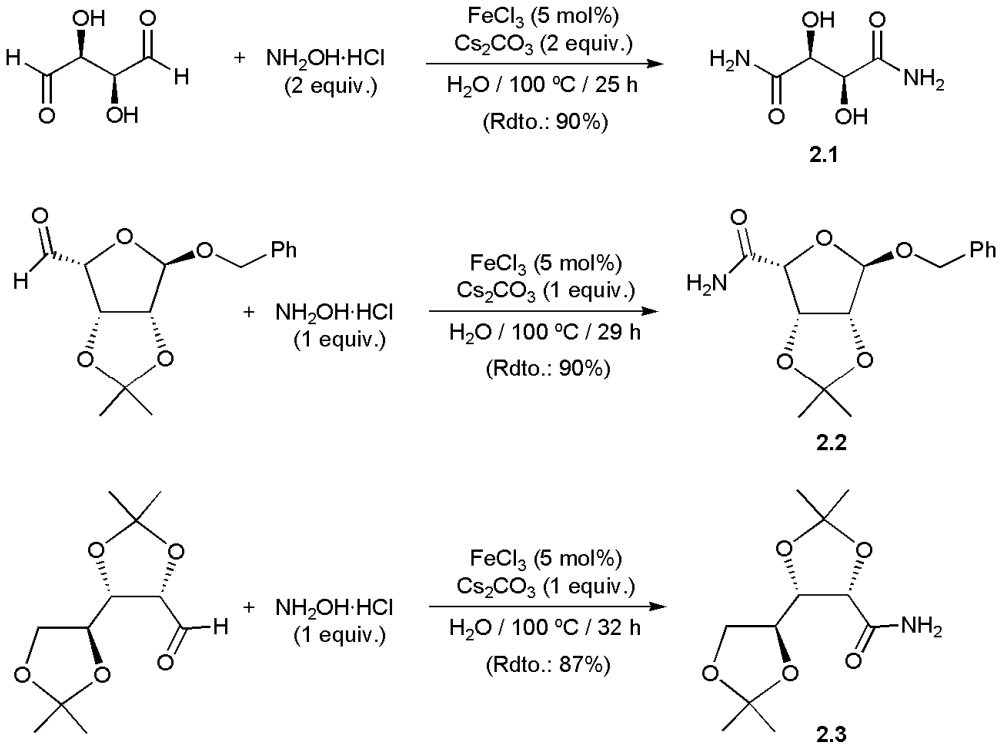
Figura 2.2: Complejos de Ru(II) activos en la formación de amidas primarias a partir de aldehídos.

En la bibliografía también se encuentran descritos unos pocos ejemplos de sistemas catalíticos activos en agua. Así, empleando cantidades catalíticas de $Rh(OH)_x/Al_2O_3$ (4 mol% de Rh) y una temperatura de trabajo de 160 ºC, N. Mizuno y colaboradores han descrito la transformación de una gran variedad de aldehídos (aromáticos, heteroaromáticos, α,β-insaturados y alifáticos) en las correspondientes amidas primarias por reacción con $(NH_2OH)_2 \cdot H_2SO_4$ en agua (6-9 horas de calentamiento).[14] No obstante, hay que hacer notar que en estas reacciones se forman cantidades variables de los correspondientes nitrilos, aldoximas y ácidos carboxílicos como productos secundarios. Como ventaja podemos

[19] M. A. Ali, T. Punniyamurthy, *Adv. Synth. Catal.* **2010**, *352*, 288.
[20] N. C. Ganguly, S. Roy, P. Mondal, *Tetrahedron Lett.* **2012**, *53*, 1413.
[21] B. Datta, M. A. Pasha, *Bull. Korean Chem. Soc.* **2012**, *33*, 2129.
[22] (a) N. Raja, M. U. Raja, R. Ramesh, *Inorg. Chem. Commun.* **2012**, *19*, 51; (b) R. N. Prabhu, R. Ramesh, *RSC Adv.* **2012**, *2*, 4515.

destacar que este catalizador heterogéneo pudo ser reciclado, tras un simple proceso de filtración, sin apenas pérdida en la actividad catalítica.

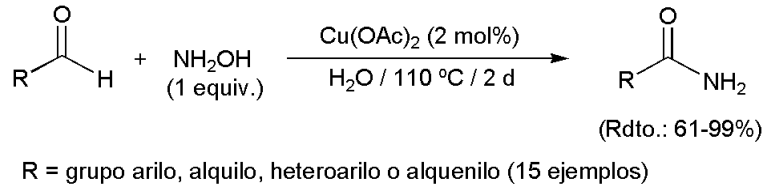
Transformaciones más selectivas de una gran variedad de aldehídos en agua han sido descritas posteriormente por D. Chakraborty[23] y K. N. Singh[24] empleando los ácidos de Lewis $FeCl_3$ (5 mol%) y $Sc(OTf)_3$ (10 mol%) como catalizadores. Con el primero de ellos, las reacciones transcurren limpiamente a 100 ºC empleado cloruro de hidroxilamonio ($NH_2OH{\cdot}HCl$) en combinación con Cs_2CO_3, si bien es cierto que los tiempos de calentamiento requeridos para obtener las amidas con buenos rendimientos son por lo general largos (14-32 horas). Cabe destacar que este protocolo demostró ser útil en la síntesis de un buen número de amidas con actividad biológica, tales como la (2*S*,3*S*)-2,3-dihidroxisuccinamida **2.1** o los derivados de la *β*-D-ribofuranosa **2.2** y **2.3** (ver Esquema 2.7).[23] En el caso del $Sc(OTf)_3$, las reacciones se llevaron a cabo empleando una combinación de $NH_2OH{\cdot}HCl$ y Na_2CO_3, e irradiación microondas como fuente de calentamiento (300 W; 125 ºC), lo que permitió reducir drásticamente los tiempos de reacción (15-35 min).



Esquema 2.7: Síntesis de las amidas **2.1-2.3** catalizada por $FeCl_3$ en agua.

[23] R. R. Gowda, D. Chakraborty, *Eur. J. Org. Chem.* **2011**, 2226.
[24] B. K. Allam, K. N. Singh, *Tetrahedron Lett.* **2011**, *52*, 5851.

Muy recientemente, con nuestro trabajo en este campo ya iniciado, el grupo de M. Yus ha descrito también un protocolo para el acoplamiento de aldehídos con hidroxilamina en agua catalizado por acetato de cobre(II), otro ácido de Lewis barato y que además es posible reciclar (Esquema 2.8).[25] A diferencia de los casos anteriores, el empleo directo de hidroxilamina en lugar de sales de hidroxilamonio evita la adición de una base al medio de reacción para eliminar el ácido generado durante la formación de la aldoxima. De esta forma se consigue minimizar la generación de subproductos. No obstante, los tiempos de reacción requeridos con este catalizador son extremadamente largos (2 días), lo que resulta inconveniente para posibles aplicaciones prácticas.



Esquema 2.8: Síntesis de amidas primarias a partir de aldehídos catalizada por $Cu(OAc)_2$ en agua.

Objetivos

Los antecedentes que acabamos de comentar ponen de manifiesto la escasez actual de sistemas catalíticos capaces de promover la formación de amidas primarias en agua a partir de aldoximas y aldehídos, no habiéndose documentado además ejemplos de catalizadores basados en rutenio que operen en este disolvente. Este hecho nos animó a estudiar este tipo de transformaciones empleando nuestros catalizadores de tipo rutenio(II)-areno. Dadas las excelentes prestaciones mostradas por el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**) (Figura 2.3) en los procesos de hidratación de nitrilos en agua discutidos en el *Capítulo 1*,[26] pensamos que este derivado era el candidato ideal para desarrollar el trabajo.

[25] A. Martínez-Asencio, M. Yus, D. J. Ramón, *Tetrahedron* **2012**, *68*, 3948.
[26] (a) R. García-Álvarez, J. Francos, P. Crochet, V. Cadierno, *Tetrahedron Lett.* **2011**, *52*, 4218; (b) R. García-Álvarez, J. Díez, P. Crochet, V. Cadierno, *Organometallics* **2011**, *30*, 5442.

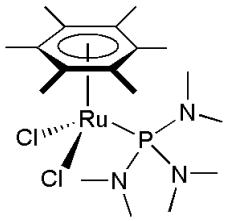


Figura 2.3: Estructura del complejo [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**).

Así, en este *Capítulo 2* se describe:

1.- El comportamiento catalítico del complejo [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) en procesos de reordenamiento de aldoximas en agua, junto con un estudio cinético de su mecanismo de acción.

2.- Nuevos protocolos para la síntesis *one-pot* de amidas primarias en agua a partir de aldehídos, empleando como catalizador el complejo [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) y cloruro de hidroxilamonio, o directamente hidroxilamina, como fuente de la unidad NH_2.

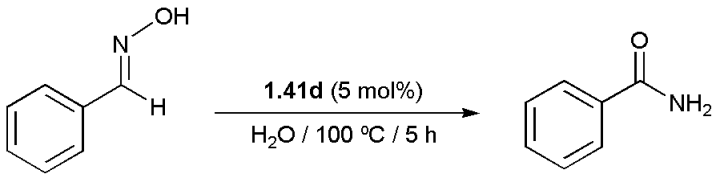
CAPÍTULO 2

2.2.- DISCUSIÓN DE RESULTADOS

Como se acaba de comentar en la *Introducción* del presente *Capítulo*, el objetivo de nuestro trabajo ha sido la puesta a punto de metodologías sintéticas que permitan acceder a amidas primarias en agua por reordenamiento catalítico de aldoximas, y por acoplamiento de aldehídos con derivados de la hidroxilamina, empleando el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) como catalizador. Este derivado fue seleccionado de entre todos los complejos areno-rutenio(II) sintetizados en el *Capítulo 1* por la remarcable actividad catalítica que mostró en las reacciones de hidratación de nitrilos, procesos que están íntimamente relacionados con los que se abordan en este *Capítulo 2*.

2.2.1.- Estudio de la actividad catalítica del complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (1.41d) en el reordenamiento de aldoximas en amidas primarias en agua.

La capacidad del complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) para promover la isomerización catalítica de aldoximas fue inicialmente evaluada utilizando la aldoxima comercial (*E*)-benzaldoxima (disposición *anti* de los grupos de mayor prioridad Ph y OH sobre el doble enlace C=N) como sustrato modelo. Así, llevando a cabo la reacción en las mismas condiciones experimentales que las empleadas previamente en los estudios de hidratación de nitrilos con este derivado (disolución 0.33 M del sustrato en agua pura, una carga de catalizador del 5 mol% y una temperatura de trabajo de 100 ºC), encontramos que **1.41d** era capaz de transformar la (*E*)-benzaldoxima en benzamida con un rendimiento determinado por CG del 98% tras 5 horas de calentamiento (Esquema 2.9). La conversión del sustrato de partida resultó ser cuantitativa, generándose un 2% de benzonitrilo como único subproducto de reacción. La evaporación a sequedad de la mezcla de reacción y posterior purificación cromatográfica del crudo sobre sílica ($MeOH/CH_2Cl_2$ como eluyente), nos permitió aislar la benzamida deseada con un rendimiento del 87%.



Rdto.: 98% (CG), 87% (aislado)

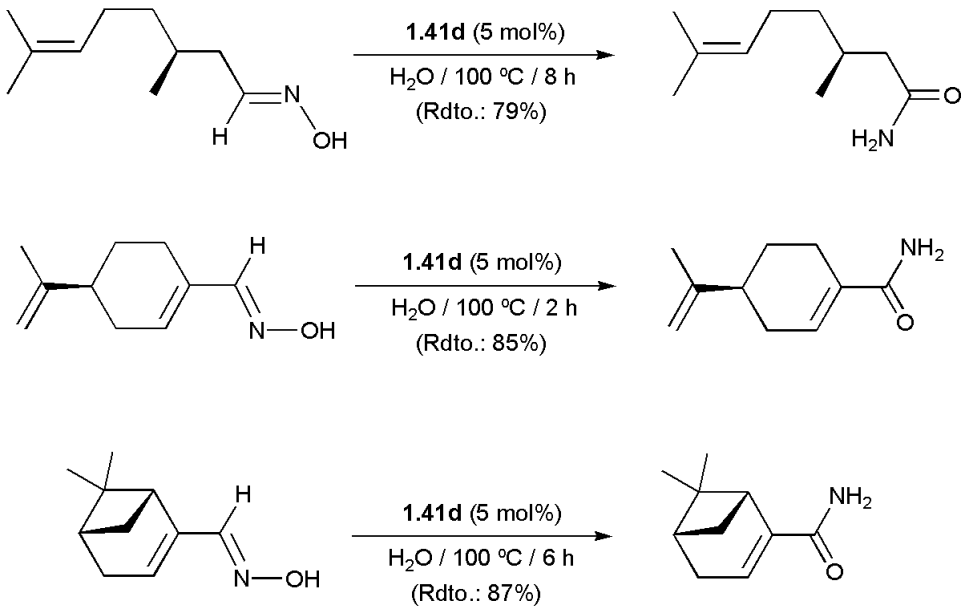
Esquema 2.9: Reordenamiento de benzaldoxima en benzamida catalizada por el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**) en agua.

Cabe destacar que, al contrario de otros sistemas catalíticos activos en medio orgánico descritos previamente en la bibliografía, no es necesaria la adición al medio de reacción de ningún ácido como co-catalizador para que la reacción tenga lugar.[8,10a] Por otro lado, en comparación con el sistema catalítico $Rh(OH)_x/Al_2O_3$ activo en agua descrito por N. Mizuno y colaboradores,[14] el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**) resultó ser más activo, ya que es capaz de promover la isomerización de la benzaldoxima a una temperatura más baja (100 ºC *vs.* 160 ºC), en un tiempo de reacción más corto (5 h *vs* 7 h), y con mayor rendimiento en la benzamida final (87% *vs* 76%).

A la vista del buen resultado obtenido, decidimos explorar la generalidad del proceso empleando las mismas condiciones experimentales de reacción. Para ello, en primer lugar, preparamos una familia variada de aldoximas (aromáticas, heteroaromáticas, alifáticas y *α,β*-insaturadas) por condensación de los correspondientes aldehídos comerciales con cloruro de hidroxilamonio, reacción que transcurre limpiamente a temperatura ambiente en una mezcla metanol/piridina. Las aldoximas sintetizadas se obtuvieron en todos los casos como mezclas de isómeros *E*/*Z* (disposiciones *anti*/*syn* de los sustituyentes sobre el doble enlace C=N) en proporciones variables (desde 95:5 hasta 30:70). No obstante, al no observarse diferencias de reactividad entre un isómero y otro, por simplicidad a la hora de presentar los resultados hemos optado por dibujar las aldoximas exclusivamente en disposición *anti* (isómeros *E*) en los esquemas correspondientes.

Como puede comprobarse en la publicación correspondiente adjunta, el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**) fue capaz de transformar la inmensa mayoría de las aldoximas sintetizadas en sus

amidas, en tiempos de reacción por lo general cortos (1-8 h) y con altos rendimientos (≥ 80% por CG; ≥ 60% de producto aislado tras purificación por cristalización selectiva o cromatografía en columna), generándose como únicos subproductos de reacción los correspondientes nitrilos.[27] Como ejemplos ilustrativos de la generalidad y utilidad sintética del proceso podemos destacar la formación selectiva de las amidas quirales (*S*)-(-)-citronelamida, (*S*)-(-)-perillamida y (1*R*)-(-)-mirtenamida.[28]



Esquema 2.10: Reordenamientos de aldoximas ópticamente activas catalizados por el complejo [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) en agua.

Así, como se muestra en el Esquema 2.10, estas amidas fueron obtenidas con buenos rendimientos (79-87%) por reordenamiento de las correspondientes aldoximas derivadas de los aldehídos ópticamente activos

[27] Las únicas aldoximas preparadas que no pudieron ser transformadas en las correspondientes amidas fueron la salicilaldoxima y la piridina-2-carboxaldoxima, sustratos que se recuperaron intactos incluso tras 24 h de calentamiento. Estos resultados negativos pueden ser debidos a la capacidad de estos derivados para formar metalaciclos estables de 5 y 6 miembros, respectivamente, por coordinación quelato *N,O*- o *N,N*- al centro metálico. De esta forma, el catalizador se quedaría bloqueado, impidiendo así que el proceso de isomerización tenga lugar. Por otra parte, tampoco se puede descartar que la falta de reactividad de estas aldoximas sea debida a formación de enlaces de hidrógeno intramoleculares dentro de las mismas, lo que podría estabilizarlas y hacerlas resistentes a la deshidratación.

[28] La (*S*)-(-)-citronelamida y la (*S*)-(-)-perillamida son compuestos conocidos que presentan propiedades organolépticas y antimicrobianas interesantes, tal y como se indica en las siguientes patentes: (a) M. Oku, Y. Fujikura, J. Etsuno, *Jpn. Kokai Tokkyo Koho* JP 07138213, **1995**; (b) A. Rieks, M. Kähler, U. Kirchner, K. Wiggenhorn, M. Kinzer, S. Risch, *PTC Int. Appl.* WO 2004/076400, **2004**; (c) A. Ray, S. M. Boyle, *PTC Int. Appl.* WO 2011/130726, **2011**.

(*S*)-(-)-citronelal, (*S*)-(-)-perillaldehído y (1*R*)-(-)-mirtenal. Los espectros de RMN de ^{1}H y $^{13}C\{^{1}H\}$ de la (1*R*)-(-)-mirtenamida, producto que no había sido descrito con anterioridad en la bibliografía, se muestran en la Figura 2.4. El alto rendimiento con el que se obtuvo la fragancia (*S*)-(-)-citronelamida (79%) merece ser resaltado, ya que estudios previos llevados a cabo en medio orgánico y empleando acetato de níquel como catalizador,[6a] o exceso de Ni Raney,[29] condujeron a la amida deseada con menor rendimiento (50-62%).

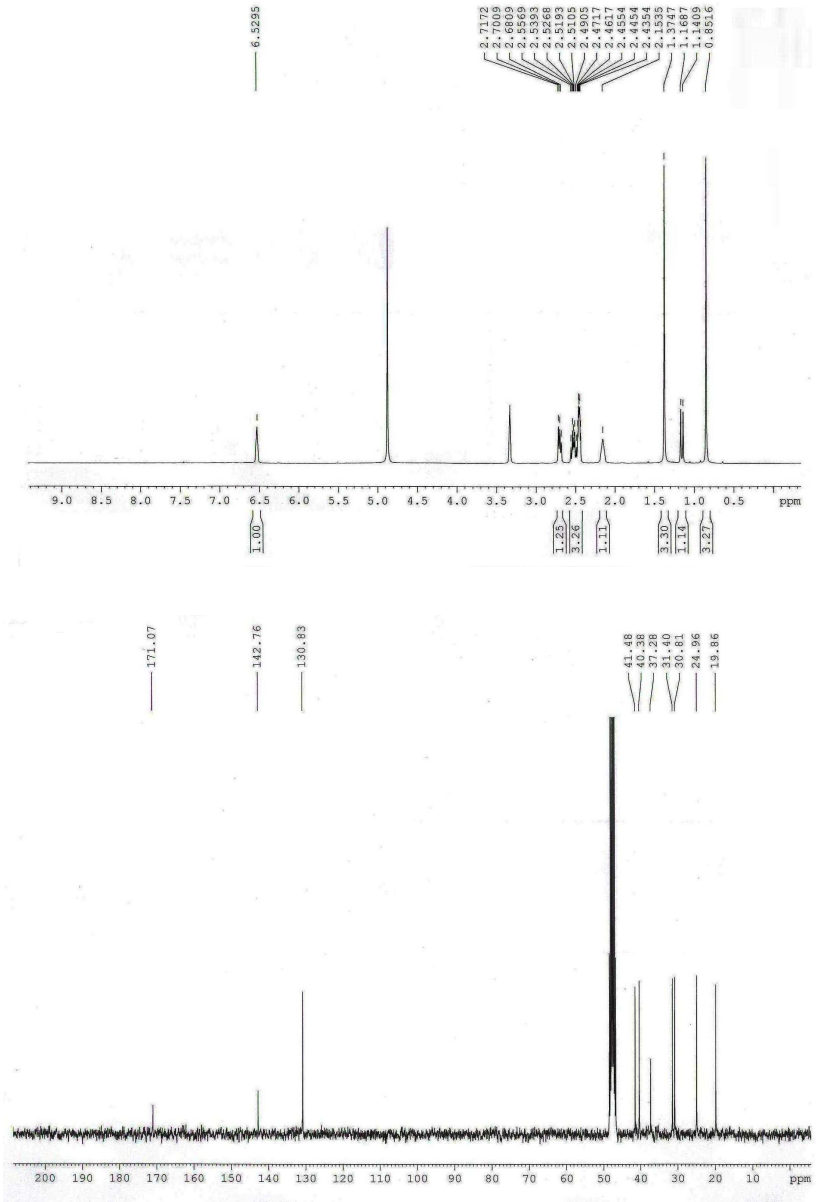
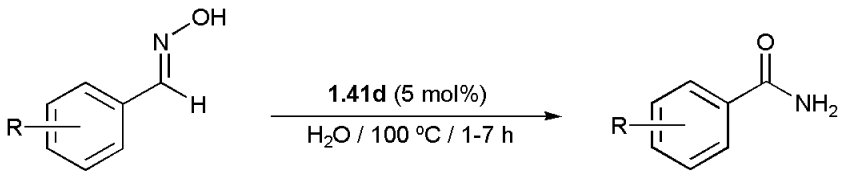


Figura 2.4: Espectros de RMN de ^{1}H y $^{13}C\{^{1}H\}$ (CD_3OD) obtenidos para la (1*R*)-(-)-mirtenamida sintetizada a partir de la aldoxima derivada del (1*R*)-(-)-mirtenal.

[29] A. G. Caldwell, E. R. H. Jones, *J. Chem. Soc.* **1946**, 599.

Empleando diferentes benzaldoximas sustituidas pudimos demostrar también la alta tolerancia que presenta el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) hacia grupos funcionales, ya que mostró ser compatible con la presencia en los sustratos de grupos haluro, hidroxilo, nitro, éter, amino o tioéter. Por otro lado, merece la pena destacar que las reacciones con estas benzaldoximas pusieron de manifiesto una ligera influencia del patrón de sustitución del anillo aromático en la velocidad del proceso de reordenamiento. Así, debido probablemente a factores estéricos, los sustratos que presentan sustitución en *orto* requieren tiempos de reacción por lo general más largos, en comparación con aquellos que se encuentran sustituidos en posiciones *meta* o *para*, para generar las amidas finales con rendimientos similares (ejemplos representativos se muestran en el Esquema 2.11).



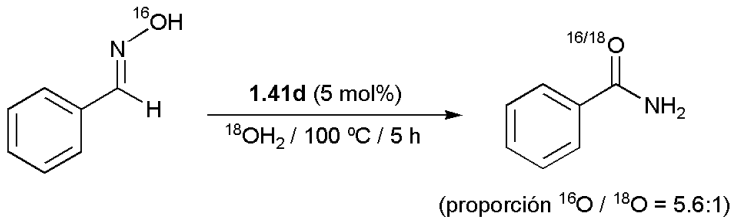
R = 2-Cl (Rdto.: 71%; 5 h)	R = 2-Me (Rdto.: 87%; 7 h)
R = 3-Cl (Rdto.: 84%; 1 h)	R = 3-Me (Rdto.: 88%; 3 h)
R = 4-Cl (Rdto.: 82%; 2 h)	R = 4-Me (Rdto.: 86%; 2 h)

Esquema 2.11: Reactividad observada con algunas benzaldoximas seleccionadas.

2.2.2.- Aspectos mecanísticos y cinéticos de las reacciones de reordenamiento de aldoximas catalizadas por el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (1.41d).

Una vez demostrada la capacidad del complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) para promover el reordenamiento de aldoximas, nos planteamos elucidar su mecanismo de acción. Como hemos comentado en la *Introducción* de este *Capítulo* existen dos propuestas mecanísticas para esta transformación, que se diferencian básicamente en la especie que actúa como agente hidratante (aldoxima o agua) en la etapa final de hidratación del nitrilo formado inicialmente (Esquema 2.4). En este sentido, para confirmar o descartar la participación del agua en el proceso,

llevamos a cabo el reordenamiento de la (*E*)-benzaldoxima en agua marcada isotópicamente con ^{18}O (Esquema 2.12).

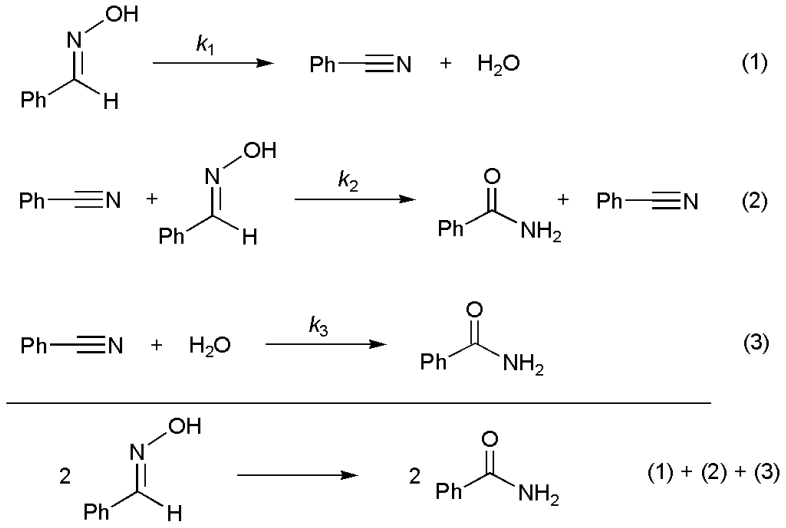


Esquema 2.12: Reordenamiento de la (*E*)-benzaldoxima catalizada por [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) en agua marcada isotópicamente con ^{18}O.

Un análisis a través de espectrometría de masas de alta resolución (HRMS) de la benzamida formada en esta reacción puso de manifiesto la incorporación de aproximadamente un 18% de ^{18}O en su estructura. Este hecho confirma que una parte del producto final es generado a través de un proceso de hidratación clásica del benzonitrilo intermedio por adición de agua al triple enlace C≡N (mecanismo (a) en el Esquema 2.4). No obstante, la presencia mayoritaria de benzamida no marcada parece sugerir que el mecanismo propuesto por J. M. J. Williams y colaboradores, en el que una segunda molécula de aldoxima actúa como agente hidratante (mecanismo (b) en el Esquema 2.4), es el camino de reacción predominante en el proceso. A favor de esta hipótesis está también el hecho de que, al monitorizar nuestras reacciones catalíticas por CG, hemos observado que la velocidad con la que se forman las amidas finales es mucho más rápida cuando todavía está presente en el medio de reacción la aldoxima de partida.

Con el propósito de obtener más información mecanística, en colaboración con el Dr. Javier Borge del Departamento de Química Física y Analítica de la Universidad de Oviedo, llevamos a cabo un estudio cinético del reordenamiento de la (*E*)-bezaldoxima en benzamida a 60 ºC. A esta temperatura el proceso se ralentiza lo suficiente como para tener una colección de datos significativa de los tres compuestos orgánicos involucrados en el proceso que se detectan por CG, *i.e.* la benzaldoxima inicial, el benzonitrilo intermedio y la benzamida final. Como "modelo cinético" se escogió el sistema de 3 reacciones independientes que se recoge en el Esquema 2.13. Este modelo, muy simple e intuitivo, describe a

la perfección la reacción objeto de estudio, y los dos mecanismos posibles. Así, mientras que la suma de los procesos (1) y (3) representa el mecanismo recientemente propuesto por Williams y colaboradores (mecanismo (b) en el Esquema 2.4), la suma de los procesos (1) y (2) da cuenta del mecanismo clásico donde el nitrilo intermedio es hidratado por acción del agua (mecanismo (a) en el Esquema 2.4).



Esquema 2.13: Modelo para describir el reordenamiento de la benzaldoxima.

Como se detalla en la publicación correspondiente adjunta, un análisis de la variación de la concentración de la benzaldoxima con el tiempo, así como un estudio independiente de la reacción de hidratación del benzonitrilo en agua catalizada por el complejo **1.41d** a 60 °C, nos permitió determinar los ordenes de reacción con respecto a estos reactivos, y plantear un sistema de ecuaciones diferenciales apropiado para describir los tres procesos independientes representados en el Esquema 2.13. A partir de este sistema de ecuaciones, y los datos experimentales obtenidos por CG, se pudieron estimar los valores de las tres constantes de velocidad (k_1 = 0.0145 min^{-1}, k_2 = 0.0562 min^{-1} y k_3 = 0.0316 $dm^3\ mol^{-1}\ min^{-1}$) y determinar así las velocidades relativas de los tres procesos. Dichas velocidades confirmaron que el mecanismo de Williams, en el que una segunda molécula de aldoxima actúa como agente hidratante ((1) + (2)), transcurre a mucha más velocidad que el mecanismo clásico ((1) + (3)), siendo este último el que opera con exclusividad al final de la reacción (cuando toda la benzaldoxima ha sido consumida), si bien a una velocidad muy lenta.

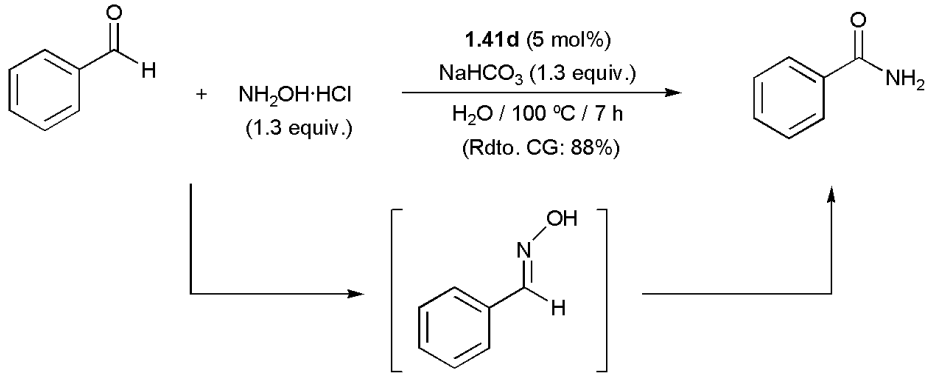
Merece la pena destacar que, en nuestro conocimiento, el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) representa el primer ejemplo demostrado de un catalizador metálico capaz de operar simultáneamente a través de estos dos caminos de reacción independientes.

2.2.3.- Estudio de la actividad catalítica del complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (1.41d) en la síntesis *one-pot* de amidas primarias a partir de aldehídos en agua.

Los aldehídos son productos de partida muy atractivos en síntesis orgánica dada su alta disponibilidad y baja toxicidad. En este sentido, como ya se ha comentado en la *Introducción* de este *Capítulo*, el desarrollo de nuevos procesos *one-pot* que permitan la formación directa de amidas primarias a partir de aldehídos, por reordenamiento de aldoximas generadas *in situ* en el medio de reacción, ha tomado una gran relevancia en los últimos años (ver Esquema 2.6).[1] Este hecho, unido a la excelente actividad catalítica mostrada por el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) en el reordenamiento de aldoximas, nos animó a explorar la capacidad de **1.41d** para promover la síntesis de amidas primarias en agua por acoplamiento de aldehídos con derivados de la hidroxilamina.

Con tales fines, inicialmente llevamos a cabo una optimización de las condiciones de reacción empleando benzaldehído como sustrato modelo y cloruro de hidroxilamonio ($NH_2OH{\cdot}HCl$) como fuente de la unidad "NH_2" (ver detalles en el artículo correspondiente adjunto). Como condiciones generales de reacción escogimos las empleadas en nuestros estudios previos de hidratación de nitrilos y de reordenamiento de aldoximas, es decir, empleamos disoluciones 0.33 M en agua del sustrato a transformar, una carga de catalizador del 5 mol% y una temperatura de trabajo de 100 ºC. Ensayamos diferentes proporciones benzaldehído/$NH_2OH{\cdot}HCl$ y, para eliminar el HCl desprendido en la formación de la benzaldoxima intermedia, introdujimos en el medio de reacción diferentes bases ($NaHCO_3$, NaOH, KOH, Na_2CO_3, K_2CO_3 o Cs_2CO_3) en proporción relativa 1:1 con respecto al cloruro de hidroxilamonio. Los mejores resultados se obtuvieron al emplear un ligero exceso de $NH_2OH{\cdot}HCl$ (1.3 equiv.) en combinación con $NaHCO_3$ (1.3 equiv.). En estas condiciones, la benzamida deseada se formó con un 88% de rendimiento (determinado por

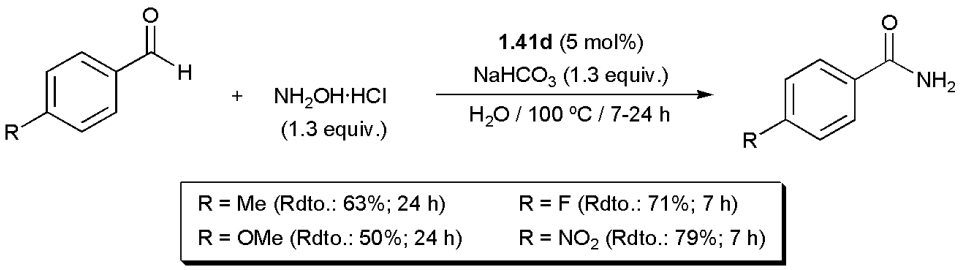
cromatografía de gases) tras 7 horas de calentamiento (Esquema 2.14). Es importante destacar en este punto que, cuando las mismas reacciones se llevaron a cabo empleando un disolvente orgánico (tolueno, 1,2-dicloroetano o 2-propanol) en lugar de agua, se alcanzaron rendimientos inferiores en benzamida (22-63%) incluso tras 24 h de calentamiento. Este hecho ratifica la necesidad de un exceso de agua para que el reordenamiento de la benzaldoxima intermedia sea efectivo, ya que, como hemos discutido anteriormente, el agua presente en el medio de reacción es en parte responsable de la hidratación del benzonitrilo inicialmente generado en la etapa inicial de deshidratación de la benzaldoxima. Como era de esperar, la utilización de cargas menores de catalizador, o temperaturas de trabajo más bajas, se tradujo en una disminución en el rendimiento de la benzamida. Por otro lado, merece la pena comentar también que la presencia de una base resulta determinante en la selectividad del proceso, obteniéndose ácido benzoico como producto mayoritario de reacción (aprox. 40% por CG frente a un 21% de benzamida) al llevar a cabo la reacción en ausencia de $NaHCO_3$. El ácido benzoico es el resultado de la hidrólisis de la amida promovida por el HCl liberado en la formación de la benzaldoxima intermedia.



Esquema 2.14: Transformación de benzaldehído en benzamida catalizada por **1.41d**.

Una vez optimizadas las condiciones de reacción (*i.e.* relación [sustrato]:[Ru]:[NH_2OH·HCl]:[$NaHCO_3$] = 100:5:130:130, disoluciones 0.33 M de sustrato en agua y temperatura de trabajo de 100 ºC), se estudió la generalidad del proceso empleando una familia variada de aldehídos. Como puede verse en el artículo adjunto correspondiente, el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) fue capaz de transformar un buen número de

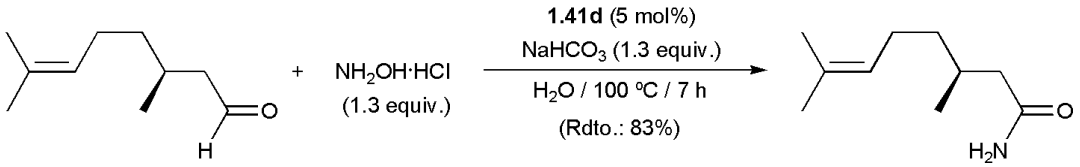
aldehídos aromáticos, heteroaromáticos, alifáticos y α,β-insaturados en las correspondientes amidas primarias, que pudieron ser aisladas con rendimientos de moderados a buenos (50-92%) tras 7-24 h de calentamiento a 100 ºC, posterior evaporación a sequedad de la mezcla de reacción, extracción de la amida con diclorometano y recristalización final en agua (en algunos casos fue necesaria una etapa adicional de purificación por cromatografía en columna). En el caso de los aldehídos aromáticos, el proceso resultó operativo independientemente del patrón de sustitución y naturaleza electrónica del anillo bencénico. No obstante, se observó una influencia importante de las propiedades electrónicas de los sustituyentes en la eficiencia del proceso. Así, los benzaldehídos sustituidos con grupos electrodonadores mostraron una menor reactividad en comparación con sus análogos sustituidos con grupos electroatractores, requiriendo tiempos de reacción más largos (24 *vs* 7 h) para obtener las amidas deseadas con rendimientos tan sólo moderados. Ejemplos representativos de este efecto electrónico, que está relacionado con la mayor facilidad de los benzaldehídos pobres en densidad electrónica para sufrir procesos de condensación del grupo carbonilo, se muestran en el Esquema 2.15. En todos los casos, los únicos subproductos detectados por cromatografía de gases en los crudos de reacción fueron los aldehídos de partida y los correspondientes nitrilos (resultantes de la deshidratación de las aldoximas intermedias).



Esquema 2.15: Reactividad observada con algunos benzaldehídos seleccionados.

Como ejemplo ilustrativo de la generalidad del proceso, cabe destacar que la utilización del complejo **1.41d** nos permitió llevar a cabo por primera vez la síntesis directa de la fragancia (*S*)-(-)-citronelamida a partir del aldehído comercial (*S*)-(-)-citronelal (Esquema 2.16). La amida quiral deseada se obtuvo con un rendimiento del 83% y alta pureza, como

demuestran los espectros de RMN de ^{1}H y $^{13}C\{^{1}H\}$ obtenidos para la misma (ver Figura 2.5).



Esquema 2.16: Síntesis de la (*S*)-(-)-citronelamida a partir del (*S*)-(-)-citronelal.

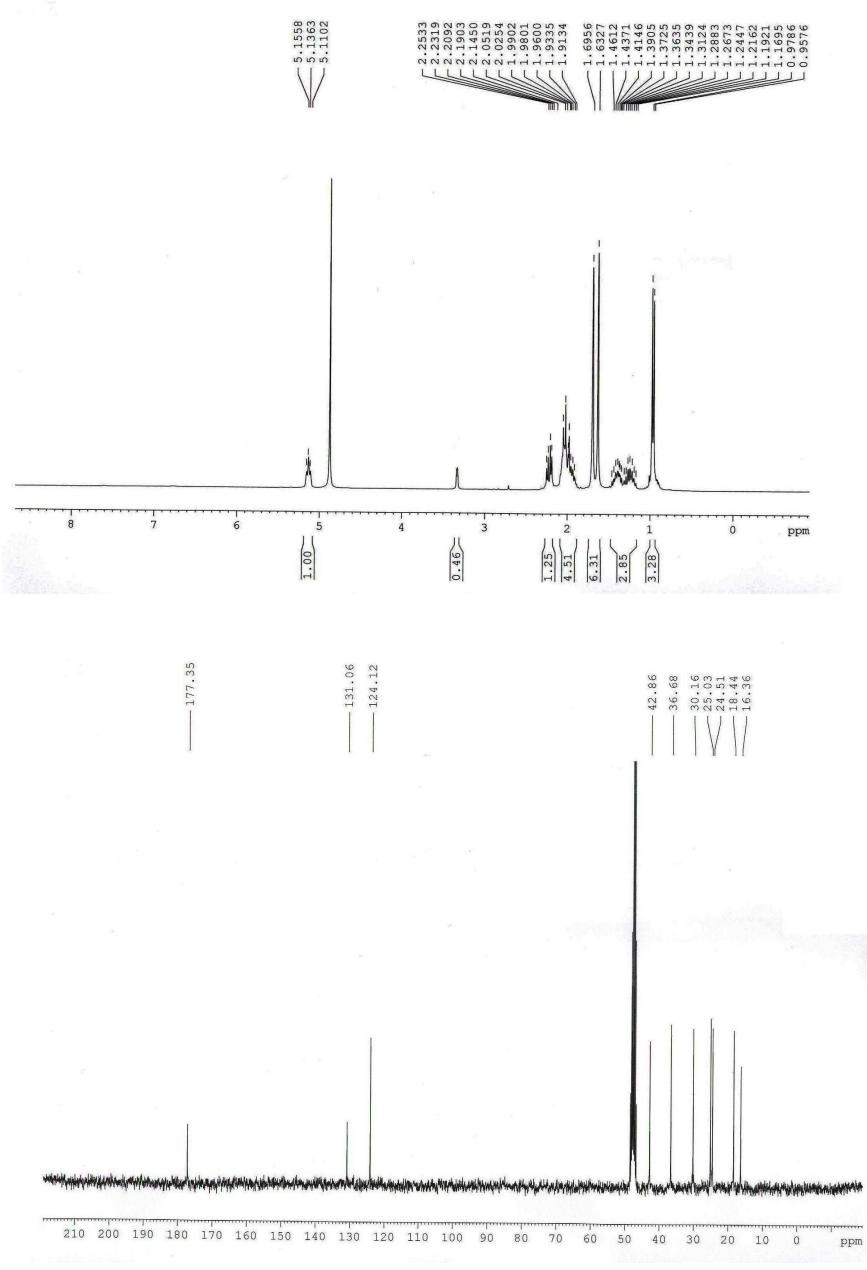
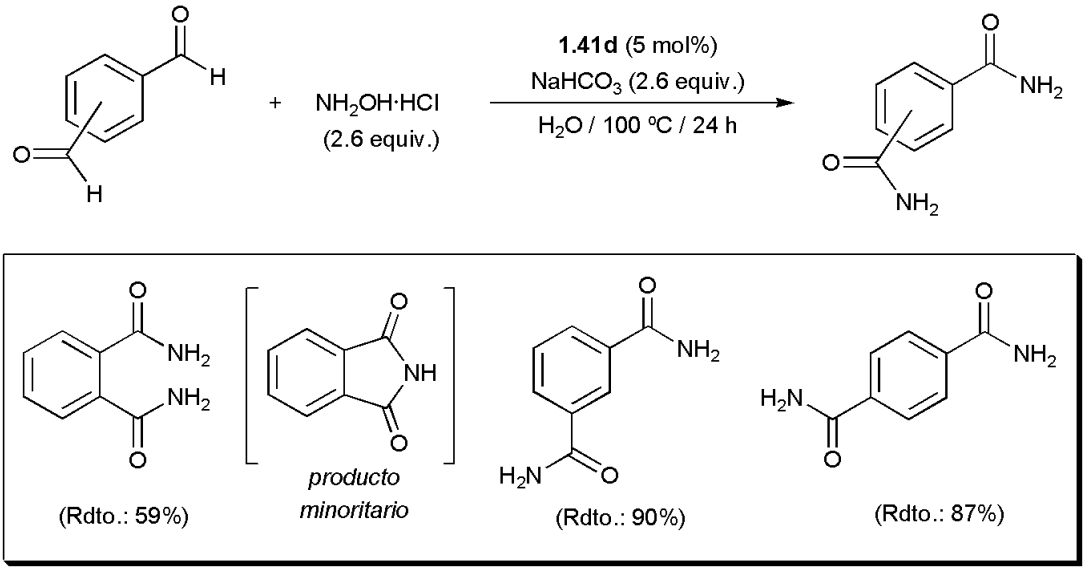


Figura 2.5: Espectros de RMN de ^{1}H y $^{13}C\{^{1}H\}$ (CD_3OD) de la (*S*)-(-)-citronelamida sintetizada a partir del (*S*)-(-)-citronelal y cloruro de hidroxilamonio.

Por otro lado, debemos hacer notar que esta nueva metodología también es útil para la síntesis de diamidas. De esta forma, añadiendo un exceso de $NH_2OH{\cdot}HCl$ y $NaHCO_3$ (2.6 equiv. de cada uno) y empleando un 5 mol% del complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**), pudimos transformar el 1,2-, 1,3- y 1,4-bencenodicarboxaldehído en las diamidas correspondientes, *i.e.* ftalamida, isoftalamida y tereftalamida, respectivamente, tras 24 horas de calentamiento (Esquema 2.17). En el caso particular de la ftalamida, ésta se obtuvo con un rendimiento tan sólo moderado (59%), debido a la formación minoritaria de ftalimida como resultado de un proceso de ciclación intramolecular en competencia,[30] lo que hizo necesario varias recristalizaciones para obtener la diamida deseada en forma pura.



Esquema 2.17: Transformación de dialdehídos en diamidas empleando el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**).

Otra aplicación sintética interesante que hemos podido desarrollar empleando el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**) es la transformación directa del ferrocenocarboxaldehído en ferrocenocarboxamida. La ferrocenocarboxamida es un derivado del

[30] La formación de ftalimidas por ciclación intramolecular de las correspondientes ftalamidas intermedias ha sido reciente descrita por B. Singh y colaboradores al estudiar procesos de hidratación de 1,2-cianobencenos: P. K. Verma, U. Sharma, M. Bala, B. Singh, *RSC Adv.* **2013**, *3*, 895.

ferroceno que presenta interesantes propiedades coordinativas,[31] electroquímicas[32] y fotoquímicas.[33] Es también un intermedio avanzado utilizado con asiduidad en la preparación de otros derivados del ferroceno, entre los que se incluyen ligandos ópticamente activos para catálisis asimétrica,[34] y ha sido empleada en años recientes en el diseño de electrodos nanoestructurados,[35] polímeros conductores[36] y diferentes dispositivos fotoelectrónicos.[37]

La ferrocenocarboxamida se prepara comúnmente a partir del ácido ferrocenocarboxílico, producto disponible comercialmente, a través de una secuencia de reacción en dos etapas (ver Esquema 2.18). En la primera de ellas, el ácido ferrocenocarboxílico es transformado en el cloruro de ácido correspondiente por reacción con cloruro de tionilo, u otros agentes de cloración tales como el pentacloruro de fósforo o el cloruro de oxalilo. Posteriormente, el cloruro es tratado con amoniaco acuoso generando la amida deseada.[38] A pesar de la simplicidad aparente de esta síntesis,

---

[31] Ver, por ejemplo: (a) M. Auzias, B. Therrien, G. Labat, H. Stoeckli-Evans, G. Süss-Fink, *Inorg. Chim. Acta* **2006**, *359*, 1012; (b) D. Salazar-Mendoza, S. A. Baudron, M. W. Hosseini, N. Kyritsakas, A. D. Cian, *Dalton Trans.* **2007**, 565.

[32] Ver, por ejemplo: (a) S. Lu, V. V. Strelets, M. F. Ryan, W. J. Pietro, A. B. P. Lever, *Inorg. Chem.* **1996**, *35*, 1013; (b) H.-G. Hong, *Bull. Korean Chem. Soc.* **1996**, *17*, 961; (c) E. Baciocchi, M. Bietti, M. D. Fusco, O. Lanzalunga, *J. Org. Chem.* **2007**, *72*, 8748; (d) E. Baciocchi, M. Bietti, C. D´Alfonso, O. Lanzalunga, A. Lapi, M. Salamone, *Org. Biomol. Chem.* **2011**, *9*, 4085.

[33] Ver, por ejemplo: (a) L. H. Ali, A. Cox, T. J. Kemp, *J. Chem. Soc., Chem. Commun.* **1972**, 265; (b) L. H. Ali, A. Cox, T. J. Kemp, *J. Chem. Soc., Dalton Trans.* **1973**, 1468.

[34] Ver, por ejemplo: (a) R. Peters, D. F. Fischer, *Org. Lett.* **2005**, *7*, 4137; (b) L. Chen, Q. Wang, R. Huang, C. Mao, J. Shang, H. Song, *Adv. Organomet. Chem.* **2005**, *19*, 45; (c) M. E. Weiss, D. F. Fischer, Z.-Q. Xin, S. Jautze, W. B. Schweizer, R. Peters, *Angew. Chem. Int. Ed.* **2006**, *45*, 5694; (d) R. Zhang, W. Wang, Y. Wu, H. Fu, J. Yao, *Org. Lett.* **2008**, *10*, 3065; (e) D. F. Fischer, A. Barakat, Z.-Q. Xin, M. E. Weiss, R. Peters, *Chem. Eur. J.* **2009**, *15*, 8722; (f) M. Cetina, V. Kovač, V. Rapić, *Acta Cryst. Sect.* E **2011**, *E67*, m610.

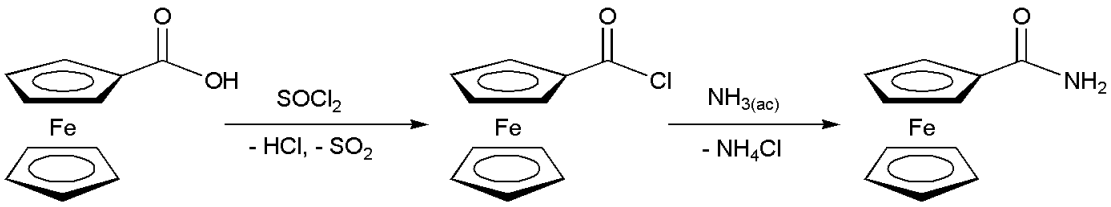
[35] Ver, por ejemplo: (a) M. Chahma, J. S. Lee, H.-B. Kraatz, *J. Electroanal. Chem.* **2004**, *567*, 283; (b) P. J. Costanzo, E. Liang, T. E. Patten, S. D. Collins, R. L. Smith, *Lab Chip* **2005**, *5*, 606; (c) X.-H. Deng, S.-F. Jiao, Y. Yan, C. Wang, G.-F. Wang, B. Fang, *Russ. J. Electrochem.* **2006**, *42*, 873; (d) C. Wang, G. Wang, B. Fang, *Microchim. Acta* **2009**, *164*, 113.

[36] Ver, por ejemplo: (a) S. Y. Oh, H. S. Choi, H. J. Kim, J. K. Park, *Polymer* **2005**, *29*, 331; (b) S. Y. Oh, C. M. Chung, D. E. Kim, S. G. Lee, *Colloids Surf. A* **2008**, *313-314*, 600.

[37] Ver, por ejemplo: (a) J. Yu, J. Huang, S. Liu, Y. Jiang, *Faming Zhuanli Shenquing* CN 102208543, **2011**; (b) Y. Jiang, J. Yu, L. Li, Z. Ma, *Faming Zhuanli Shenquing* CN 102208559, **2011**.

[38] Ver, por ejemplo: (a) F. S. Arimoto, A. C. Haven Jr., *J. Am. Chem. Soc.* **1955**, *77*, 6295; (b) H. H. Lau, H. Hart, *J. Org. Chem.* **1959**, *24*, 280; (c) T. Katada, M. Nishida, S. Kato, M. Mizuta, *J. Organomet. Chem.* **1977**, *129*, 189; (d) S. T.

debemos hacer notar que la transformación del ácido ferrocenocarboxílico en su cloruro no está exenta de problemas, y generalmente transcurre con bajo rendimiento. Esto es debido a la formación competitiva de productos secundarios de reacción (dímeros y oligómeros) que se generan a través de procesos de acilación tipo Friedel-Crafts de la unidad ferrocenilo, como consecuencia de la alta nucleofilia de la misma. Este hecho, unido a la tendencia del cloruro de ácido a sufrir procesos de hidrólisis, hace que el aislamiento y purificación de este intermedio sean tediosos.[39] Con el objetivo de evitar estos problemas se han descrito métodos alternativos más selectivos para la síntesis de la ferrocenocarboxamida, que involucran la transformación inicial del ácido ferrocenocarboxílico en fluorocarbonilferroceno[39] o *N*-ferrocenoil-benzotriazol,[40] y posterior tratamiento con $NH_{3(ac)}$. No obstante, estas rutas, comparativamente mucho más elaboradas, no han encontrado en la práctica una gran aceptación.[41]



Esquema 2.18: Síntesis clásica de la ferrocenocarboxamida.

Como se muestra en el Esquema 2.19, con ayuda del complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**) es posible preparar la ferrocenocarboxamida a partir de ferrocenocarboxaldehído y cloruro de hidroxilamonio en una sola etapa. Así, llevando a cabo la reacción en condiciones muy similares a las anteriores, se pudo aislar la ferrocenocarboxamida en forma pura con un 79% de rendimiento tras 24 horas de calentamiento. La adición de una pequeña cantidad de metanol

---

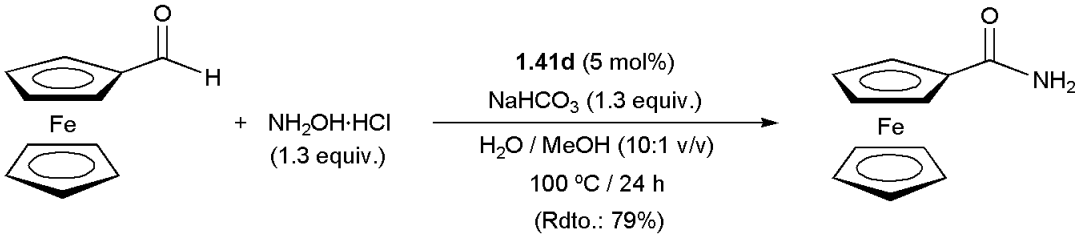
Mabrouk, W. P. Hart, M. D. Rausch, *J. Organomet. Chem.* **1997**, *527*, 43; (e) P. Štěpnička, I. Císařová, D. Nižňanský, S. Bakardjieva, *Polyhedron* **2010**, *29*, 134.

[39] T. H. Galow, J. Rodrigo, K. Cleary, G. Cooke, V. M. Rotello, *J. Org. Chem.* **1999**, *64*, 3745.

[40] S. F. Ekti, D. Hür, *Inorg. Chem. Commun.* **2008**, *11*, 1027.

[41] Otros métodos de síntesis alternativos de la ferrocenocarboxamida descritos en la literatura incluyen el tratamiento directo de ferroceno con cloruro de carbamoilo, o la hidratación de ferrocenocarbonitrilo. No obstante, los bajos rendimientos con los que transcurren estas síntesis hacen que no tengan interés práctico: (a) W. F. Little, R. Eisenthal, *J. Am. Chem. Soc.* **1960**, *82*, 1577; (b) A. N. Nesmeyanov, E. G. Perevalova, L. P. Yur´eva, K. I. Grandberg, *Izv. Akad. Nauk SSSR Ser. Khim.* **1963**, 1377.

fue necesaria para facilitar la solubilidad completa del ferrocenocarboxaldehído en el medio de reacción, alcanzándose un rendimiento menor en la amida (aprox. 60%) al llevar a cabo la reacción en agua pura.[42]



Esquema 2.19: Síntesis directa de ferrocenocarboxamida a partir de ferrocenocarboxaldehído y cloruro de hidroxilamonio.

En nuestro conocimiento, este es el primer protocolo descrito hasta la fecha para la preparación de ferrocenocarboxamida a partir de ferrocenocarboxaldehído. Por otro lado, en comparación con la ruta sintética clásica a partir del ácido ferrocenocarboxílico (Esquema 2.18), creemos además que este nuevo método de síntesis es ventajoso por las siguientes razones: *(i)* involucra una sola etapa de reacción, *(ii)* hace uso de un material de partida mucho más barato,[43] *(iii)* transcurre con alto rendimiento en un medio de reacción respetuoso con el medioambiente, y *(iv)* no requiere de procesos de purificación tediosos.

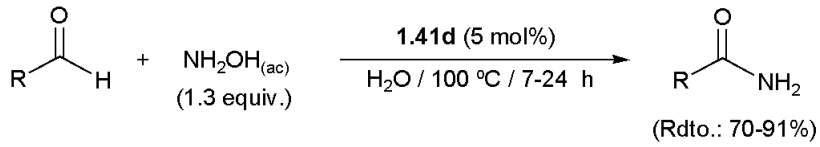
Finalmente, teniendo en cuenta que el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) es activo en agua y que la hidroxilamina (NH_2OH) se comercializa como disolución acuosa (disolución al 50% en peso en agua), exploramos la posibilidad de llevar a cabo estos procesos de acoplamiento empleando directamente este reactivo comercial en lugar del cloruro de hidroxilamonio. De este modo ya no es necesaria la introducción

[42] También ensayamos en esta reacción los compuestos $FeCl_3$, $Cu(OAc)_2$ y $Pd(OAc)_2$ como catalizadores. Como se ha comentado en la introducción de este capítulo, estos compuestos son capaces de catalizar el acoplamiento de aldehídos con derivados de la hidroxilamina en agua. No obstante, bajo las mismas condiciones de reacción, su efectividad fue ligeramente inferior a la mostrada por el complejo [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**), conduciendo a la ferrocenocarboxamida deseada con rendimientos del orden del 50-65%. Estas observaciones confirman el extraordinario potencial sintético que presenta el catalizador de rutenio [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**).

[43] En efecto, de acuerdo con los precios actuales recogidos en los catálogos de las compañías Sigma-Aldrich, Alfa Aesar y Acros Organics, el ferrocenocarboxaldehído es de 3 a 5 veces más barato por gramo que el ácido ferrocenocarboxílico.

en el medio de reacción de una base ($NaHCO_3$) para neutralizar el HCl desprendido en la formación de la aldoxima intermedia, minimizando así el coste del proceso y la generación de residuos.

Como se muestra en el Esquema 2.20, empleando directamente $NH_2OH_{(ac)}$ (1.3 equiv.) y un 5 mol% del complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**), el proceso de acoplamiento transcurrió de manera efectiva a 100 ºC para una familia de aldehídos de naturaleza variada. Es importante destacar que no se observaron diferencias significativas, en cuanto a rendimientos y tiempos de reacción con respecto a las reacciones llevadas a cabo previamente empleando $NH_2OH{\cdot}HCl$ en presencia de $NaHCO_3$. Además, cabe mencionar también que una ventaja asociada a este nuevo protocolo es que los procesos de purificación de las amidas finales se vieron simplificados al no formarse sales (se evita la extracción de las amidas del crudo de reacción con CH_2Cl_2, previa a la recristalización o a la columna cromatográfica). Debemos hacer notar llegados a este punto que, a excepción del trabajo descrito recientemente por M. Yus y colaboradores (Esquema 2.8),[25] la utilización directa de $NH_2OH_{(ac)}$ en lugar de sales de hidroxilamonio no había sido considerada previamente en la bibliografía.



R = Ph, 2-C_6H_4F, 3-C_6H_4F, 4-C_6H_4Cl, C_6F_5, 3-$C_6H_4NO_2$, 4-C_6H_4Me, 2-C_6H_4OMe, 2-Tienilo, *n*-C_6H_{13}, Cy, CH_2CH_2Ph, (E)-CH=CHPh *(7 horas de reacción)*

R = Ferrocenilo *(24 horas de reacción en una mezcla H_2O / MeOH (10:1 v/v))*

Esquema 2.20: Síntesis de amidas primarias a partir de aldehídos y $NH_2OH_{(ac)}$ catalizada por el complejo $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**1.41d**) en agua.

CAPÍTULO 2

2.3.- PUBLICACIONES

Los resultados obtenidos en este capítulo han dado lugar a las dos publicaciones que se adjuntan:

1) "Ruthenium-catalyzed rearrangement of aldoximes to primary amides in water". Rocío García-Álvarez, Alba E. Díaz-Álvarez, Javier Borge, Pascale Crochet, Victorio Cadierno. *Organometallics* **2012**, *31*, 6482-6490.

2) "Ruthenium-catalyzed one-pot synthesis of primary amides from aldehydes in water". Rocío García-Álvarez, Alba E. Díaz-Álvarez, Pascale Crochet, Victorio Cadierno. *RSC Advances* **2013**, en imprenta (DOI: 10.1039/c3ra23195j).

ORGANOMETALLICS

Article

pubs.acs.org/Organometallics

Ruthenium-Catalyzed Rearrangement of Aldoximes to Primary Amides in Water

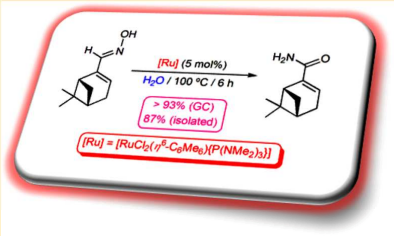
Rocío García-Álvarez,[†] Alba E. Díaz-Álvarez,[†] Javier Borge,[‡] Pascale Crochet,*[,†] and Victorio Cadierno*[,†]

[†]Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles", Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain

[‡]Departamento de Química Física y Analítica, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain

Supporting Information

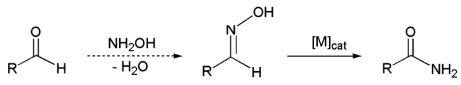
ABSTRACT: The rearrangement of aldoximes to primary amides has been studied using the readily available arene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (5 mol %) as catalyst. Reactions proceeded cleanly in pure water at 100 °C without the assistance of any cocatalyst, affording the desired amides in high yields (70−90%) after short reaction times (1−7 h). The process was operative with both aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldoximes and tolerated several functional groups. Reaction profiles and experiments using ^{18}O-labeled water indicate that two different mechanisms are implicated in these transformations. In both of them, nitrile intermediates are initially formed by dehydration of the aldoximes. These intermediates are then hydrated to the corresponding amides by the action of a second molecule of aldoxime or water. A kinetic analysis of the rearrangement of benzaldoxime to benzamide is also discussed.



INTRODUCTION

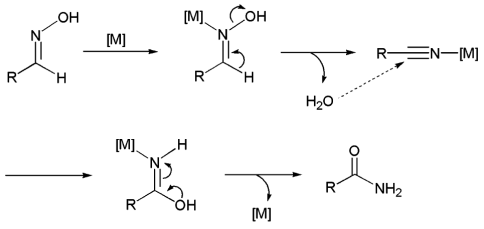
Amides are one of the most important functional groups in nature, constitute versatile building blocks in synthetic organic chemistry, and also exhibit a wide range of industrial applications and pharmacological interest.[1] Most syntheses of amides are based on the reaction of carboxylic acids and derivatives (halides, anhydrides, or esters) with amines.[1,2] However, these methods present several drawbacks, such as the use of toxic, corrosive, and/or expensive materials, highly exothermic reactions, low tolerance to sensitive functional groups, complex reaction conditions, and wasteful procedures. As a matter of fact, in 2005, the ACS GCIPR (American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable) identified amide formation as one of the most problematic syntheses in the pharmaceutical industry and labeled it as a high-priority research field.[3,4] Hence, the development of atom-efficient catalytic methods for amide formation has turned into a prime goal in modern chemistry.[5] In this context, the metal-catalyzed rearrangement of aldoximes, a process closely related to the well-known Beckmann rearrangement of ketoximes,[6] has emerged in recent years as an appealing tool for the generation of primary amides (Scheme 1).[5,7] Several Ni-, Pd-, Cu-, Au-, Ru-, Rh-, Ir-, Zn-, and In-based systems able to promote this atom-economical transformation are presently known.[8] In addition, examples allowing amide formation starting directly from aldehydes have also been described by performing the catalytic reactions in the presence of hydroxylamine, via *in situ* generation of the corresponding aldoxime intermediates.[8f,h,i,k,p,n,u,9,10]

Scheme 1. Metal-Catalyzed Rearrangement of Aldoximes to Amides



From a mechanistic point of view, two different reaction pathways have been proposed for this metal-catalyzed rearrangement. The first one involves the initial dehydration of the aldoxime into a nitrile intermediate, which is subsequently hydrated by the water released in the previous step to generate the final amide (Scheme 2). Both individual

Scheme 2. Catalytic Rearrangement of Aldoximes to Amides: The Classical Dehydration/Rehydration Mechanism



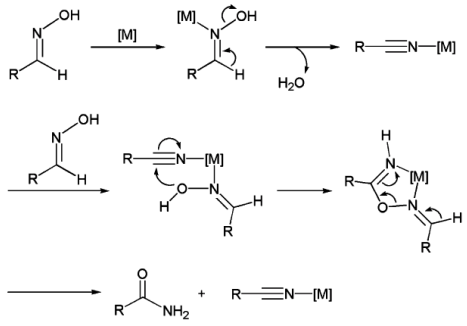
Received: July 23, 2012
Published: August 27, 2012

dx.doi.org/10.1021/om3006917 | *Organometallics* 2012, 31, 6482−6490

steps are promoted by the metal and have been independently reported in the literature with a broad range of metal catalysts.[11,12] The operativity of this mechanism was usually supported by the detection of small amounts of nitrile byproduct at the end of the catalytic reactions and, in one case, by their formation in the early stages before subsequent formation of the corresponding amides.[8h,i]

The second proposed mechanism involves again the initial metal-promoted dehydration of the aldoxime to form the corresponding nitrile, which now evolves into the final amide by the aid a second molecule of aldoxime, which acts as a water surrogate (Scheme 3).[13] Thus, intramolecular attack on the

Scheme 3. Catalytic Rearrangement of Aldoximes to Amides: Aldoximes As Water Surrogates



nitrile by a coordinated aldoxime leads to a five-membered cyclic intermediate, which decomposes into the final amide product and another coordinated nitrile, which continues with the catalytic cycle.[8l,m] Remarkably, despite that the dehydration/rehydration pathway involving water (Scheme 2) has been the generally accepted mechanism for the rearrangement of aldoximes to amides, a recent study by Williams and co-workers using ^{18}O-labeled substrates has pointed out that most of the metal catalysts described so far in the literature for this reaction really operate through the pathway depicted in Scheme 3.[8t]

During the last years, in the context of our studies on metal-catalyzed reactions in water,[14] we have developed a large number of hydrophilic ruthenium complexes able to promote efficiently the selective hydration of nitriles to primary amides in pure aqueous medium under neutral conditions.[15] Among them, best results in terms of activity were obtained with the arene-ruthenium(II) derivative $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$, which contains the commercially available and inexpensive P-donor ligand tris(dimethylamino)phosphine (Figure 1).[15e,f] The effectiveness of this readily accessible complex is ascribed to the excellent hydrogen bond accepting

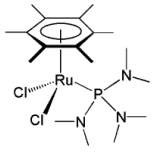


Figure 1. Structure of the arene-ruthenium(II) catalyst employed in this work.

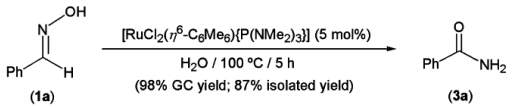
properties of $P(NMe_2)_3$, which activates the water molecule by H-bonding, thus enhancing its nucleophilic character.[16]

Herein, as a continuation of our work,[15e,f] the utility of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ for the catalytic rearrangement of aldoximes to primary amides in water is presented, along with evidence supporting that both mechanisms depicted in Schemes 2 and 3 are in this case operative. It is worthy of note that, despite the increasing interest in the use of environmentally friendly water as solvent for synthetic organic chemistry,[17,18] efforts devoted to develop such a catalytic rearrangement in water have been scarce. In fact, to the best of our knowledge, only one previous example involving the heterogeneous system $Rh(OH)_x/Al_2O_3$ has been quoted in the literature.[8h,i,19] A classical dehydration/rehydration mechanism of action, in which the nitrile intermediates are hydrated by water, was proposed for this heterogeneous system on the basis of reaction profiles.

RESULTS AND DISCUSSION

Catalytic Activity and Scope of Complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$. First, the ability of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ to promote the catalytic rearrangement of aldoximes was evaluated employing commercially available (*E*)-benzaldoxime (**1a**) as model substrate (Scheme 4). In this

Scheme 4. Ruthenium-Catalyzed Rearrangement of Benzaldoxime (1a) to Benzamide (3a) in Water



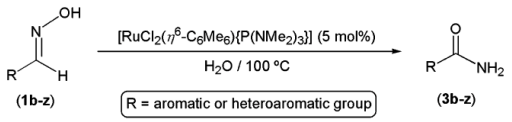
sense, we were pleased to find that, under the same experimental conditions previously employed in our nitrile hydration studies (0.33 M solution of the substrate in water, 5 mol % of Ru, 100 °C),[15e,f] the reaction proceeded efficiently to afford the desired benzamide (**3a**) in 98% GC yield after 5 h of heating. Complete consumption of **1a** along with the formation of a very minor amount of benzonitrile (**2a**; ca. 2%) as the only byproduct was observed by gas chromatography (GC). Solvent removal and subsequent chromatographic workup provided analytically pure benzamide in 87% isolated yield (details are given in the Experimental Section). It is important to note that, contrary to other catalytic systems previously described in the literature, no acidic cocatalysts were needed.[8g,l] In addition, compared with the aqueous $Rh(OH)_x/Al_2O_3$ heterogeneous system developed by Mizuno and co-workers,[8h,i] complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ was more active since a higher temperature (160 °C) and a longer reaction time (7 h) were required with $Rh(OH)_x/Al_2O_3$ (4 mol % of Rh) to generate **3a** in high yield (76%). Complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ proved also more effective than the related hydration catalysts $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (PTA-Bn = 1-benzyl-3,5-diaza-1-azonia-7-phosphatricyclo[3.3.1.1^{3,7}]decane chloride)[15a] and $[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(THPA)]$ ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl; THPA = 2,4,10-trimethyl-1,2,4,5,7,10-hexaaza-3-phosphatricyclo[3.3.1.1^{3,7}]decane)[15b] previously developed by us (under the same experimental conditions they led to benzamide in 76% and 60% GC yield, respectively, after 5 h of heating).[20]

Encouraged by this result, the scope of the process was next explored by carrying out the rearrangement of differently

dx.doi.org/10.1021/om3006917 | Organometallics 2012, 31, 6482−6490

substituted benzaldoximes **1b–u** (Table 1).[21] As observed for **1a**, all of them could be transformed into the corresponding

Table 1. Ruthenium-Catalyzed Rearrangement of Aromatic and Heteroaromatic Aldoximes in Water[a]



entry	aldoxime **1**	time (h)	yield (%) of **3**[b]
1	R = 2-F-C_6H_4 (**1b**)	5	**3b**; 91 (84)
2	R = 4-F-C_6H_4 (**1c**)	5	**3c**; 92 (86)
3	R = 2-Cl-C_6H_4 (**1d**)	5	**3d**; 80 (71)
4	R = 3-Cl-C_6H_4 (**1e**)	1	**3e**; 98 (84)
5	R = 4-Cl-C_6H_4 (**1f**)	2	**3f**; 94 (82)
6	R = 2,4-Cl_2-C_6H_3 (**1g**)	5	**3g**; 81 (69)
7	R = 2,6-Cl_2-C_6H_3 (**1h**)	5	**3h**; 96 (83)
8	R = 2-Cl-6-F-C_6H_3 (**1i**)	3	**3i**; 95 (84)
9	R = 3,5-Br_2-4-OH-C_6H_2 (**1j**)	7	**3j**; 96 (88)
10	R = C_6F_5 (**1k**)	1	**3k**; > 99 (93)
11	R = 2-NO_2-C_6H_4 (**1l**)	7	**3l**; 82 (75)
12	R = 4-NO_2-C_6H_4 (**1m**)	2	**3m**; 99 (91)
13	R = 2-Me-C_6H_4 (**1n**)	7	**3n**; 97 (87)
14	R = 3-Me-C_6H_4 (**1o**)	3	**3o**; 95 (88)
15	R = 4-Me-C_6H_4 (**1p**)	2	**3p**; 95 (86)
16	R = 2-OMe-C_6H_4 (**1q**)	24	**3q**; 74 (60)
17	R = 4-OMe-C_6H_4 (**1r**)	5	**3r**; 83 (72)
18	R = 4-OCF_3–C_6H_4 (**1s**)	5	**3s**; 99 (88)
19	R = 4-NH_2-C_6H_4 (**1t**)	7	**3t**; 95 (84)
20	R = 4-SMe-C_6H_4 (**1u**)	3	**3u**; 85 (76)
21	R = 2-naphthyl (**1v**)	5	**3v**; 93 (80)
22	R = 9-anthracenyl (**1w**)	7	**3w**; 94 (85)
23	R = 3-pyridyl (**1x**)	7	**3x**; 94 (82)
24	R = 5-Me-2-furyl (**1y**)	1	**3y**; 99 (90)
25	R = 2-thienyl (**1z**)	2	**3z**; 97 (86)

[a]Reactions performed under N_2 atmosphere at 100 °C using 1 mmol of the corresponding aldoxime (0.33 M in water). Substrate/Ru ratio: 100/5. [b]Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate chromatographic workup are given in parentheses.

primary amides **3b–u** in high yields (≥80% by GC; ≥71% after chromatographic purification; entries 1–20) after only 1–7 h of heating, regardless of their substitution pattern and electronic nature. However, due probably to steric factors, *ortho*-substituted substrates showed a lower reactivity compared to their *meta*- or *para*-substituted counterparts (e.g., entry 3 vs 4, 5; entry 11 vs 12; entry 13 vs 14, 15; or entry 16 vs 17). Remarkably, the present catalytic system tolerates different functional groups, such as halides (entries 1–10) or hydroxy (entry 9), nitro (entries 11–12), ethers (entries 16–18), amino (entry 19), or thioether (entry 20) functionalities, the latter being worthy of note since sulfur species are well-known poisons for homogeneous catalysts due to the formation of strong metal–sulfur bonds.[22] Polyaromatic substrates, such as naphthyl-2-carboxaldoxime (**1v**) and anthracenyl-9-carboxaldoxime (**1w**), as well as the heteroaromatic ones **1x–z**, containing pyridyl, furyl, and thienyl units, also participated in this reaction, delivering the desired primary amides **3v–z** in high yields after 1–7 h (≥93% by GC; ≥80% after chromatographic purification; entries 21–25 in Table 1). As in the case of **1a**, in all the reactions collected in Table 1, total consumption of the starting aldoximes was observed by GC and the only byproducts detected were the corresponding organonitriles RC≡N (**2b–z**).

At this point, we must note that despite the high generality shown by complex [$RuCl_2(\eta^6$-$C_6Me_6)${$P(NMe_2)_3$}] for the catalytic rearrangement of aromatic and heteroaromatic aldoximes, it was completely inoperative when salicylaldoxime (**1aa**) and pyridine-2-carboxaldoxime (**1ab**) were used as substrates (Figure 2). In both cases, the starting material was

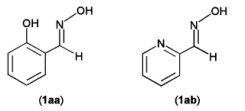
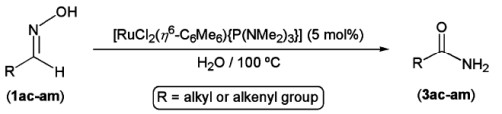


Figure 2. Structure of the unreactive aldoximes **1aa** and **1ab**.

recovered intact after 24 h of heating. These negative results could be explained by the high tendency of **1aa** and **1ab** to form stable six- and five-membered metallacycles, respectively, with metal ions.[23] Such a chelating *N,O*- or *N,N*-coordination of the aldoximes could block the ruthenium catalyst, thus preventing their rearrangement into the corresponding amides. This effect may also be responsible for the low reactivity observed with 2-methoxybenzaldoxime (**1q**), which required a long reaction period (24 h) to generate 2-methoxybenzamide (**3q**) in only 74% GC yield (Table 1; entry 16). On the other hand, intramolecular hydrogen bonds can also be established within **1aa** and **1ab** (particularly for its *Z* isomer), which may alternatively explain the lack of reactivity observed.

As shown in Table 2, complex [$RuCl_2(\eta^6$-$C_6Me_6)${P-$(NMe_2)_3$}] was also effective in the rearrangement of a variety of aliphatic and α,β-unsaturated aldoximes, thus confirming the wide scope of this catalytic transformation. Again, reactions proceeded in the absence of any additive. Thus, under the

Table 2. Ruthenium-Catalyzed Rearrangement of Aliphatic and α,β-Unsaturated Aldoximes in Water[a]



entry	aldoxime **1**	time (h)	yield (%) of **3**[b]
1	R = Me (**1ac**)	7	**3ac**; 99 (92)
2	R = Et (**1ad**)	3	**3ad**; 98 (90)
3	R = *n*-C_5H_{11} (**1ae**)	1	**3ae**; 96 (84)
4	R = *n*-C_6H_{13} (**1af**)	3	**3af**; 97 (88)
5	R = Cy (**1ag**)	3	**3ag**; 97 (89)
6	R = CH_2CH_2Ph (**1ah**)	1	**3ah**; 98 (86)
7	R = CH_2CH_2OPh (**1ai**)	2	**3ai**; 96 (87)
8	R = (*E*)-CH=CHPh (**1aj**)	1	**3aj**; 99 (88)
9	R = (*E*)-CH=CH-4–Cl-C_6H_4 (**1ak**)	2	**3ak**; 98 (89)
10	R = (*E*)-CH=CH-2-OMe-C_6H_4 (**1al**)	2	**3al**; 98 (91)
11	R = (*E*)-CH=CH-4-OMe-C_6H_4 (**1am**)	2	**3am**; 87 (79)

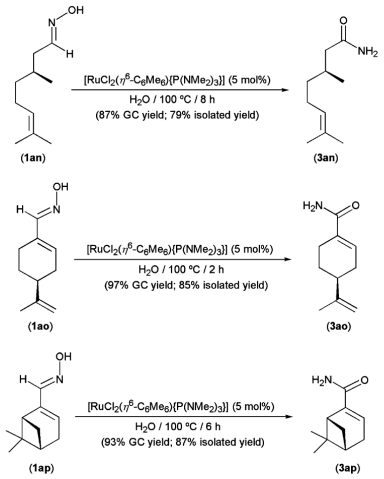
[a]Reactions performed under N_2 atmosphere at 100 °C using 1 mmol of the corresponding aldoxime (0.33 M in water). Substrate/Ru ratio: 100/5. [b]Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate chromatographic workup are given in parentheses.

dx.doi.org/10.1021/om3006917 | *Organometallics* 2012, 31, 6482–6490

standard reaction conditions (5 mol % of Ru, 100 °C), aldoximes **1ac−am** were readily converted into the corresponding amides **3ac−am** with high yields and selectivities (87−99%). As in the precedent cases, formation of minor amounts of the respective nitriles **2ac−am** was also observed by GC.

Finally, the synthetic utility of the present method was further demonstrated in the preparation of the chiral amides **3an−ap** (Scheme 5). To our delight, they were cleanly

Scheme 5. Ruthenium-Catalyzed Rearrangement of Optically Active Aldoximes 1an−ap in Water



generated (79−87% isolated yields) by rearrangement of the known optically pure aldoximes **1an−ap**, derived from the naturally occurring aldehydes (*S*)-(−)-citronellal, (*S*)-(−)-perillaldehyde, and (1*R*)-(−)-myrtenal, respectively. The high-yield formation of the fragrance citronellamide (**3an**) (79%) merits highlighting since previous studies in organic media using nickel acetate as catalyst,[7c] or an excess of Raney Ni,[24] led to lower conversions (50−62%).[25] It is also worthy of note that, to the best of our knowledge, the catalytic transformations of **1ao-ap** to **3ao-ap** are unprecedented.[26,27]

Some Mechanistic Aspects. Once the scope of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ was demonstrated, we became interested in the elucidation of its mechanism of action. In this sense, the monitoring of the catalytic reactions by GC showed, in all the cases, that the starting aldoximes are readily consumed in the early stages of the catalytic events, generating a mixture of the corresponding nitriles and the final amides. As a representative example, the product distribution as a function of time for the ruthenium-catalyzed rearrangement of benzaldoxime (**1a**) to benzamide (**3a**) at 100 °C (Scheme 4) is given in Figure 3. As shown in the graphic, **1a** is totally consumed after 15 min of heating, with benzonitrile (**2a**; ca. 23%) and the final benzamide (**3a**; ca. 77%) being the only organic products present in solution. So, hydration of benzonitrile by the aid of benzaldoxime can be discarded from that moment, and only a classical hydration pathway by the water molecules present in the medium can be evoked (Scheme 2). However, we must note that, once the starting benzaldoxime has been consumed, conversion of benzonitrile into benzamide is a much slower

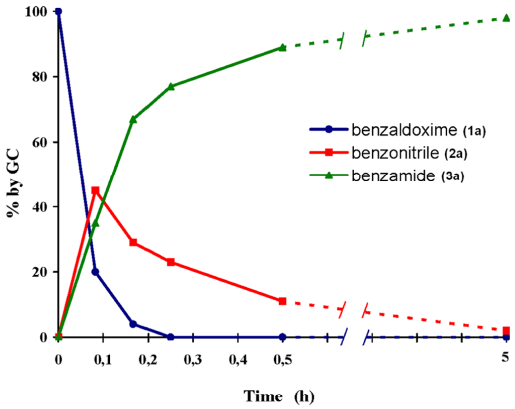


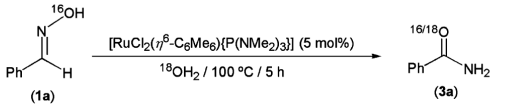
Figure 3. Product distribution as a function of time for the ruthenium-catalyzed rearrangement of benzaldoxime (**1a**) to benzamide (**3a**) at 100 °C in water (see Scheme 4).

process (additional 4.75 h are needed to completely hydrate the remaining 23% of **2a**).

The high initial reaction rate observed when benzaldoxime is still present in solution seems to indicate that the Williams mechanism depicted in Scheme 3 is probably operative at the beginning of the reaction. In line with this, when the catalytic rearrangement of benzaldoxime (**1a**) was carried out in organic media (anhydrous toluene or 1,2-dichloroethane) under the same experimental conditions (5 mol % of Ru; 100 °C), the process was also operative although less effective. Thus, 61−66% of benzamide (**2a**) was detected by GC in the crude reaction mixtures after 24 h of heating (to be compared with the data given in Scheme 4). As in the case of water, rapid dehydration of **1a** into **2a** also occurs (10−15 min) in toluene and 1,2-dichloroethane. At that time, the amount of benzamide (**3a**) formed is already 47−53% by GC, pointing out again remarkable rate differences in the presence or absence of benzaldoxime (**1a**). In addition, it seems also that the stoichiometric amount of water released during the dehydration of **1a** is not sufficient for completion of the subsequent rehydration step.

The catalytic rearrangement of **1a** in 97% ^{18}O-labeled water was also performed (Scheme 6). Analysis of the resulting

Scheme 6. Catalytic Rearrangement of Benzaldoxime (1a) to Benzamide (3a) in ^{18}O-Labeled Water



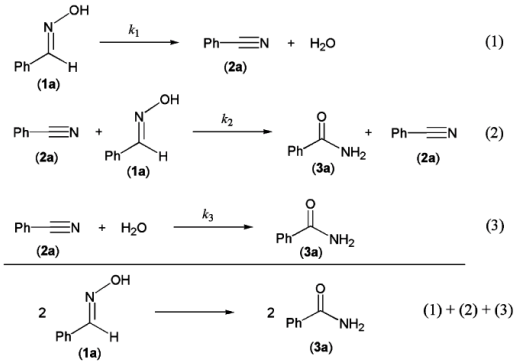
reaction product by high-resolution mass spectrometry (HRMS) showed the presence of both nonlabeled (m/z = 121.0551) and ^{18}O-labeled (m/z = 123.0574) benzamide in ca. 5.6:1 ratio (copies of the spectra of this sample and that generated from the reaction given in Scheme 4 are included in the Supporting Information). Incorporation of ^{18}O in the final benzamide clearly indicates that water molecules from the

dx.doi.org/10.1021/om3006917 | *Organometallics* 2012, 31, 6482−6490

solvent are to some extent participating in the reaction. However, the low ^{18}O-incorporation (ca. 15%) suggests that the classical dehydration/rehydration mechanism involving water (Scheme 2) is not the preferred pathway. The major formation of nonlabeled benzamide strongly supports the Williams mechanism as the main and faster path for the reaction in the early stages, in accord with the profile given in Figure 3.

Kinetic Analysis. In order to gain more information on these catalytic reactions, a kinetic analysis of the rearrangement of benzaldoxime (**1a**) to benzamide (**3a**) was performed. The proposed mechanisms for the rearrangement of aldoximes consist of several different chemical species and elementary reactions (see Schemes 2 and 3). Generally speaking, once a reaction mechanism has been established, it is possible to write the corresponding kinetic equations, to obtain therefrom a system of ordinary differential equations and to find, by means of a numerical method, the finest values of the rate constants of all the elementary steps. However, in our case, we can record experimental data (GC yields vs time) for only three compounds: benzaldoxime (**1a**), benzonitrile (**2a**), and benzamide (**3a**). Therefore, it is impossible to deal with the kinetic problem as conceived. Fortunately, a mechanism can be substituted by a "model" without losing its essential characteristics. The goal of this model is not to represent the whole chemistry of the process, but create a system of ordinary differential equations (easy to solve) that keep the essence of the original process. In this sense, as outlined in Scheme 7, a

Scheme 7. Adopted Model to Explain the Rearrangement of Benzaldoxime into Benzamide



very simple and intuitive model (3 steps and 3 independent chemical species; solvent is excluded) can be adopted to rationalize the overall rearrangement of benzaldoxime (**1a**) to benzamide (**3a**). It includes (i) the initial dehydration of **1a** into benzonitrile (**2a**), a common step in both mechanisms depicted in Schemes 2 and 3; (ii) the rehydration of **2a** by the aid of a second molecule of **1a**, step characteristic of the Williams mechanism (Scheme 3); and (iii) the classical hydration of **2a** by means of a water molecule to generate **3a**.

The sum of these three independent processes perfectly accounts for the observed rearrangement. Thus, while steps 1 and 2 represent the Williams mechanism (Scheme 3), steps 1 and 3 represent the classical one involving hydration of the nitrile by means of a water molecule (Scheme 2). Note that all steps in this model are assumed to be irreversible. Although this drastic reduction greatly simplifies the mathematical treatment, it is impossible to tackle, with guarantees of success, the resolution of the problem since the numerical methods that will be applied require, as usual, that the number of independent data is much higher than the number of unknowns (the rate constants k_1, k_2, and k_3 and the partial orders). As the disappearance of benzaldoxime (**1a**) takes place rapidly at 100 °C (see Figure 3), we decided to diminish the working temperature. At T = 60 °C the reaction rate slows down enough to get an appropriate set of experimental data, and thus the kinetic analysis was performed at this working temperature.[20] The analysis of the variation of the concentration of **1a** as a function of time (from 0 to 50 min; for t > 50 min, [**1a**] = 0 mol dm^{-3}) shows that the process follows a pseudo-first-order kinetics (linear correlation coefficient r = −0.9806). Also, using only the last six data points (from 60 to 1440 min; **1a** is already completely consumed) it can be assured that the hydration of benzonitrile (**2a**) into benzamide (**3a**) by means of a water molecule (Scheme 7, step 3) follows a pseudo-second-order kinetics (r = 0.9990) with respect to **2a**.[28] Combining all this information, it is possible to put forward the following system of three ordinary differential equations:

$$\frac{d[\mathbf{1a}]}{dt} = -k_1[\mathbf{1a}] - k_2[\mathbf{1a}] \quad (4)$$

$$\frac{d[\mathbf{2a}]}{dt} = +k_1[\mathbf{1a}] - k_3[\mathbf{2a}]^2 \quad (5)$$

$$\frac{d[\mathbf{3a}]}{dt} = +k_2[\mathbf{1a}] + k_3[\mathbf{2a}]^2 \quad (6)$$

The application of the "concentration−time integrals" (CTI)[29] method allows, on one hand, to obtain the values of the three rate constants and, on the other hand, to check the validity of the proposed model. The values of the rate constants obtained by the CTI method are dependent on the mathematical function chosen to fit the experimental data. In order to remove this dependence, the results of the CTI method were optimized with the aid of a nonlinear least-squares (NLLS) algorithm. We carried out all the calculations using MATLAB R2012a. The optimized values of the rate constants (at T = 60 °C) are

$$k_1 = 0.0145\ \text{min}^{-1} \quad k_2 = 0.0562\ \text{min}^{-1}$$
$$k_3 = 0.0316\ \text{dm}^3\ \text{mol}^{-1}\ \text{min}^{-1} \quad (7)$$

Figure 4 shows that the agreement between the observed and calculated data is fully satisfactory. The sum of squares due to error (SSE) is only 1.8 × 10^{-3}. Calculated data were obtained by numerical integration (using the optimized values of the rate constants, eq 7) of the system of differential equations described by eqs 4−6.[30]

Starting from the values of the three rate constants it is possible to calculate the rates of the three steps of the proposed model ($v_1 = k_1[\mathbf{1a}]$, $v_2 = k_2[\mathbf{1a}]$, and $v_3 = k_3[\mathbf{2a}]^2$). The overall rates of the Williams ($v_1 + v_2$) and classic ($v_1 + v_3$) mechanisms are shown in Figure 5. It is clearly observed that, when benzaldoxime (**1a**) is still present in solution, the Williams mechanism is predominant, particularly at the initial stages of the catalytic reaction. Once **1a** is consumed, only the classic mechanism involving water operates at very slow rates. These facts are in complete accord with the experimental observations made at 100 °C (see Figure 3) and previously commented on.

dx.doi.org/10.1021/om3006917 | Organometallics 2012, 31, 6482−6490

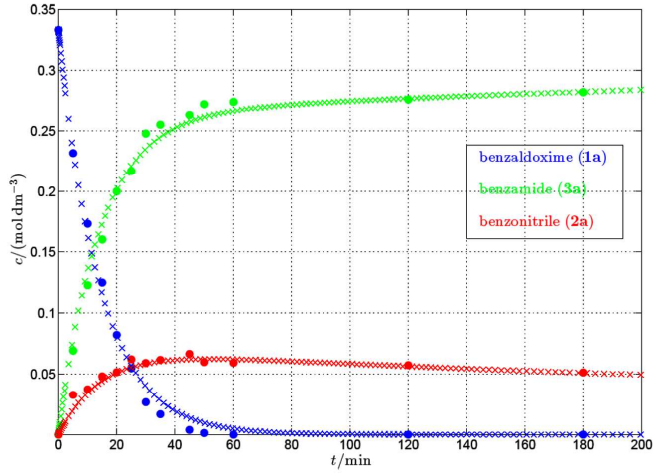


Figure 4. Experimental (filled circles) and calculated (cross) product distribution as a function of time for the ruthenium-catalyzed rearrangement of **1a** to **3a** at 60 °C in water.

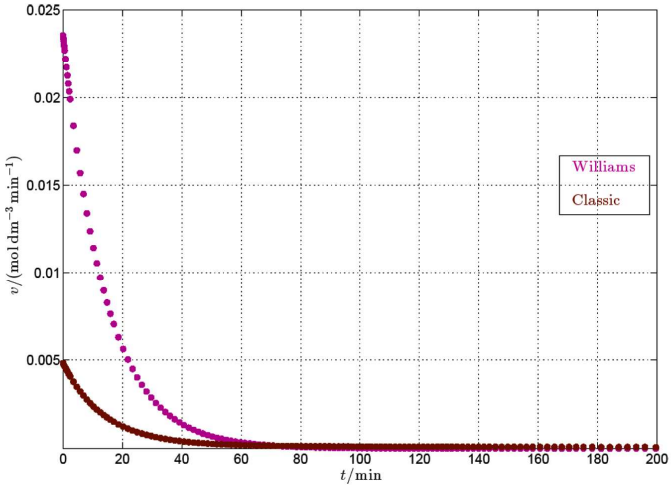


Figure 5. Overall rates (at T = 60 °C) of the Williams and classic mechanisms.

To further confirm the validity of the proposed kinetic model (eqs 4−6), we decided to apply it to the data set experimentally collected at T = 100 °C. Following the same mathematical procedure (CTI + NLLS) as above, the optimized values of the rate constants at this temperature are

$$k_1 = 0.2662\ \text{min}^{-1} \quad k_2 = 0.0641\ \text{min}^{-1}$$
$$k_3 = 0.9812\ \text{dm}^3\ \text{mol}^{-1}\ \text{min}^{-1} \qquad (8)$$

As expected, the values of the rate constants are all higher since the temperature has increased from 60 to 100 °C, with those of k_1 and k_3 showing a much higher increase in comparison with that of k_2.[31] The high quality of the fit (SSE = 5.9×10^{-4}) is shown in Figure 6.

■ CONCLUSION

In summary, we have developed a new protocol for the selective rearrangement of aldoximes to primary amides in a neutral aqueous medium, whose generality has been demonstrated for a huge range of substrates, including aromatic, heteroaromatic, α,β-unsaturated, and aliphatic ones. In addition, the high tolerance toward functional groups and the accessibility of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$, which makes use of a commercially available and inexpensive phosphine ligand, confer this efficient synthetic approach of amides genuine potential for practical applications avoiding the use of classical organic solvents. It is also worthy of note that, from a mechanistic point of view, our work demonstrates for the first time that the two mechanisms proposed in the literature for this transformation are compatible for a single

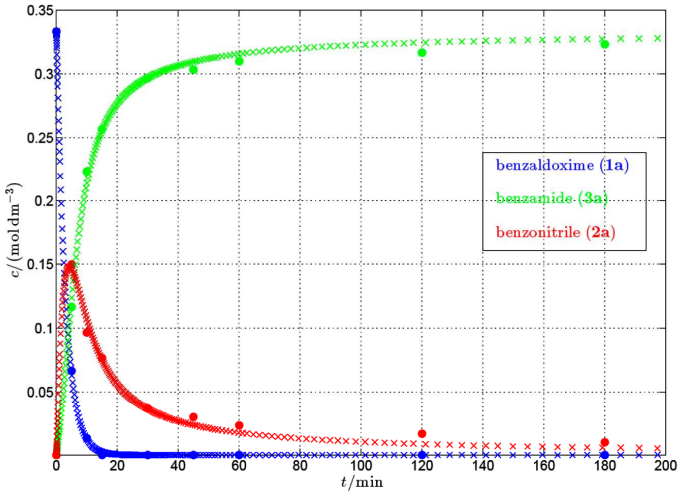


Figure 6. Experimental (filled circles) and calculated (cross) product distribution as a function of time for the ruthenium-catalyzed rearrangement of **1a** to **3a** at 100 °C in water.

catalyst, with that involving the hydration of the corresponding nitrile intermediates by a second molecule of aldoxime being predominant.

■ EXPERIMENTAL SECTION

GC measurements were performed on a Hewlett-Packard HP6890 equipment using a Supelco Beta-Dex 120 column (30 m length; 250 μm diameter). GC/MSD measurements were made with an Agilent 6890N equipment coupled to a 5973 mass detector (70 eV electron impact ionization) using a HP-1MS column. High-resolution mass spectra were provided by the mass spectrometry service of the University of Sevilla. Infrared spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. NMR spectra were recorded on a Bruker DPX-300 instrument at 300.1 MHz (^{1}H) or 75.47 MHz (^{13}C). The chemical shift values (δ) are given in parts per million and are referenced to the residual peak of the deuterated solvent used (CD_3OD). Elemental analyses were performed with a Perkin-Elmer 2400 microanalyzer. Optical rotations (α) at 20 °C at the sodium D-line were measured in a Perkin-Elmer 343 polarimeter. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). Complexes $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$,[15f] $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$,[15a] and $[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(THPA)]$[15b] were prepared by following the methods previously reported by us.

General Procedure for the Synthesis of Aldoximes. Aldoximes **1b**−**1ap** (all of them known compounds) were synthesized by condensation of the corresponding aldehyde with $NH_2OH{\cdot}HCl$ as follows: To a solution of the appropriate aldehyde (40 mmol) in a mixture of methanol (20 mL) and pyridine (10 mL) was added hydroxylamine hydrochloride (4.5 g, 65 mmol), and the mixture stirred at room temperature for 24 h. Solvents were removed *in vacuo*, and the residual oil was extracted with diethyl ether (ca. 200 mL). The extract was then washed with water (3 × 15 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The crude product was purified by column chromatography over silica gel using diethyl ether/hexane (1:1) as eluent. The identity of aldoximes **1b**−**1ap**, which were in general obtained in 70−80% yield as mixtures of the corresponding *E* and *Z* isomers, was confirmed by mass spectrometry and ^{1}H and ^{13}C{^{1}H} NMR spectroscopy.

General Procedure for the Catalytic Rearrangement of Aldoximes. Under a nitrogen atmosphere, the corresponding aldoxime **1a**−**ap** (1 mmol), water (3 mL), and the ruthenium(II) catalyst $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (0.025 g, 0.05 mmol; 5 mol %) were introduced into a Teflon-capped sealed tube, and the reaction mixture was stirred at 100 °C for the indicated time (see Tables 1 and 2 and Schemes 4 and 5). The course of the reaction was monitored by regularly taking samples of ca. 20 μL, which after extraction with CH_2Cl_2 (3 mL) were analyzed by GC. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using methanol/CH_2Cl_2 mixtures as eluent. In some cases, direct crystallization from the aqueous solution also allowed the isolation of pure products. The identity of the resulting primary amides was assessed by comparison of their ^{1}H and ^{13}C{^{1}H} NMR spectroscopic data with those reported in the literature and by their fragmentation in GC/MSD (copies of the ^{1}H and ^{13}C{^{1}H} NMR spectra of all the amides synthesized in this work (^{19}F NMR spectrum in the case of **3k**) are included in the Supporting Information). Characterization data for the novel amides **3ao** and **3ap** are as follows:

(*S*)-(−)-Perillamide (3ao): white solid. Yield: 85% (0.140 g). ^{1}H NMR (300.1 MHz, CD_3OD): δ 1.53 (m, 1H), 1.78 (s, 3H), 1.93 (m, 1H), 2.09−2.45 (m, 5H), 4.76 (s, 1H), 4.78 (s, 1H), 6.72 (br, 1H) ppm. NH_2 signals not observed. ^{13}C{^{1}H} NMR (75.47 MHz, CD_3OD): δ 19.5, 24.3, 27.0, 30.5, 40.1, 108.3, 132.2, 134.0, 148.8, 172.0 ppm. IR (KBr): ν 3350 (m), 3193 (w), 3079 (w), 2938 (m), 1660 (s), 1607 (s), 1521 (m), 1429 (m), 1367 (w), 1129 (w), 1043 (w), 943 (w), 923 (m), 883 (s), 723 (w), 637 (w), 477 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* 165 (20%, M$^+$), 137 (30), 122 (50), 107 (40), 91 (50), 67 (80), 44 (100), 27 (40). $[\alpha]^{20}_D$ = −111.8 (*c* = 0.03 M in MeOH). Anal. Calcd (%) for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.58; H, 9.23.

(1*R*)-(−)-Myrtenamide (3ap): white solid. Yield: 87% (0.144 g). ^{1}H NMR (300.1 MHz, CD_3OD): δ 0.85 (s, 3H), 1.15 (d, *J* = 8.3 Hz, 1H), 1.37 (s, 3H), 2.15 (br, 1H), 2.43−2.56 (m, 3H), 2.70 (m, 1H), 6.53 (br, 1H) ppm. NH_2 signals not observed. ^{13}C{^{1}H} NMR (75.47 MHz, CD_3OD): δ 19.9, 25.0, 30.8, 31.4, 37.3, 40.4, 41.5, 130.8, 142.8, 171.1 ppm. IR (KBr): ν 3392 (m), 3195 (w), 2918 (m), 1647 (s), 1601 (s), 1465 (w), 1404 (m), 1383 (w), 1331 (w), 1264 (w), 1109 (w), 1075 (w), 968 (w), 888 (m), 846 (w), 767 (m), 687 (w), 615 (w), 584 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* 165 (10%, M$^+$), 150 (10), 122 (80), 105 (90), 79 (100), 63 (30), 44 (90), 27 (40). $[\alpha]^{20}_D$ = −35.2 (*c* = 0.03 M in MeOH). Anal. Calcd (%) for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.75; H, 9.04.

dx.doi.org/10.1021/om3006917 | *Organometallics* 2012, 31, 6482−6490

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of all the amides synthesized in this work (^{19}F NMR spectrum in the case of **3k**) and HRMS spectra of benzamide (**3a**) isolated from the reactions described in Schemes 4 and 6. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: crochetpascale@uniovi.es (P.C.); vcm@uniovi.es (V.C.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the Ministerio de Economía y Competitividad of Spain (Projects CTQ2010-14796/BQU and CSD2007-00006) is gratefully acknowledged.

■ REFERENCES

(1) See, for example: (a) *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970. (b) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Greenberg, A.; Breneman, C. M.; Liebman, J. F., Eds.; Wiley: New York, 2000. (c) *Polyesters and Polyamides*; Deopura, B. L.; Gupta, B.; Joshi, M.; Alagirusami, R., Eds.; CRC Press: Boca Raton, 2008. (d) Johansson, I. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley: New York, 2004; Vol. 2, pp 442−463.

(2) See, for example: (a) Bailey, P. D.; Mills, T. J.; Pettecrew, R.; Price, R. A. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. 5, pp 201−294. (b) *Methoden Organic Chemistry (Houben Weyl)*; Dopp, D.; Dopp, H., Eds.; Thieme Verlag: Stuttgart, 1985; Vol. *E5*(2), pp 1024−1031.

(3) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zacks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411−420.

(4) A related industry-led survey highlighting the need for efficient amide formation methods can be found in: Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337−2347.

(5) For recent reviews covering innovative approaches for amide bond formation, see: (a) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405−3415. (b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471−479.

(6) For reviews on the Beckmann rearrangement, see: (a) Kumar, R. R.; Vanithan, K. A.; Balasubramanian, M. In *Name Reactions for Homologations - Part 2*; Li, J. J., Ed.; John Wiley & Sons: Hoboken, NJ, 2009; pp 274−292. (b) Gawley, R. E. *Org. React.* **1988**, *35*, 1−420.

(7) Typically, the isomerization of aldoximes to primary amides has been performed using stoichiometric acidic reagents under harsh conditions. See, for example: (a) Horning, E. C.; Stromberg, V. L. *J. Am. Chem. Soc.* **1952**, *74*, 5151−5152. (b) Hoffenberg, D. S.; Hauser, C. R. *J. Org. Chem.* **1955**, *20*, 1496−1500. (c) Field, L.; Hughmark, P. B.; Shumaker, S. H.; Marshall, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 1983−1987.

(8) (a) Leusink, A. J.; Meerbeek, T. G.; Noltes, J. G. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 123−125. (b) Leusink, A. J.; Meerbeek, T. G.; Noltes, J. G. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 142−145. (c) Setsuda, T. Jpn. Kokai Tokkyo Koho JP 52128302, 1977. (d) Komiya, S.; Shimazu, H.; Tamashima, T. Jpn. Kokai Tokkyo Koho JP 2003342245, 2003. (e) Park, S.; Choi, Y.; Han, H.; Yang, S. H.; Chang, S. *Chem. Commun.* **2003**, 1936−1937. (f) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 73−75. (g) Oewston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 3599−3601. (h) Fujiwara, H.; Ogasawara, Y.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 5202−5205. (i) Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Yamaguchi, K.; Mizuno, N. *Chem. Asian J.* **2008**, *3*, 1715−1721. (j) Mishra, A.; Ali, A.; Upreti, S.; Gupta, R. *Inorg. Chem.* **2008**, *47*, 154−161. (k) Gnanamgari, D.; Crabtree, R. H. *Organometallics* **2009**, *28*, 922−924. (l) Kim, M.; Lee, J.; Lee, H.-Y.; Chang, S. *Adv. Synth. Catal.* **2009**, *351*, 1807−1812. (m) Allen, C. L.; Davulcu, S.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 5096−5099. (n) Allen, C. L.; Burel, C.; Williams, J. M. J. *Tetrahedron Lett.* **2010**, *51*, 2724−2726. (o) Ramón, R. S.; Bosson, J.; Díez-González, S.; Marion, N.; Nolan, S. P. *J. Org. Chem.* **2010**, *75*, 1197−1202. (p) Hull, J. F.; Hilton, S. T.; Crabtree, R. H. *Inorg. Chim. Acta* **2010**, *363*, 1243−1245. (q) Saidulu, G.; Anand, N.; Rao, K. S. R.; Burri, A.; Park, S.-E.; Burri, D. R. *Catal. Lett.* **2011**, *141*, 1865−1871. (r) Kumar, P.; Singh, A. K.; Pandey, R.; Pandey, D. S. *J. Organomet. Chem.* **2011**, *696*, 3454−3464. (s) Sharma, S. K.; Bishopp, S. D.; Allen, C. L.; Lawrence, R.; Bamford, M. J.; Lapkin, A. A.; Plucinski, P.; Watson, R. J.; Williams, J. M. J. *Tetrahedron Lett.* **2011**, *52*, 4252−4255. (t) Allen, C. L.; Lawrence, R.; Emmett, L.; Williams, J. M. J. *Adv. Synth. Catal.* **2011**, *353*, 3262−3268. (u) Martínez-Asensio, A.; Yus, M.; Ramón, D. J. *Tetrahedron* **2012**, *68*, 3948−3951.

(9) (a) Ali, M. A.; Punniyamurthy, T. *Adv. Synth. Catal.* **2010**, *352*, 288−292. (b) Gowda, R. R.; Chakraborty, D. *Eur. J. Org. Chem.* **2011**, 2226−2229. (c) Allam, B. K.; Singh, K. N. *Tetrahedron Lett.* **2011**, *52*, 5851−5854. (d) Raja, N.; Raja, M. U.; Ramesh, R. *Inorg. Chem. Commun.* **2012**, *19*, 51−54. (e) Prabhu, R. N.; Ramesh, R. *RSC Adv.* **2012**, *2*, 4515−4524.

(10) Note that the direct transformation of aldehydes to primary amides is especially exigent and usually requires the use of highly reactive reagents in excess quantities. See, for example: (a) Loupy, A.; Régnier, S. *Tetrahedron Lett.* **1999**, *40*, 6221−6224. (b) Sharghi, H.; Hosseini, M. *Synthesis* **2002**, 1057−1060. (c) Sharghi, H.; Sarvari, M. H. *Tetrahedron* **2002**, *58*, 10323−10328. (d) Ekoue-Kovi, K.; Wolf, C. *Chem.—Eur. J.* **2008**, *14*, 6302−6315 , and references therein.

(11) Examples of catalytic systems able to effect the selective dehydration of aldoximes to nitriles can be found in: (a) Attanasi, O.; Palma, P.; Serra-Zanetti, F. *Synthesis* **1983**, 741−742. (b) Hart-Davis, J.; Battioni, P.; Boucher, J.-L.; Mansuy, D. *J. Am. Chem. Soc.* **1998**, *120*, 12524−12530. (c) Yang, S. H.; Chang, S. *Org. Lett.* **2001**, *3*, 4209−4211. (d) Choi, E.; Lee, C.; Na, Y.; Chang, S. *Org. Lett.* **2002**, *4*, 2369−2371. (e) Ishihara, K.; Furuya, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2983−2986. (f) Yan, P.; Batamack, P.; Prakash, G. K. S.; Olah, G. A. *Catal. Lett.* **2005**, *101*, 141−143. (g) Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3922−3925. (h) Kim, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1717−1719. (i) Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2010**, *51*, 4479−4481. (j) Li, Y.-T.; Liao, B. S.; Chen, H.-P.; Liu, S.-T. *Synthesis* **2011**, 2639−2643.

(12) For reviews on metal-catalyzed nitrile hydration reactions, see: (a) Parkins, A. W. *Platinum Met. Rev.* **1996**, *40*, 169−174. (b) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771−1802. (c) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *358*, 1−21. (d) Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* **2011**, *255*, 949−974.

(13) Examples of catalytic hydrations of nitriles to amides using aldoximes as the water source have been described in: (a) Kim, E. S.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 2973−2975. (b) Lee, J.; Kim, M.; Chang, S.; Lee, H.-Y. *Org. Lett.* **2009**, *11*, 5598−5601. (c) Kim, E. S.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2010**, *51*, 1589−1591. (d) Kim, E. S.; Kim, Y. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2010**, *31*, 700−703. (e) Kiss, Á.; Hell, Z. *Tetrahedron Lett.* **2011**, *52*, 6021−6023. (f) Ma, X.-Y.; He, Y.; Hu, Y.-L.; Lu, M. *Tetrahedron Lett.* **2012**, *53*, 449−452. (g) Ma, X.; He, Y.; Wang, P.; Lu, M. *Appl. Organomet. Chem.* **2012**, *26*, 377−382.

(14) For selected recent examples, see: (a) Cadierno, V.; Francos, J.; Gimeno, J. *Green Chem.* **2010**, *12*, 135−143. (b) Lastra-Barreira, B.; Crochet, P. *Green Chem.* **2010**, *12*, 1311−1314. (c) Francos, J.; Cadierno, V. *Green Chem.* **2010**, *12*, 1552−1555. (d) Cadierno, V.; Francos, J.; Gimeno, J. *Chem. Commun.* **2010**, *46*, 4175−4177.

(e) Lastra-Barreira, B.; Francos, J.; Crochet, P.; Cadierno, V. *Green Chem.* **2011**, *13*, 307−313. (f) Cadierno, V.; Francos, J.; Gimeno, J. *Organometallics* **2011**, *30*, 852−862. (g) Cadierno, V.; Francos, J.; García-Garrido, S. E.; Gimeno, J. *Green Chem. Lett. Rev.* **2011**, *4*, 55−61. (h) Varela-Álvarez, A.; Sordo, J. A.; Piedra, E.; Nebra, N.; Cadierno, V.; Gimeno, J. *Chem.—Eur. J.* **2011**, *17*, 10583−10599. (i) Tomás-Mendivil, E.; Díez, J.; Cadierno, V. *Catal. Sci. Technol.* **2011**, *1*, 1605−1615. (j) Tomás-Mendivil, E.; Toullec, P. Y.; Díez, J.; Conejero, S.; Michelet, V.; Cadierno, V. *Org. Lett.* **2012**, *14*, 2520−2523.

(15) (a) Cadierno, V.; Francos, J.; Gimeno, J. *Chem.—Eur. J.* **2008**, *14*, 6601−6605. (b) Cadierno, V.; Díez, J.; Francos, J.; Gimeno, J. *Chem.—Eur. J.* **2010**, *16*, 9808−9817. (c) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno, V. *Organometallics* **2010**, *29*, 3955−3965. (d) García-Garrido, S. E.; Francos, J.; Cadierno, V.; Basset, J.-M.; Polshettiwar, V. *ChemSusChem* **2011**, *4*, 104−111. (e) García-Álvarez, R.; Francos, J.; Crochet, P.; Cadierno, V. *Tetrahedron Lett.* **2011**, *52*, 4218−4220. (f) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno, V. *Organometallics* **2011**, *30*, 5442−5451. (g) García-Álvarez, R.; García-Garrido, S. E.; Díez, J.; Crochet, P.; Cadierno, V. *Eur. J. Inorg. Chem.* **2012**, in press (DOI: 10.1002/ejic.201200592).

(16) This property has been recently exploited by Tyler and co-workers in the challenging catalytic hydration of cyanohydrins to the corresponding α-hydroxyamides, where the related arene-Ru(II) complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(NMe_2)_3\}]$ showed an unprecedented reactivity: Knapp, S. M. M.; Sherbow, T. J.; Juliette, J. J.; Tyler, D. R. *Organometallics* **2012**, *31*, 2941−2944.

(17) For leading references in this field, see: (a) Li, C. J.; Chan, T. H. In *Comprehensive Organic Reactions in Aqueous Media*; John Wiley & Sons: NJ, 2007. (b) *Organic Reactions in Water: Principles, Strategies and Applications*; Lindstrom, U. M., Ed.; Blackwell Publishing Ltd.: Oxford, 2007. (c) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*; Cornils, B.; Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1998. (d) Joó, F. In *Aqueous Organometallic Catalysis*; Kluwer: Dordrecht, 2001.

(18) One of the crucial points in realizing a "green chemical" process involves the choice of a safe, nontoxic, and cheap solvent. In this context, water is the first solvent of choice regarding the aforementioned considerations: (a) Nelson, W. M. In *Green Solvents for Chemistry: Perspectives and Practice*; Oxford University Press: New York, 2003. (b) Clark, J. H.; Taverner, S. J. *Org. Process Res. Dev.* **2007**, *11*, 149−155. (c) Kerton, F. M. In *Alternative Solvents for Green Chemistry*; RSC Publishing: Cambridge, 2009.

(19) A limited number of examples of amide formation reactions starting directly from aldehydes and hydroxylamine (Scheme 1) in aqueous media have also been described. See refs 8u and 9a−c.

(20) (a) As expected, the use of lower temperatures and/or loadings of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ reduces the yield of **3a** and slows the reaction. For example, when using 5 mol % of Ru at 60 °C, 24 h were needed to produce **3a** in 94% GC yield (87% after 5 h), while the use of 2 mol % of Ru at 100 °C led to **3a** in only 82% yield after 24 h (74% after 5 h). (b) As observed in our previous nitrile hydration studies (ref 15f), complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ slowly decomposes under the catalytic reaction conditions to generate the inactive species $[RuCl_2(\eta^6\text{-}C_6Me_6)(NHMe_2)]$, via hydrolysis of the $P(NMe_2)_3$ ligand. On the other hand, a Brønsted acid catalysis has been discarded since only a minor amount of benzamide (ca. 15%) is formed using catalytic HCl (5 mol%) instead of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ under the same reaction conditions.

(21) Most of the aldoximes employed in this work were synthesized as mixtures of the corresponding *E* and *Z* isomers in ratios ranging from 95:5 to 30:70. As previously observed in related works (see ref 8), no differences in reactivity between both stereoisomers were observed.

(22) (a) Dunleavy, J. *Platinum Met. Rev.* **2006**, *50*, 110. (b) For a recent example of the poisoning of a homogeneous ruthenium catalyst by the methylsulfanyl group, see: Díaz-Álvarez, A. E.; Crochet, P.; Cadierno, V. *Tetrahedron* **2012**, *68*, 2611−2620.

(23) Representative examples of stable metal complexes gerenated by chelation of **1aa** and **1ab** can be found in: (a) Hultgren, V. M.; Atkinson, I. M.; Beddoes, R. L.; Collison, D.; Garner, C. D.; Helliwell, M.; Lindoy, L. F.; Tasker, P. A. *Chem. Commun.* **2001**, 573−574. (b) Babu, M. S. S.; Krishna, P. G.; Reddy, K. H.; Philip, G. H. *J. Chil. Chem. Soc.* **2009**, *54*, 339−344. (c) Abu-Youssef, M. A. M.; Soliman, S. M.; Langer, V.; Gohar, Y. M.; Hasanen, A. A.; Makhyoun, M. A.; Zaky, A. H.; Öhrström, L. R. *Inorg. Chem.* **2010**, *49*, 9788−9797. (d) Zeheng, L.; Zhang, S.; Li, K.; Chen, W.; Chen, Y.; Xu, B.; Hu, B.; Li, Y.; Li, W. *J. Mol. Struct.* **2010**, *984*, 153−156. (e) Rusanova, J. A.; Buvaylo, E. A.; Rusanov, E. B. *Acta Crystallogr., Sect. E* **2011**, *E67*, m222−m223. (f) Konidaris, K. F.; Polyzou, C. D.; Kostakis, G. E.; Tasiopoulos, A. J.; Roubeau, O.; Teat, S. J.; Manessi-Zoupa, E.; Powell, A. K.; Perlepes, S. P. *Dalton Trans.* **2012**, *41*, 2862−2865.

(24) Caldwell, A. G.; Jones, E. R. H. *J. Chem. Soc.* **1946**, 599−601.

(25) Isomerization of **1an** into **3an** could be achieved in 85% yield by means of excess KOH at 180 °C under anhydrous conditions: Oku, M.; Fujikura, Y.; Etsuno, J. Jpn. Kokai Tokkyo Koho JP 07138213, 1995.

(26) Perillamide (**3ao**), which seems to possess interesting olfactory and antimicrobial properties, has been mentioned in a couple of patents. However, neither details on its synthesis nor characterization data were given in the documents: (a) Rieks, A.; Kähler, M.; Kirchner, U.; Wiggenhorn, K.; Kinzer, M.; Risch, S. PCT Int. Appl. WO 2004/076400, 2004. (b) Ray, A.; Boyle, S. M. PCT Int. Appl. WO 2011/130726, 2011.

(27) Myrtenamide (**3ap**) is a new compound that has not been previously described in the literature.

(28) In an independent experiment, the hydration of benzonitrile (**2a**) into benzamide (**3a**) in water (0.33 M) mediated by complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (0.5 mol%) was studied at $T = 60$ °C, and a pseudo-second-order kinetics with respect to **2a** was also found ($r = 0.9889$).

(29) (a) French, D. *J. Am. Chem. Soc.* **1950**, 72, 4806−4807. (b) Saville, D. *J. Phys. Chem.* **1971**, 75, 2215−2217.

(30) The selected routine for the numerical integration, *ode15s*, is a variable-order stiff solver based on numerical differentiation formulas. The relative and absolute error tolerances were set to 10^{-6} and 10^{-10}, respectively.

(31) This fact indicates that the classic mechanism (Scheme 2) is much more dependent on the temperature than the Williams one (Scheme 3). However, we must note that the accuracy of the calculated values of the rate constants in eq 8 is low (for $t > 15$ min, [**1a**] = 0 mol dm^{-3} at 100 °C). The remarkable increase of k_3 with temperature is not unexpected since harsh conditions are usually required in metal-catalyzed nitrile hydration processes (see ref 12).

RSC Advances

RSC Publishing

PAPER

Ruthenium-catalyzed one-pot synthesis of primary amides from aldehydes in water†

Cite this: DOI: 10.1039/c3ra23195j

Rocío García-Álvarez, Alba E. Díaz-Álvarez, Pascale Crochet* and Victorio Cadierno*

Received 5th December 2012,
Accepted 5th February 2013

DOI: 10.1039/c3ra23195j

www.rsc.org/advances

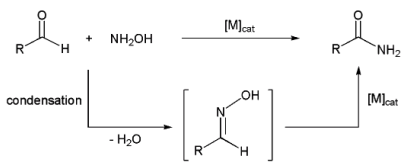
The readily available arene–ruthenium(II) complex $[RuCl_2\{\eta^6\text{-}C_6Me_6\}\{P(NMe_2)_3\}]$ (5 mol%) proved to be an efficient catalyst for the direct synthesis of primary amides from aldehydes and hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) in water at 100 °C. The process, which requires the presence of $NaHCO_3$ to catch the HCl released during the formation of the key aldoxime intermediates, was operative with both aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes, and tolerated several functional groups. A greener approach using commercially available NH_2OH solution (50 wt.% in water) is also presented.

Introduction

The amide bond is unarguably one of the most abundant functional groups in natural products, polymers and pharmaceuticals.[1] Amides are routinely prepared through the union of carboxylic acids and derivatives (halides, anhydrides or esters) with amines.[1,2] However, these classical methods present several drawbacks, such as the use of toxic, corrosive and/or expensive materials, highly exothermic reactions, low tolerance to sensitive functional groups, complex reaction conditions and wasteful procedures. The availability of new efficient and sustainable synthetic routes for this important class of compounds is therefore needed.[3] In the search for improved methods, metal-catalyzed transformations have emerged in the last two decades as the most promising alternatives for the atom-economical and cost effective synthesis of amides, opening also previously unavailable routes from substrates other than carboxylic acids and their derivatives.[4]

Aldehydes are highly desirable starting materials for amide synthesis due to their availability and non-toxic nature. In this context, the one-pot coupling of aldehydes with hydroxylamine catalyzed by metal complexes has been revealed in recent years as an appealing tool for the generation of primary amides (Scheme 1).[4,5] The reaction involves the Beckmann-type rearrangement of an aldoxime intermediate, generated *in situ* by the condensation of an aldehyde with NH_2OH, *via* initial dehydration to the corresponding nitrile followed by hydration of the C≡N bond.[4] Several catalytic systems, based on ruthenium,[6] iron,[7] rhodium,[8] iridium,[9] palladium,[10] copper,[11] zinc,[12] indium[12] and scandium[13] compounds, able to promote this catalytic transformation have already been described in the literature.[14]

On the other hand, the development of organic transformations in water has become one of the major cornerstones in modern chemistry.[15] In addition to the enhanced reactivities and selectivities observed in some cases,[16] the use of water as an alternative, available, safe, and cost-effective solvent fulfils the principles of "Green Chemistry",[17] thus creating an answer to the growing concerns associated with the environmental impact of chemical processes.[18] Despite this growing interest, metal catalysts that are able to promote the coupling of aldehydes with hydroxylamine in water remain scarce. Pioneering work in the field was published by Mizuno and co-workers in 2007 using the heterogeneous system $Rh(OH)_x/Al_2O_3$ (4 mol% of Rh).[8] The reactions, performed with the hydroxylammonium salt $(NH_2OH)_2{\cdot}H_2SO_4$, delivered the desired amides in high yields after 7 h of heating at 120–160 °C. $FeCl_3$ (5 mol%), in combination with Cs_2CO_3, proved also effective for the coupling of several aldehydes with hydroxylammonium hydrochloride in water under homogeneous and milder conditions (100 °C). However, longer reaction



Scheme 1 Catalytic formation of primary amides by the coupling of aldehydes with hydroxylamine.

Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Departamento de Química Orgánica e Inorgánica. Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo. Julián Claveria 8, 33006 Oviedo, Spain. E-mail: crochetpascale@uniovi.es (PC); vcm@uniovi.es (VC); Fax: (+34)985103446; Tel: (+34)985103453

† Electronic supplementary information (ESI) available: Copies of the ^1H and $^{13}C\{^1H\}$ NMR spectra of all the amides synthesized in this work (the ^{19}F NMR spectrum in the case of amide **2k**). See DOI: 10.1039/c3ra23195j

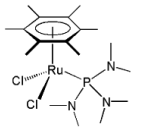


Fig. 1 Structure of the arene-ruthenium(II) catalyst employed in this work.

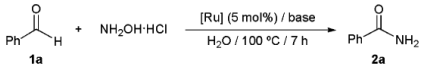
times (17–32 h) were needed in this case.[7] Faster transformations (15–35 min) were subsequently described by Singh and Allam, employing scandium(III) triflate (10 mol%), $NH_2OH{\cdot}HCl$ and Na_2CO_3, but a relatively high temperature was still required to attain good conversions (135 °C under controlled MW irradiation).[13] Quite recently, a protocol involving $Cu(OAc)_2$ (2 mol%) and aqueous hydroxylamine solution has been reported by Ramón and co-workers.[11b] The direct use of $NH_2OH_{(aq)}$, instead of a hydroxylammonium salt, eliminated the need for a base, thus minimizing the generation of wastes. However, the extremely long reaction times required (2 days at 110 °C) is a serious drawback for further applications of this catalytic system.

Following on with our current interest in catalytic amide bond forming reactions,[4c,19] herein we report an alternative and more efficient catalyst, namely $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (Fig. 1), for the direct conversion of aldehydes to primary amides in water. This versatile arene–ruthenium(II) complex, which contains the inexpensive P-donor ligand tris(dimethylamino)phosphine, has already proved to be effective for the catalytic hydration of organonitriles[19e,f] and the catalytic rearrangement of aldoximes[19g] in aqueous media. As the reader will see, by means of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$, the coupling process depicted in Scheme 1 can be conveniently performed using solid hydroxylammonium hydrochloride in the presence of $NaHCO_3$, or by directly employing commercially available hydroxylamine solution (50 wt% in H_2O) under base-free conditions.

Results and discussion

The ability of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ to promote the catalytic conversion of aldehydes into primary amides was evaluated by employing commercially available hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) as the "NH_2 source", and benzaldehyde (**1a**) as a model substrate (results are collected in Table 1). For the initial reaction conditions, we took those previously employed in our nitrile hydration and aldoxime rearrangement studies, *i.e.*, the use of a 0.33 M solution of the substrate in water, a ruthenium loading of 5 mol% and a working temperature of 100 °C.[19e–g] Under these conditions, when benzaldehyde (**1a**) was reacted with 1 equiv. of $NH_2OH{\cdot}HCl$, the desired benzamide (**2a**) was formed in only 21% GC-yield after 7 h of heating (Table 1, entry 1). In addition to unreacted **1a** (*ca.* 24%) and benzonitrile (*ca.* 15%), the major product of the reaction turned out to be benzoic acid (*ca.*

Table 1 Ruthenium-catalyzed one-pot synthesis of benzamide (**2a**) from benzaldehyde (**1a**) in water using hydroxylammonium hydrochloride[a]

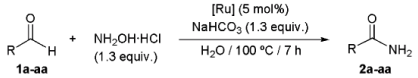


Entry	$NH_2OH{\cdot}HCl$	Base	Yield of **2a**[b]
1	1 equiv.	—	21%[c]
2	1 equiv.	$NaHCO_3$ (1 equiv.)	60%
3	1.1 equiv.	$NaHCO_3$ (1.1 equiv.)	69%
4	1.2 equiv.	$NaHCO_3$ (1.2 equiv.)	80%
5	1.3 equiv.	$NaHCO_3$ (1.3 equiv.)	88%
6	1.3 equiv.	NaOH (1.3 equiv.)	83%
7	1.3 equiv.	KOH (1.3 equiv.)	81%
8	1.3 equiv.	Na_2CO_3 (1.3 equiv.)	84%
9	1.3 equiv.	K_2CO_3 (1.3 equiv.)	87%
10	1.3 equiv.	Cs_2CO_3 (1.3 equiv.)	88%
11[d]	0.65 equiv.	$NaHCO_3$ (1.3 equiv.)	85%
12[e]	1.3 equiv.	$NaHCO_3$ (1.3 equiv.)	22%
13[f]	1.3 equiv.	$NaHCO_3$ (1.3 equiv.)	57%
14[g]	1.3 equiv.	$NaHCO_3$ (1.3 equiv.)	63%
15[h]	1.3 equiv.	$NaHCO_3$ (1.3 equiv.)	55%
16[i]	1.3 equiv.	$NaHCO_3$ (1.3 equiv.)	46%

[a] Reactions performed under a N_2 atmosphere at 100 °C starting from 1 mmol of benzaldehyde (0.33 M in water). [b] Yields determined by GC (uncorrected GC areas). [c] Benzoic acid in *ca.* 40% yield is formed. [d] Reaction performed using $(NH_2OH)_2{\cdot}H_2SO_4$ instead of $NH_2OH{\cdot}HCl$. [e] Reaction performed in toluene for 24 h. [f] Reaction performed in 1,2-dichloroethane for 24 h. [g] Reaction performed in 2-propanol for 24 h. [h] Reaction performed at 80 °C. [i] Reaction performed using a ruthenium loading of 2 mol%.

40%), resulting from the hydrolysis of **2a** promoted by the HCl released during the generation of the key benzaldoxime intermediate (see Scheme 1). This latter intermediate was not observed by GC in the crude reaction mixture, in accordance with the great ability shown by $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ to promote its dehydration into benzonitrile.[19g] To avoid the competitive hydrolysis of the amide, 1 equiv. of $NaHCO_3$ was introduced into the medium, and the yield of **2a** could be increased to 60% without detecting benzoic acid in the crude product (Table 1, entry 2). Further improvements to the yield of **2a** were achieved by increasing the quantities of $NH_2OH{\cdot}HCl$ and $NaHCO_3$ employed (Table 1, entries 3–5), reaching a maximum 88% GC-yield with 1.3 equiv. of these reagents (Table 1, entry 5; *ca.* 4% of unreacted **1a** and 8% of benzonitrile were detected by GC in the crude reaction mixture). As shown in Table 1, entries 6–10, different alkali metal hydroxides and carbonates were screened as potential bases for this reaction. Marked differences in reactivity compared with $NaHCO_3$ were not observed. Similarly, the use of $(NH_2OH)_2{\cdot}H_2SO_4$ instead of $NH_2OH{\cdot}HCl$ led to comparable results (Table 1, entry 11). In contrast, remarkably poorer yields of **2a** were attained when the catalytic coupling of **1a** with $NH_2OH{\cdot}HCl$ was carried out in organic media (*e.g.*, toluene, 1,2-dichloroethane or 2-propanol), even after 24 h of heating (Table 1, entries 12–14). These last observations are in complete accordance with the need for an excess of water for the effective rearrangement of the intermediate benzaldoxime

Table 2 Ruthenium-catalyzed one-pot synthesis of primary amides (**2**) from aldehydes (**1**) in water using hydroxylammonium hydrochloride[a]

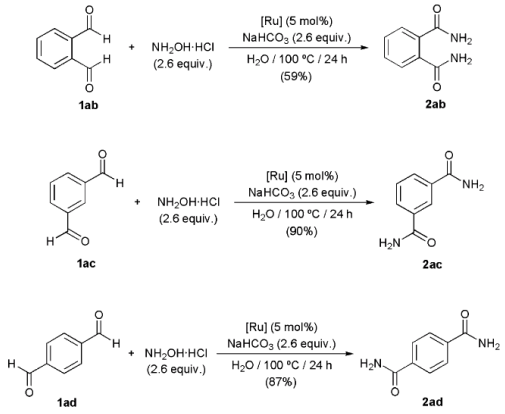


Entry	Aldehyde **1**	Yield of **2**[b]
1	R = Ph (**1a**)	**2a**; 88% (79%)
2	R = 2-F-C_6H_4 (**1b**)	**2b**; 92% (82%)
3	R = 3-F-C_6H_4 (**1c**)	**2c**; 94% (83%)
4	R = 4-F-C_6H_4 (**1d**)	**2d**; 85% (71%)
5	R = 2-Cl-C_6H_4 (**1e**)	**2e**; 97% (87%)
6	R = 3-Cl-C_6H_4 (**1f**)	**2f**; 86% (74%)
7	R = 4-Cl-C_6H_4 (**1g**)	**2g**; 97% (89%)
8	R = 2-Br-C_6H_4 (**1h**)	**2h**; 87% (76%)
9	R = 3-Br-C_6H_4 (**1i**)	**2i**; 90% (80%)
10	R = 4-Br-C_6H_4 (**1j**)	**2j**; 82% (70%)
11	R = C_6F_5 (**1k**)	**2k**; 99% (90%)
12	R = 3-NO_2-C_6H_4 (**1l**)	**2l**; 99% (92%)
13	R = 4-NO_2-C_6H_4 (**1m**)	**2m**; 88% (79%)
14[c]	R = 2-Me-C_6H_4 (**1n**)	**2n**; 80% (71%)
15[c]	R = 4-Me-C_6H_4 (**1o**)	**2o**; 74% (63%)
16[c]	R = 2-OMe-C_6H_4 (**1p**)	**2p**; 72% (61%)
17[c]	R = 4-OMe-C_6H_4 (**1q**)	**2q**; 63% (50%)
18[c]	R = 4-SMe-C_6H_4 (**1r**)	**2r**; 80% (70%)
19	R = 3-Furyl (**1s**)	**2s**; 84% (72%)
20	R = 2-Thienyl (**1t**)	**2t**; 92% (85%)
21	R = *n*-C_6H_{13} (**1u**)	**2u**; 95% (88%)
22	R = Cy (**1v**)	**2v**; 91% (80%)
23	R = CH_2CH_2Ph (**1w**)	**2w**; 89% (79%)
24	R = (*E*)-CH=CHPh (**1x**)	**2x**; 90% (80%)
25	R = (*E*)-CH=CH-2-C_6H_4OMe (**1y**)	**2y**; 76% (63%)
26	R = (*E*)-CH=CH-4-C_6H_4OMe (**1z**)	**2z**; 83% (75%)
27	R = (*S*)-CH_2CH(Me)$(CH_2)_2CH$=CMe_2 (**1aa**)	**2aa**; 92% (83%)

[a] Reactions performed under N_2 atmosphere at 100 °C starting from 1 mmol of the corresponding aldehyde (0.33 M in water). Substrate/Ru/NH_2OH·HCl/$NaHCO_3$ ratio: 100/5/130/130. [b] Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate work-up are given in brackets. [c] Reaction time: 24 h.

since, as previously discussed in ref. 19*g*, the hydration of the initially formed benzonitrile is the rate limiting step of the rearrangement process. As expected, the use of lower temperatures or ruthenium loadings also reduced the yield of **2a** considerably (Table 1, entries 15–16).

Using the optimal reaction conditions (0.33 M solution of the aldehyde in water; aldehyde/Ru/NH_2OH·HCl/$NaHCO_3$ ratio = 100/5/130/130; 100 °C), the generality of the process was then explored. The results obtained are summarized in Table 2. Thus, as observed for **1a** (Table 2, entry 1), [$RuCl_2$(η^6-C_6Me_6){$P(NMe_2)_3$}] was able to convert other aromatic aldehydes (**1b–r**; Table 2, entries 1–18) into the corresponding primary amides **2b–r** in moderate to good yields (63–99% GC-yield), regardless of the substitution pattern of the aromatic ring. However, an important influence of the electronic properties of the substituents on the efficiency of the process was observed. Thus, aldehydes with electron-donating groups showed lower reactivities (Table 2, entries 14–18) compared to substrates with electron-withdrawing functionalities (Table 2, entries 2–13), the former requiring longer reaction times (24 *vs.* 7 h) to generate the final products in high yields.

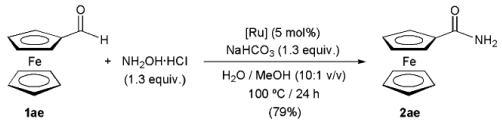


Scheme 2 Catalytic transformation of benzenedicarboxaldehydes **1ab–ad** in benzenediamides **2ab–ad** using complex [$RuCl_2$(η^6-C_6Me_6){$P(NMe_2)_3$}].

As expected, this coupling reaction is not restricted to aromatic aldehydes, heteroaromatic (**1s–t**; Table 2, entries 19–20), aliphatic (**1u–w**; Table 2, entries 21–23) and α,β-unsaturated ones (**1x–z**; Table 2, entries 24–26) also gave the desired amides **2s–z** in 76–95% GC-yield after 7 h of heating. Remarkably, as shown in entry 27 (Table 2), the use of [$RuCl_2$(η^6-C_6Me_6){$P(NMe_2)_3$}] allowed, for the first time, the direct preparation of the fragrance (*S*)-(−)-citronellamide (**2aa**) from the naturally occurring aldehyde (*S*)-(−)-citronellal (**1aa**).[19g,20] In all cases, the starting aldehydes, and the nitriles derived from these, were the only by-products detected at the end of the reactions by GC. Solvent removal, extraction of the crude product with dichloromethane, and recrystallization from hot water, provided analytically pure samples of the amides **2a–aa** in 50–92% isolated yield (in some cases additional purification by column chromatography was needed).

It is also worthy of note that the present coupling process proved useful for the synthesis of diamides. Thus, using an excess of hydroxylammonium hydrochloride and $NaHCO_3$ (2.6 equiv. of each), [$RuCl_2$(η^6-C_6Me_6){$P(NMe_2)_3$}] (5 mol%) was able to convert 1,2-, 1,3- and 1,4-benzenedicarboxaldehyde (**1ab–ad**) into phthalamide (**2ab**), isophthalamide (**2ac**) and terephthalamide (**2ad**), respectively, after 24 h of heating (Scheme 2).[21]

The outstanding performance of [$RuCl_2$(η^6-C_6Me_6){$P(NMe_2)_3$}] was further exploited in the catalytic synthesis of ferrocenecarboxamide (**2ae**), a valuable starting material in the chemistry of ferrocene,[22] by the coupling of ferrocenecarboxaldehyde (**1ae**) with NH_2OH·HCl (Scheme 3). Thus, performing the reaction in a water/MeOH (10 : 1 v/v) mixture for 24 h, **2ae** could be isolated in 79% yield following the standard work-up procedure described above. The use of a small amount of methanol was key to ensuring the total solubilisation of **1ae** during the process, with the same



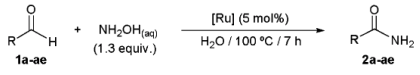
Scheme 3 Catalytic transformation of ferrocenecarboxaldehyde (**1ae**) into ferrocenecarboxamide (**2ae**) using $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$.

reaction performed in pure water delivering **2ae** in a remarkably lower yield (*ca.* 60%).

To the best of our knowledge, this is the first protocol described in the literature for the direct formation of **2ae** starting from **1ae**. The method commonly used for the preparation of ferrocenecarboxamide (**2ae**) involves a two-step sequence consisting of the conversion of ferrocenecarboxylic acid into the corresponding acid chloride, by action of harmful thionyl chloride, followed by treatment with aqueous ammonia.[22] In comparison with this classical method, the synthetic route depicted in Scheme 3 presents the following advantages: (*i*) it involves a single synthetic operation, (*ii*) it makes use of a cheaper starting material,[23] (*iii*) it proceeds in environmentally friendly aqueous medium, and (*iv*) it does not require tedious purification procedures.[24]

Finally, taking advantage of the operability of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ in aqueous medium, a simpler and greener procedure that employs commercially available hydroxylamine solution (50 wt% in H_2O) instead of solid $NH_2OH{\cdot}HCl$ was developed. The direct use of $NH_2OH_{(aq)}$ avoided the introduction of a base in the medium to catch the acid released during the generation of the corresponding aldoxime intermediate, thus simplifying the isolation of the amide and minimizing the generation of waste (extraction with CH_2Cl_2 to eliminate salts was not longer required). As shown in Table 3, in the studied examples, no marked differences in terms of activity relative to those observed using $NH_2OH{\cdot}HCl$ were found.

Table 3 Ruthenium-catalyzed one-pot synthesis of primary amides (**2**) from aldehydes (**1**) in water using hydroxylamine solution[a]



Entry	Aldehyde **1**	Yield of **2**[b]
1	R = Ph (**1a**)	**2a**; 83% (73%)
2	R = 2-F-C_6H_4 (**1b**)	**2b**; 93% (84%)
3	R = 3-F-C_6H_4 (**1c**)	**2c**; 91% (80%)
4	R = 4-Cl-C_6H_4 (**1g**)	**2g**; 94% (86%)
5	R = C_6F_5 (**1k**)	**2k**; 97% (89%)
6	R = 3-NO_2-C_6H_4 (**1l**)	**2l**; 99% (91%)
7[c]	R = 4-Me-C_6H_4 (**1o**)	**2o**; 78% (70%)
8[c]	R = 4-OMe-C_6H_4 (**1q**)	**2q**; 70% (61%)
9	R = 2-Thienyl (**1t**)	**2t**; 93% (86%)
10	R = *n*-C_6H_{13} (**1u**)	**2u**; 95% (87%)
11	R = Cy (**1v**)	**2v**; 82% (73%)
12	R = CH_2CH_2Ph (**1w**)	**2w**; 85% (74%)
13	R = (*E*)-CH=CHPh (**1x**)	**2x**; 93% (81%)
14[d]	R = Ferrocenyl (**1ae**)	**2ae**; 87%

[a] Reactions performed under a N_2 atmosphere at 100 °C, starting from 1 mmol of the corresponding aldehyde (0.33 M in water). Substrate/Ru/NH_2OH ratio: 100/5/130. [b] Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate work-up are given in brackets. [c] Reaction time: 24 h. [d] Reaction performed in a water/methanol mixture (10 : 1 v/v) for 24 h (the isolated yield is given).

Conclusions

In summary, simple and general protocols for the one-pot conversion of aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes into primary amides in water have been developed with the aid of the readily available arene–ruthenium(II) catalyst $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$. In the protocols, solid hydroxylammonium hydrochloride or hydroxylamine solution (50 wt% in H_2O) were employed as the "NH_2 source". The possibility of using the latter is particularly attractive because it prevents the introduction of a base into the medium, thus reducing the cost and generation of waste. In general, compared to other catalytic systems previously described in the literature for this one-pot transformation, $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ shows a superior activity under lower temperature regimes, attributes which provide it with a great potential for practical applications.

Experimental

General methods

The manipulations were performed under an inert N_2 atmosphere using vacuum-line and standard sealed-tube techniques. All reagents were obtained from commercial suppliers and used as received, with the exception of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$, which was prepared following the method previously reported by us.[19e,f] GC measurements were performed on Hewlett-Packard HP6890 equipment using a Supelco Beta-Dex™ 120 column (30 m length; 250 μm diameter).

General procedure for the ruthenium-catalyzed conversion of aldehydes into primary amides using $NH_2OH{\cdot}HCl$

Under a nitrogen atmosphere, the corresponding aldehyde (1 mmol), hydroxylamine hydrochloride (0.090 g, 1.3 mmol; 0.180 g, 2.6 mmol in the case of aldehydes **1ab–ad**), $NaHCO_3$ (0.109 g, 1.3 mmol; 0.218 g, 2.6 mmol in the case of aldehydes **1ab–ad**), 3 mL of water (a water/methanol mixture (10 : 1 v/v) in the case of aldehyde **1ae**), and the ruthenium(II) catalyst $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (0.025 g, 0.05 mmol; 5 mol%) were introduced into a teflon-capped sealed-tube and the reaction mixture was stirred at 100 °C for 7–24 h. After this time, the mixture was evaporated to dryness, the solid residue extracted with CH_2Cl_2 (10–20 mL) and filtered over kieselguhr. Evaporation of the extract led to a solid, which was redissolved in hot water (5–10 mL) and stored in a freezer at −20 °C for 10 h. This led to the crystallization of the corresponding amide,

which was separated, washed with hexane (2 × 5 mL) and vacuum-dried (in some cases additional purification by column chromatography over silica gel, using a methanol/CH_2Cl_2 mixture as the eluent, was needed). The identities of the resulting primary amides **2a–ae** were assessed by comparison of their ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data with those reported in the literature, and by their fragmentation in GC/MSD.

General procedure for the ruthenium-catalyzed conversion of aldehydes into primary amides using $NH_2OH_{(aq)}$ solution

Under a nitrogen atmosphere, the corresponding aldehyde (1 mmol), hydroxylamine (50 wt% solution in water; 80 μL, 1.3 mmol), 3 mL of water (a water/methanol mixture (10 : 1 v/v) in the case of aldehyde **1ae**), and the ruthenium(II) catalyst $[RuCl_2\{\eta^6\text{-}C_6Me_6\}\{P(NMe_2)_3\}]$ (0.025 g, 0.05 mmol; 5 mol%) were introduced into a teflon-capped sealed-tube and the reaction mixture stirred at 100 °C for 7–24 h. After this time, the hot mixture was passed through a filter paper, allowed to reach room temperature, and subsequently stored in freezer at −20 °C for 10 h. This led to the crystallization of the corresponding primary amide, which was separated, washed with hexane (2 × 5 mL) and vacuum-dried (in some cases additional purification by column chromatography over silica gel, using a methanol/CH_2Cl_2 mixture as the eluent, was needed).

Acknowledgements

Financial support from the Ministerio de Economía y Competitividad of Spain (Projects CTQ2010-14796/BQU and CSD2007-00006) is gratefully acknowledged.

References

1 See for example: (*a*) *The Chemistry of Amides*, ed. J. Zabicky, Wiley-Interscience, New York, 1970; (*b*) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*, ed. A. Greenberg, C. M. Breneman and J. F. Liebman, John Wiley & Sons, New York, 2000; (*c*) *Polyesters and Polyamides*, ed. B. L. Deopura, B. Gupta, M. Joshi and R. Alagirusami, CRC Press, Boca Raton, 2008; (*d*) I. Johansson, in *Kirk-Othmer Encyclopedia of Chemical Technology*, John Wiley & Sons, New York, 2004, vol. 2, pp. 442–463.

2 (*a*) See for example: *Methoden Org. Chem.* (Houben Weyl), ed. D. Dopp and H. Dopp, Thieme Verlag, Stuttgart, 1985, vol. E5(2), pp. 1024–1031; (*b*) P. D. Bailey, T. J. Mills, R. Pettecrew and R. A. Price, in *Comprehensive Organic Functional Group Transformations II*, ed. A. R. Katritzky and R. J. K. Taylor, Elsevier, Oxford, 2005, vol. 5, pp. 201–294; (*c*) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606.

3 Industrial-led surveys highlighting the need for efficient amide formation methods can be found in: (*a*) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337; (*b*) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411.

4 For recent reviews covering innovative approaches for amide bond formation see: (*a*) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405; (*b*) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471; (*c*) R. García-Álvarez, P. Crochet and V. Cadierno, *Green Chem.*, 2013, **15**, 46.

5 This method is complementary to the catalytic amidation of aldehydes with amines which proved particularly useful for the preparation of secondary and tertiary amides. For a specific review on this reaction, see: K. Ekoue-Kovi and C. Wolf, *Chem.–Eur. J.*, 2008, **14**, 6302.

6 (*a*) D. Gnanamgari and R. H. Crabtree, *Organometallics*, 2009, **28**, 922; (*b*) J. F. Hull, S. T. Hilton and R. H. Crabtree, *Inorg. Chim. Acta*, 2010, **363**, 1243; (*c*) N. Raja, M. U. Raja and R. Ramesh, *Inorg. Chem. Commun.*, 2012, **19**, 51; (*d*) R. N. Prabhu and R. Ramesh, *RSC Adv.*, 2012, **2**, 4515.

7 R. R. Gowda and D. Chakraborty, *Eur. J. Org. Chem.*, 2011, 2226.

8 (*a*) H. Fujiwara, Y. Ogasawara, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2007, **46**, 5202; (*b*) H. Fujiwara, Y. Ogasawara, M. Kotani, K. Yamaguchi and N. Mizuno, *Chem.–Asian J.*, 2008, **3**, 1715.

9 N. A. Owston, A. J. Parker and J. M. J. Williams, *Org. Lett.*, 2007, **9**, 73.

10 M. A. Ali and T. Punniyamurthy, *Adv. Synth. Catal.*, 2010, **352**, 288.

11 (*a*) N. C. Ganguly, S. Roy and P. Mondal, *Tetrahedron Lett.*, 2012, **53**, 1413; (*b*) A. Martínez-Asensio, M. Yus and D. J. Ramón, *Tetrahedron*, 2012, **68**, 3948.

12 C. L. Allen, C. Burel and J. M. J. Williams, *Tetrahedron Lett.*, 2010, **51**, 2724.

13 B. K. Allam and K. N. Singh, *Tetrahedron Lett.*, 2011, **52**, 5851.

14 The use of a glycerol-based carbon catalyst and silica chloride both in organic media, has also been recently described: (*a*) K. Ramesh, S. N. Murthy, K. Karnakar, K. H. V. Reddy, Y. V. D. Nageswar, M. Vijay, B. L. A. P. Devi and R. B. N. Prasad, *Tetrahedron Lett.*, 2012, **53**, 2636; (*b*) B. Datta and M. A. Pasha, *Bull. Korean Chem. Soc.*, 2012, **33**, 2129.

15 For leading books covering this field see: (*a*) C. J. Li and T. H. Chan, *Comprehensive Organic Reactions in Aqueous Media*, John Wiley & Sons, New Jersey, 2007; (*b*) *Organic Reactions in Water Principles, Strategies and Applications*, ed. U. M. Lindstrom, Blackwell Publishing Ltd., Oxford, 2007; (*c*) *Handbook of Green Chemistry*, ed. C.-J. Li and P. T. Anastas, Wiley-VCH, Weinheim, 2010, vol. 5; (*d*) *Water in Organic Synthesis*, ed. S. Kobayashi, Thieme-Verlag:, Stuttgart, 2012; (*e*) *Aqueous-Phase Organometallic Catalysis Concepts and Applications*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 1998; (*f*) *Aqueous Organometallic Catalysis*, ed. I. T. Horváth and F. Joó, Kluver, Dordrecht, 2001; (*g*) *Metal-Catalyzed Reactions in Water*, ed. P. H. Dixneuf and V. Cadierno, Wiley-VCH, Weinheim, 2013; (*h*) V. Polshettiwar and R. S. Varma, *Chem. Soc. Rev.*, 2008, **37**, 1546; (*i*) V. Polshettiwar and R. S. Varma, *Chem.–Eur. J.*, 2009, **15**, 1582; (*j*) A. Fihri, D. Cha, M. Bouhrara, N. Almana and V. Polshettiwar, *ChemSusChem*, 2012, **5**, 85.

16 The pioneering discoveries made by Breslow Grieco in the early 1980s on the positive effect of water on the rate *endo/exo* selectivity of Diels–Alder reactions are the most illustrative examples: (*a*) D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816; (*b*) P. A. Grieco, K. Yoshida and P. Garner, *J. Org. Chem.*, 1983, **48**, 3137.

17 (*a*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998; (*b*) P. T. Anastas and T. C. Williamson, *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processes*, Oxford University Press, Oxford, 1998; (*c*) A. S. Matlack, *Introduction to Green Chemistry*, Marcel Dekker, New York, 2001; (*d*) M. Lancaster, in *Handbook of Green Chemistry and Technology*, ed. J. H. Clark and D. J. Macquarrie, Blackwell Publishing, Abingdon, 2002; (*e*) M. Lancaster, *Green Chemistry: An Introductory Text*, RSC Publishing, Cambridge, 2002.

18 (*a*) W. M. Nelson, *Green Solvents for Chemistry: Perspectives and Practice*, Oxford University Press, New York, 2003; (*b*) J. H. Clark and S. J. Taverner, *Org. Process Res. Dev.*, 2007, **11**, 149; (*c*) F. M. Kerton, *Alternative Solvents for Green Chemistry*, RSC Publishing, Cambridge, 2009.

19 (*a*) V. Cadierno, J. Francos and J. Gimeno, *Chem.–Eur. J.*, 2008, **14**, 6601; (*b*) R. García-Álvarez, J. Díez, P. Crochet and V. Cadierno, *Organometallics*, 2010, **29**, 3955; (*c*) V. Cadierno, J. Díez, J. Francos and J. Gimeno, *Chem.–Eur. J.*, 2010, **16**, 9808; (*d*) S. E. García-Garrido, J. Francos, V. Cadierno, J.-M. Basset and V. Polshettiwar, *ChemSusChem*, 2011, **4**, 104; (*e*) R. García-Álvarez, J. Francos, P. Crochet and V. Cadierno, *Tetrahedron Lett.*, 2011, **52**, 4218; (*f*) R. García-Álvarez, J. Díez, P. Crochet and V. Cadierno, *Organometallics*, 2011, **30**, 5442; (*g*) R. García-Álvarez, A. E. Díaz-Álvarez, J. Borge, P. Crochet and V. Cadierno, *Organometallics*, 2012, **31**, 6482; (*h*) R. García-Álvarez, S. E. García-Garrido, J. Díez, P. Crochet and V. Cadierno, *Eur. J. Inorg. Chem.*, 2012, 4218; (*i*) A. E. Díaz-Álvarez, R. García-Álvarez, P. Crochet and V. Cadierno, in *Glycerol: Production, Structure and Applications*, ed. M. D. S. Silva and P. C. Ferreira, Nova Science Publishers, New York, 2012, pp. 249–262; (*j*) M. L. Buil, V. Cadierno, M. A. Esteruelas, J. Gimeno, J. Herrero, S. Izquierdo and E. Oñate, *Organometallics*, 2012, **31**, 6861.

20 (*a*) A. G. Caldwell and E. R. H. Jones, *J. Chem. Soc.*, 1946, 599; (*b*) L. Field, P. B. Hughmark, S. H. Shumaker and W. S. Marshall, *J. Am. Chem. Soc.*, 1961, **83**, 1983; (*c*) M. Oku, Y. Fujikura and J. Etsuno, *Jpn. Pat.*, JP07138213, 1995; (*d*) A. P. S. Narula and A. J. Janczuk, *US Pat. Appl.*, US20070055082, 2007.

21 Due to the competitive formation of phthalimide as the result of an intramolecular cyclization process, the yield of phthalamide (**2ab**) was remarkably lower (59%) in comparison with those of **2ab** and **2ac** (87–90%). Several successive recrystallizations were, in this case, required to obtain **2ab** in pure form. We must note that the catalytic synthesis of phthalimides from 1,2-benzenedinitriles, *via* double hydration followed by cyclization of the corresponding 1,2-benzenediamide intermediates, has been recently described: P. K. Verma, U. Sharma, M. Bala, N. Kumar and B. Singh, *RSC Adv.*, 2013, **3**, 895.

22 Compound **2ae** possesses interesting coordinating electrochemical and photochemical properties, it is an advanced intermediate for the preparation of other ferrocene derivatives, including optically active ligands for asymmetric catalysis, and has been employed in recent years for the design of nanocomposite electrodes, new conducting polymeric materials and photoelectronic devices. For leading references, see: (*a*) L. H Ali, A. Cox and T. J. Kemp, *J. Chem. Soc., Dalton Trans.*, 1973, 1468; (*b*) P. J. Costanzo, E. Liang, T. E. Patten, S. D. Collins and R. L. Smith, *Lab Chip*, 2005, **5**, 606; (*c*) S. Y. Oh, H. S. Choi, H. J. Kim and J. K. Park, *Polymer*, 2005, **29**, 331; (*d*) D. Salazar-Mendoza, S. A. Baudron, M. W. Hosseini, N. Kyritsakas and A. D. Cian, *Dalton Trans.*, 2007, 565; (*e*) E. Baciocchi, M. Bietti, M. D. Fusco and O. Lanzalunga, *J. Org. Chem.*, 2007, **72**, 8748; (*f*) R. Zhang, Z. Wang, Y. Wu, H. Fu and J. Yao, *Org. Lett.*, 2008, **10**, 3065; (*g*) S. Y. Oh, C. M. Chung, D. H. Kim and S. G. Lee, *Colloids Surf., A*, 2008, **313–314**, 600; (*h*) C. Wang, G. Wang and B. Fang, *Microchim. Acta*, 2009, **164**, 113; (*i*) D. F. Fischer, A. Barakat, Z.-Q. Xin, M. E. Weiss and R. Peters, *Chem.–Eur. J.*, 2009, **15**, 8722; (*j*) Y. Jiang, J. Yu, L. Li and Z. Ma, *Faming Zhuanli Shenquing*, CN102208559, 2011; (*k*) E. Baciocchi, M. Bietti, C. D'Alfonso, O. Lanzalunga, A. Lapi and M. Salamone, *Org. Biomol. Chem.*, 2011, **9**, 4085.

23 According to the current quotations of the chemical supplier companies Sigma-Aldrich, Alfa Aesar and Acros Organics, ferrocenecarboxaldehyde (**1ae**) is *ca.* 3–5 times cheaper per gram than ferrocenecarboxylic acid.

24 Transformation of ferrocenecarboxylic acid into the corresponding acid chloride is a capricious reaction that often results in low yields. This is due to the high nucleophilicity of the ferrocene nucleus, which leads to the competitive formation of dimeric and oligomeric by-products arising from Friedel–Crafts-type acylations, thus complicating its purification and isolation: T. H. Galow, J. Rodrigo, K. Cleary, G. Cooke and V. M. Rotello, *J. Org. Chem.*, 1999, **64**, 3745.

CAPÍTULO 2

2.4.- CONCLUSIONES

De los resultados descritos en el presente *Capítulo 2* pueden extraerse las siguientes conclusiones:

- ✓ El complejo [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) ha mostrado ser un catalizador eficiente, selectivo y general para promover la formación de amidas primarias por reordenamiento de las correspondientes aldoximas, representando el primer catalizador de rutenio descrito hasta la fecha en la bibliografía activo en agua.

- ✓ Los estudios cinéticos y de marcaje isotópico llevados a cabo ponen de manifiesto que, en la reacción de isomerización de aldoximas, la especie nitrilo inicialmente generada es transformada en la amida primaria final por hidratación con una segunda molécula de aldoxima (mecanismo de Williams), o bien por hidratación con una de las moléculas de agua presentes en el medio de reacción (mecanismo clásico). La hidratación del nitrilo intermedio por parte de una segunda molécula de aldoxima es el mecanismo predominante al inicio de la reacción, tomando un mayor peso la vía clásica sólo al final de la misma. En nuestro conocimiento, el complejo [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) representa el primer ejemplo demostrado de un catalizador metálico capaz de operar a través de estos dos caminos de reacción independientes.

- ✓ El complejo [$RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}$] (**1.41d**) también ha mostrado ser un catalizador eficiente, selectivo y general para la síntesis *one-pot* de amidas primarias por acoplamiento de aldehídos con hidroxilamina, o cloruro de hidroxilamonio, en agua. Con ayuda de este catalizador hemos podido desarrollar una nueva ruta de acceso a la ferrocenocarboxamida, más simple y barata que la comúnmente empleada para la síntesis de este derivado del ferroceno.

Capítulo 3

Complejos areno-rutenio(II) con ligandos guanidinato: Síntesis, caracterización y aplicación en la isomerización redox de alcoholes alílicos

CAPÍTULO 3

3.1.- ANTECEDENTES Y OBJETIVOS

Antecedentes

Las guanidinas representan una familia muy relevante de compuestos orgánicos, ya que son motivos estructurales presentes en un gran número de productos naturales y sustancias con actividad biológica y farmacológica.[1] Debido a su alta basicidad y a su capacidad para establecer enlaces de hidrógeno, las guanidinas y sus derivados acreditan también importantes aplicaciones como "superbases"[2] y organocatalizadores[3] en síntesis orgánica, y como receptores en química supramolecular.[4]

El interés en estas especies nitrogenadas abarca igualmente el campo de la Química de Coordinación y Organometálica. En particular, en años recientes, los aniones de tipo guanidinato (ver Figura 3.1) han demostrado ser ligandos auxiliares muy versátiles para el diseño de nuevos

---

[1] Revisiones bibliográficas cubriendo este campo: (a) G. J. Durant, A. M. Roe, A. L. Green, *Prog. Med. Chem.* **1970**, *7*, 124; (b) L. Heys, C. G. Moore, P. J. Murphy, *Chem. Soc. Rev.* **2000**, *29*, 57; (c) K. Nagasawa, Y. Hashimoto, *Chem. Rec.* **2003**, *3*, 201; (d) R. G. S. Berlinck, M. H. Kossuga, *Nat. Prod. Rep.* **2005**, *22*, 516; (e) L. P. Masic, *Curr. Med. Chem.* **2006**, *13*, 3627; (f) R. G. S. Berlinck, A. C. B. Burtoloso, M. H. Kossuga, *Nat. Prod. Rep.* **2008**, *25*, 919; (g) R. G. S. Berlinck, A. C. B. Burtoloso, A. E. Trindade-Silva, S. Romminger, R. P. Morais, K. Bandeira, C. M. Mizuno, *Nat. Prod. Rep.* **2010**, *27*, 1871; (h) S. S. Ebada, P. Proksch, *Mini Rev. Med. Chem.* **2011**, *11*, 225.

[2] Ver, por ejemplo: T. Ishikawa, en *Superbases for Organic Synthesis* (ed. T. Ishikawa), John Wiley & Sons, Chichester, **2009**, pp. 93-143.

[3] Revisiones bibliográficas cubriendo este campo: (a) M. P. Coles, *Chem. Commun.* **2009**, 3659; (b) Y. Sohtome, K. Nagasawa, *Synlett* **2010**, 1; (c) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145; (d) P. Merino, E. Marqués-López, T. Tejero, R. P. Herrera, *Synthesis* **2010**, 1; (e) M. Freund, S. Schenker, A. Zamfir, S. B. Tsogoeva, *Curr. Org. Chem.* **2011**, *15*, 2282; (f) J. E. Taylor, S. D. Bull, J. M. J. Williams, *Chem. Soc. Rev.* **2012**, *41*, 2109; (g) K. Nagasawa, Y. Sohtome, en *Asymmetric Organocatalysis - Science of Synthesis* (eds. B. List, K. Maruoka), Thieme-Verlag, Stuttgart, **2012**, vol. 2, pp. 1-40.

[4] Revisiones bibliográficas cubriendo este campo: (a) B. P. Orner, A. D. Hamilton, *J. Incl. Phenom. Macrocycl. Chem.* **2001**, *41*, 141; (b) M. D. Best, S. L. Tobey, E. V. Anslyn, *Coord. Chem. Rev.* **2003**, *240*, 3; (c) R. J. T. Houk, S. L. Tobey, E. V. Anslyn, *Top. Curr. Chem.* **2005**, *255*, 199; (d) C. Schmuck, *Coord. Chem. Rev.* **2006**, *250*, 3053; (e) P. Blondeau, M. Segura, R. Pérez-Fernández, J. de Mendoza, *Chem. Soc. Rev.* **2007**, *36*, 198; (f) P. A. Gale, S. E. García-Garrido, J. Garric, *Chem. Soc. Rev.* **2008**, *37*, 151; (g) P. A. Gale, *Chem. Commun.* **2011**, *47*, 82; (h) M. P. Conley, J. Valero, J. de Mendoza, en *Supramolecular Chemistry: From Molecules to Nanomaterials* (eds. P. A. Gale, J. W. Steed), John Wiley & Sons, Chichester, **2012**, vol. 3, pp. 1101-1123.

catalizadores activos en la polimerización de olefinas y ésteres, así como en el desarrollo de precursores metálicos volátiles de interés para la preparación de nuevos materiales por deposición química metalo-orgánica en fase vapor (MOCVD).[5] No obstante, debemos hacer notar en este punto que los ligandos guanidinato han sido comparativamente mucho menos estudiados que los amidinatos (ver Figura 3.1), a pesar de su similitud estructural, y la mayor modulabilidad estérica y electrónica que les confiere la presencia de un sustituyente amino (R^3R^4N) sobre el átomo de carbono central de la unidad $R^1N\text{-}C\text{-}NR^2$.[5]

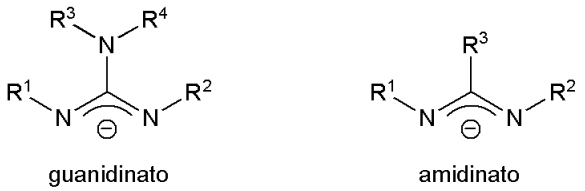
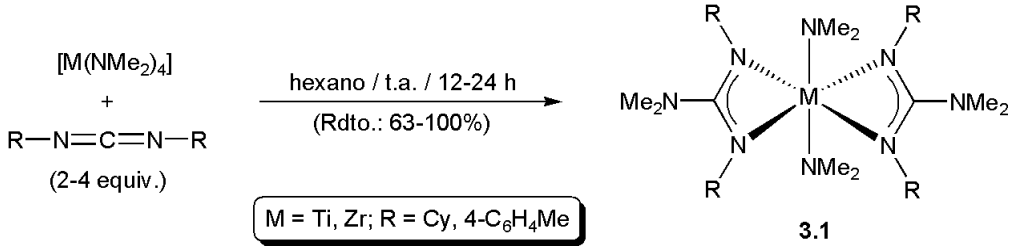


Figura 3.1: Estructura genérica de los aniones guanidinato y amidinato.

Los primeros ejemplos de complejos metálicos con ligandos guanidinato $[M(NMe_2)_2\{\kappa^2\text{-}(N,N')\text{-}C(NR)_2NMe_2\}_2]$ (**3.1**; M = Ti, Zr; R = Cy, 4-C_6H_4Me), descritos por M. F. Lappert y colaboradores en 1970,[6] fueron sintetizados por reacción de los amido-complejos $[M(NMe_2)_4]$ con carbodiimidas, *vía* inserción del heterocumuleno en el enlace M-NMe_2 de los mismos (Esquema 3.1).



Esquema 3.1: Síntesis de los primeros complejos metálicos con ligandos guanidinato.

[5] Revisiones bibliográficas cubriendo la química de coordinación y aplicaciones de ligandos de tipo amidinato y guanidinato: (a) P. J. Bailey, S. Pace, *Coord. Chem. Rev.* **2001**, *214*, 91; (b) W. E. Piers, D. J. H. Emslie, *Coord. Chem. Rev.* **2002**, *233-234*, 131; (c) F. T. Edelmann, *Adv. Organomet. Chem.* **2008**, *57*, 183; (d) F. T. Edelmann, *Chem. Soc. Rev.* **2009**, *38*, 2253; (e) C. Jones, *Coord. Chem. Rev.* **2010**, *254*, 1273; (f) A. A. Trifonov, *Coord. Chem. Rev.* **2010**, *254*, 1327; (g) S. Collins, *Coord. Chem. Rev.* **2011**, *255*, 118; (h) F. T. Edelmann, *Chem. Soc. Rev.* **2012**, *41*, 7657.

[6] G. Chandra, A. D. Jenkins, M. F. Lappert; R. C. Srivastava, *J. Chem. Soc. A.* **1970**, 2550.

Con posterioridad a este trabajo pionero de M. F. Lappert, se han descrito en la bibliografía un buen número de complejos guanidinato, que abarcan prácticamente todos los elementos metálicos de la Tabla Periódica.[5,7] En ellos, los modos de coordinación encontrados para los aniones guanidinato son muy variados, aunque, sin lugar a dudas, los más comunes son los que se muestran en la Figura 3.2.

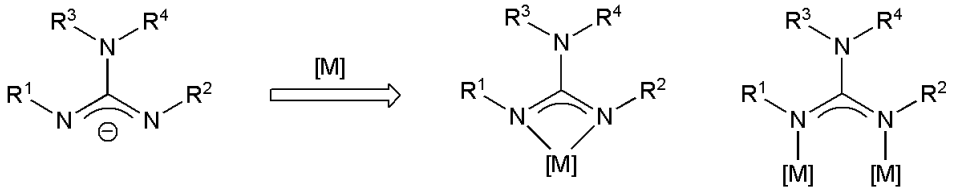


Figura 3.2: Modos de coordinación más comunes de los aniones guanidinato.

La coordinación quelato o puente del anión guanidinato viene en gran medida determinada, además de por la naturaleza del centro metálico y la estequiometría de la reacción, por los sustituyentes presentes sobre los tres átomos de nitrógeno. Esto es debido a que la orientación relativa de los pares de electrones solitarios de los átomos de nitrógeno de la unidad R^1-N-C-N-R^2 se ve influenciada por las interacciones estéricas entre dichos sustituyentes. De esta forma, cuando son voluminosos, éstos inducen una orientación convergente de los pares solitarios y se favorece el modo de coordinación quelato. Por el contrario, cuando los sustituyentes son de

[7] Ejemplos recientes pueden encontrarse en los siguientes artículos: (a) M. R. Kelley, J.-U. Rohde, *Chem. Commun.* **2012**, *48*, 2876; (b) B. L. Yonke, A. J. Keane, P. Y. Zavalij, L. R. Sita, *Organometallics* **2012**, *31*, 345; (c) D. Elorriaga, F. Carrillo-Hermosilla, A. Antiñolo, I. López-Solera, B. Menot, R. Fernández-Galán, E. Villaseñor, A. Otero, *Organometallics* **2012**, *31*, 1840; (d) T. Chlupatý, Z. Padělkova, F. DeProft, R. Willem, A. Růžička, *Organometallics* **2012**, *31*, 2203; (e) S.-J. Chen, B. A. Dougan, X.-T. Chen, Z.-L. Xue, *Organometallics* **2012**, *31*, 3443; (f) A. M. Willcocks, T. P. Robinson, C. Roche, T. Pugh, S. P. Richards, A. J. Kingsley, J. P. Lowe, A. L. Johnson, *Inorg. Chem.* **2012**, *51*, 246; (g) V. K. Rai, M. Nishiura, M. Takimoto, S. Zhao, Y. Liu, Z. Hou, *Inorg. Chem.* **2012**, *51*, 822; (h) G. M. Chiarella, F. A. Cotton, N. S. Dalal, C. A. Murillo, Z. Wang, M. D. Young, *Inorg. Chem.* **2012**, *51*, 5257; (i) R. Fernández-Galán, A. Antiñolo, F. Carrillo-Hermosilla, I. López-Solera, A. Otero, A. Serrano-Laguna, E. Villaseñor, *J. Organomet. Chem.* **2012**, *711*, 35; (j) X. Zhang, C. Qian, C. Wang, Y. Zhang, Y. Wang, Y. Yao, Q. Shen, *Eur. J. Inorg. Chem.* **2012**, 847; (k) C. Neuhäuser, M. Reinmuth, E. Kaifer, H.-J. Himmel, *Eur. J. Inorg. Chem.* **2012**, 1250; (l) K. Zelga, M. Leszczyński, I. Justyniak, A. Kornowicz, M. Cabaj, A. E. H. Wheatley, J. Lewiński, *Dalton Trans.* **2012**, *41*, 5934; (m) Y. Wang, Y. Luo, J. Chen, H. Xue, H. Liang, *New J. Chem.* **2012**, *36*, 933; (n) G. M. Chiarella, D. Y. Melgarejo, J. P. Fackler Jr., *Inorg. Chim. Acta* **2012**, 386, 13; (o) R. Fernández-Galán, A. Antiñolo, F. Carrillo-Hermosilla, I. López-Solera, A. Otero, A. Serrano-Laguna, E. Villaseñor, *Organometallics* **2012**, *31*, 8360; (p) W. Yi, J. Zhang, Z. Chen, X. Zhou, *Inorg. Chem.* **2012**, *51*, 10631; (q) S. Tanaka, K. Mashima, *Dalton Trans.* **2013**, *42*, 2831.

pequeño tamaño, éstos conducen a una orientación más paralela de los pares solitarios y, por tanto, a que la coordinación puente del ligando se vea favorecida.

En cuanto a la preparación de estos compuestos, se han descrito también una gran variedad de rutas sintéticas, siendo las más generales:

1) Por inserción de una carbodiimida en un enlace metal-nitrógeno ya existente en el complejo (ruta seguida por M. F. Lappert para la preparación de los derivados **3.1**).

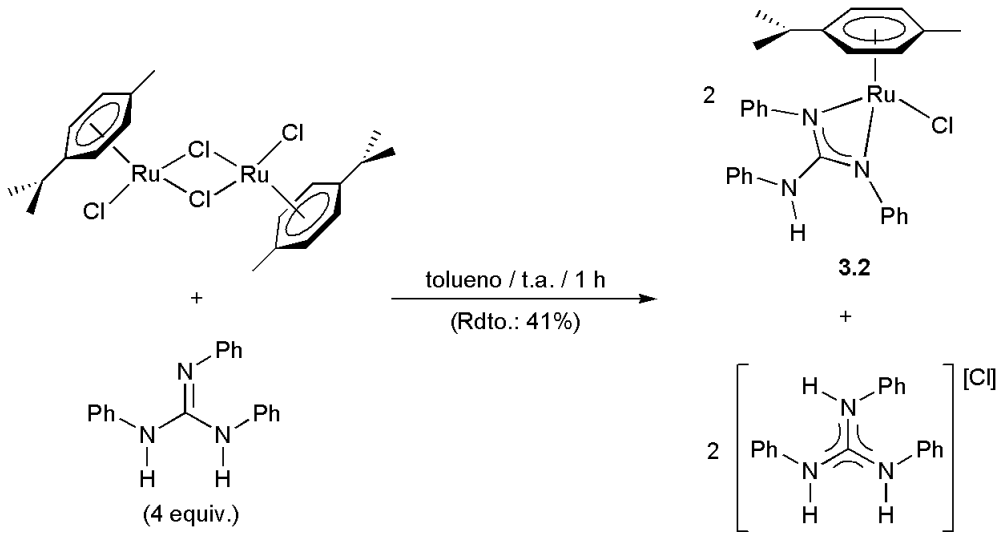
2) Por desprotonación directa de una guanidina con un compuesto metálico.

3) A través de una reacción de metátesis entre un haluro metálico y un guanidinato de un metal alcalino (generado a través de una de las dos rutas anteriores, o por simple desprotonación de una guanidina con una base).

A pesar de la gran variedad de complejos guanidinato de metales de transición que han sido descritos hasta la fecha en la bibliografía, la coordinación de este tipo de ligandos a rutenio ha sido relativamente poco estudiada. Así, el primer ejemplo de un complejo rutenio-guanidinato data de 1996 y fue descrito por P. J. Bailey y colaboradores, quienes por reacción de la especie dímera [{RuCl(μ-Cl)(η^6-*p*-cimeno)}$_2$] con un exceso de *N,N´,N''*-trifenilguanidina obtuvieron el derivado semi-sandwich de rutenio(II) [RuCl{κ^2-(*N,N´*)-C(NPh)$_2$NHPh}(η^6-*p*-cimeno)] (**3.2**) con rendimiento moderado (Esquema 3.2).[8] La reacción involucra la ruptura inicial de los puentes cloruro del dímero [{RuCl(μ-Cl)(η^6-*p*-cimeno)}$_2$] por parte de la *N,N´,N''*-trifenilguanidina. De esta forma, se genera un complejo mononuclear donde la trifenilguanidina se coordina al fragmento [RuCl$_2$(η^6-*p*-cimeno)] a través del nitrógeno imínico (C=NPh).[5a] Posteriormente, el exceso de *N,N´,N''*-trifenilguanidina presente en el medio de reacción actúa como base, desprotonando al ligando coordinado y generando así el anión guanidinato que se quelata al centro metálico. Es por ello que en la

[8] P. J. Bailey, L. A. Mitchell, S. Parsons, *J. Chem. Soc., Dalton Trans.* **1996**, 2839.

reacción se obtiene como subproducto el cloruro de *N,N´,N''*-trifenilguanidinio $[C(NHPh)_3][Cl]$.



Esquema 3.2: Síntesis del primer complejo guanidinato de rutenio **3.2**.

Con posterioridad a este trabajo se han sintetizado los derivados mononucleares octaédricos $[Ru\{\kappa^2\text{-}(N,N')\text{-}C(NPh)_2NHPh\}_2(CO)(PPh_3)]$ (**3.3**),[9] $[RuH\{\kappa^2\text{-}(N,N')\text{-}C(NPh)_2NHPh\}(CO)(PPh_3)_2]$ (**3.4**)[10] y $[Ru\{\kappa^2\text{-}(N,N')\text{-}C(NPh)_2NHPh\}_3]$ (**3.5**)[11] que contienen el anión *N,N´,N''*-trifenilguanidinato actuando como ligando quelato (Figura 3.3). Al igual que en el caso anterior, estas especies fueron obtenidas por tratamiento del correspondiente complejo precursor de rutenio, *i.e.* $[Ru(O_2CCF_3)_2(CO)(PPh_3)_2]$, $[RuH_2(CO)(PPh_3)_3]$ y $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6H_6)\}_2]$ respectivamente, con un exceso de *N,N´,N''*-trifenilguanidina.

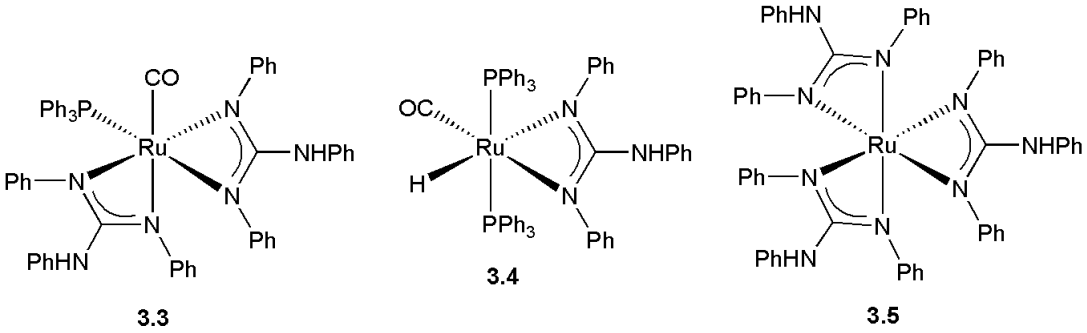
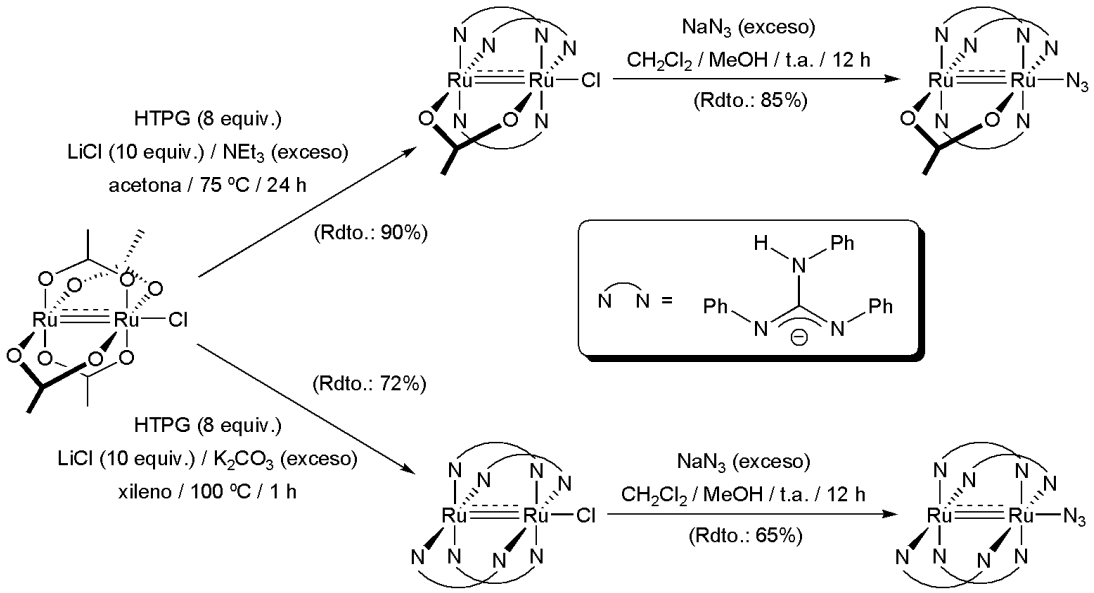


Figura 3.3: Estructura de los complejos guanidinato de rutenio **3.3-3.5**.

[9] K. T. Holman, S. D. Robinson, A. Sahajpal, J. W. Steed, *J. Chem. Soc., Dalton Trans.* **1999**, 15.
[10] S. D. Robinson, A. Sahajpal, J. Steed, *Inorg. Chim. Acta* **2000**, *303*, 265.
[11] P. J. Bailey, K. J. Grant, L. A. Mitchell, S. Pace, A. Parkin, S. Parsons, *J. Chem. Soc., Dalton Trans.* **2000**, 1887.

Además de estos complejos mononucleares,[12] se han descrito igualmente ejemplos de derivados dinucleares de rutenio donde aniones guanidinato actúan como ligandos puente en unidades de tipo Ru_2^{n+} (n = 5-7).[13] A modo de ejemplo, en el Esquema 3.3 se recogen los resultados obtenidos por J. F. Berry y colaboradores al estudiar la reactividad del complejo acetato $[Ru_2(OAc)_4Cl]$ frente a la *N,N´,N''*-trifenilguanidina (abreviada como HTPG en el esquema).[13c]



Esquema 3.3: Reactividad del complejo $[Ru_2(OAc)_4Cl]$ frente a la *N,N´,N''*-trifenilguanidina (HTPG).

Es importante destacar en este punto que, a pesar de que el rutenio se ha afianzado en las últimas décadas como uno de los metales más versátiles y más utilizados en catálisis homogénea,[14] no se conoce aplicación catalítica alguna para los derivados rutenio-guanidinato que

[12] También se conoce el complejo mononuclear [Ru{κ^2-(*N,N´*)-$C(NAc)_2$=NAc}(PPh_3)(η^6-*p*-cimeno)] que contiene un ligando guanidinato dianiónico: M. B. Dinger, W. Henderson, B. K. Nicholson, *J. Organomet. Chem.* **1998**, *556*, 75.

[13] (a) F. A. Cotton, C. A. Murillo, X. Wang, C. C. Wilkinson, *Inorg. Chim. Acta* **2003**, *351*, 191; (b) F. A. Cotton, C. A. Murillo, J. H. Reibenspies, D. Villagrán, X. Wang, C. C. Wilkinson, *Inorg. Chem.* **2004**, *43*, 8373; (c) J. S. Pap, J. L. Snyder, P. M. Piccoli, J. F. Berry, *Inorg. Chem.* **2009**, *48*, 9846; (d) G. M. Chiarella, F. A. Cotton, C. A. Murillo, M. D. Young, Q. Zhao, *Inorg. Chem.* **2010**, *49*, 3051; (e) R. Lee, Y. Yang, G. K. Tan, C.-H. Tan, K.-W. Huang, *Dalton Trans.* **2010**, *39*, 723.

[14] Ver, por ejemplo: (a) *Ruthenium in Organic Synthesis* (ed. S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**; (b) *Ruthenium Catalysts and Fine Chemistry* (eds. C. Bruneau, P. H. Dixneuf), Springer, Berlin, **2004**; (c) *Ruthenium: Properties, Production and Applications* (ed. D. B. Watson), Nova Science Publishers, New York, **2011**; (d) *Ruthenium Oxidation Complexes: Their Uses as Homogeneous Organic Catalysts* (ed. W. P. Griffith), Springer, Dordrecht, **2011**.

han sido descritos hasta la fecha. Este hecho contrasta con la química de sus análogos amidinato, para los que se han encontrado aplicaciones en diferentes transformaciones catalíticas. Así, por ejemplo, es conocido que, entre otros, los complejos [RuCp*{κ^2-(*N,N'*)-C(N^{i}Pr)$_2$Me}] (**3.6**) (Cp* = pentametilciclopentadienilo), [RuClCp*{κ^2-(*N,N'*)-C(N^{i}Pr)$_2$Me}] (**3.7**) y [RuBr{κ^2-(*N,N'*)-C(N^{i}Pr)$_2$Me}(η^6-C$_6$H$_6$)] (**3.8**) (Figura 3.4) son catalizadores activos en procesos de alilación tipo Tsuji-Trost, en reacciones de Kharasch ("adiciones por transferencia de átomo radicalaria" (ATRA)) o en la polimerización de olefinas por metátesis de apertura de anillo (ROMP; en combinación con un diazocompuesto), respectivamente.[15]

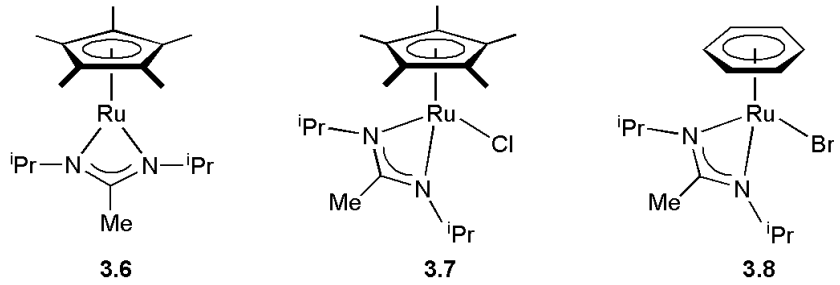


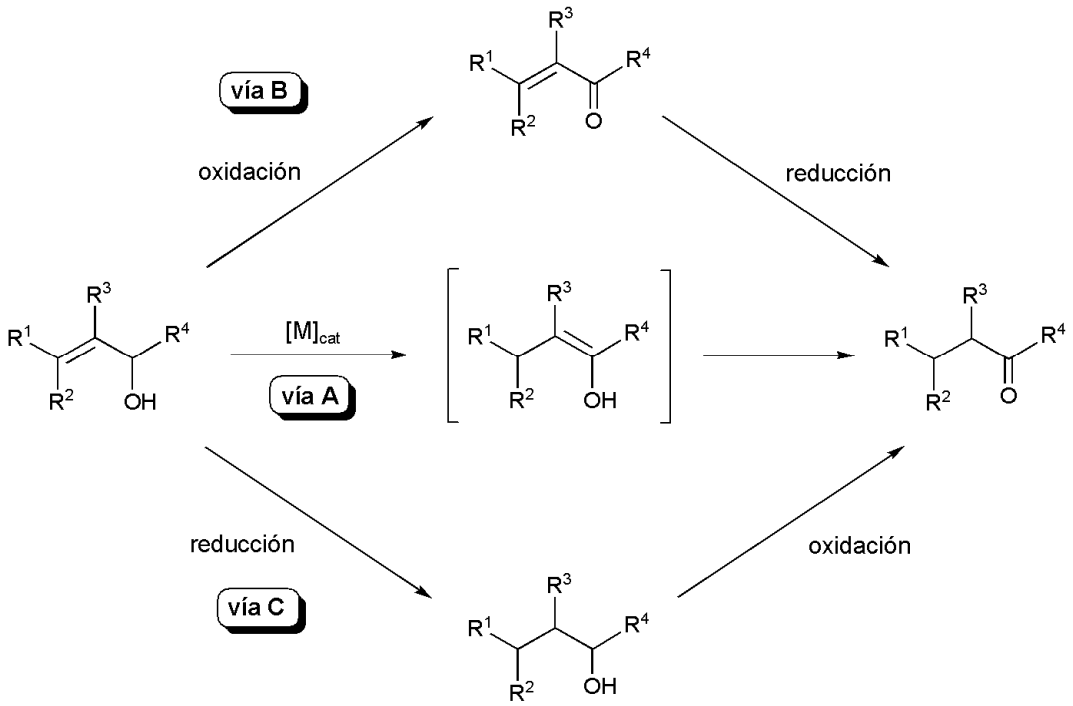
Figura 3.4: Estructura de los complejos amidinato de rutenio **3.6-3.8**.

En otro orden de cosas, una de las transformaciones catalíticas en la que los catalizadores de rutenio juegan un papel preponderante es la isomerización redox de alcoholes alílicos en compuestos carbonílicos.[16] La isomerización redox de un alcohol alílico consiste, formalmente, en la reducción de su doble enlace carbono-carbono y la oxidación de la función alcohol en cetona o aldehído. El proceso involucra un paso inicial de migración del doble enlace C=C promovido por un metal de transición,

[15] Ver, por ejemplo: (a) H. Nagashima, H. Kondo, T. Hayashida, Y. Yamaguchi, M. Gondo, S. Masuda, K. Miyazaki, K. Matsubara, K. Kirchner, *Coord. Chem. Rev.* **2003**, *245*, 177 y refencias allí citadas; (b) J.-I. Terasawa, H. Kondo, T. Matsumoto, K. Kirchner, Y. Motoyama, H. Nagashima, *Organometallics* **2005**, *24*, 2713; (c) Y. Motoyama, S. Hanada, S. Niibayashi, K. Shimamoto, N. Takaoka, H. Nagashima, *Tetrahedron* **2005**, *61*, 10216.

[16] Artículos de revisión cubriendo esta transformación catalítica: (a) R. C. van der Drift, E. Bouwman, E. Drent, *J. Organomet. Chem.* **2002**, *650*, 1; (b) R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27; (c) V. Cadierno, P. Crochet, J. Gimeno, *Synlett* **2008**, 1105; (d) L. Mantilli, C. Mazet, *Chem. Lett.* **2011**, *40*, 341; (e) N. Ahlsten, A. Bartoszewicz, B. Martín-Matute, *Dalton Trans.* **2012**, *41*, 1660; (f) P. Lorenzo-Luis, A. Romerosa, M. Serrano-Ruiz, *ACS Catal.* **2012**, *2*, 1079; (g) J. García-Álvarez, S. E. García-Garrido, P. Crochet, V. Cadierno, *Curr. Top. Catal.* **2012**, *10*, 35.

seguido de la tautomerización espontánea del enol resultante para generar el derivado carbonílico saturado final (Esquema 3.4; vía A).



Esquema 3.4: Diferentes rutas para transformar alcoholes alílicos en compuestos carbonílicos.

Esta síntesis directa de cetonas y aldehídos a partir de alcoholes alílicos, además de transcurrir con una economía de átomos completa,[17] es experimentalmente más atractiva que las metodologías tradicionales, no catalizadas, que requieren dos pasos de reacción independientes: la oxidación del grupo OH, y la posterior reducción del doble enlace C=C o viceversa (Esquema 3.4; vías B y C).[16] En estas reacciones clásicas tienen que emplearse agentes oxidantes y reductores, generalmente caros y tóxicos, en cantidades estequiométricas, por lo que además resultan mucho más dañinas para el medio ambiente.

La isomerización redox de alcoholes alílicos ha sido ampliamente estudiada durante los últimos años, dedicándose esfuerzos importantes a la búsqueda de sistemas catalíticos altamente activos (entre los diferentes complejos metálicos de los Grupos 6-10 estudiados, los basados en

[17] (a) B. M. Trost, *Science* **1991**, *254*, 1471; (b) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; (c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695; (d) B. M. Trost, M. U. Fredericksen, M. T. Rudd, *Angew. Chem. Int. Ed.* **2005**, *44*, 6630; (e) R. A. Sheldon, *Chem. Commun.* **2008**, 3352.

rutenio,[16,18] rodio[16,19] e iridio[16,20] son los que presentan una mayor reactividad) y a establecer sus mecanismos de acción.[21] El conocimiento acumulado ha permitido que esta reacción de isomerización, inicialmente limitada a sustratos sencillos, pueda aplicarse ahora a alcoholes alílicos de estructura cada vez más elaborada, ofreciendo así una nueva vía de acceso a productos de alto valor añadido. En este sentido, podemos destacar su implicación reciente en la síntesis total de varios productos naturales, tales como las feromonas muscona[22] e (+)-*iso*-*exo*-brevicomina[23] o el alcaloide

---

[18] Ejemplos recientes de catalizadores de rutenio han sido descritos en: (a) B. Lastra-Barreira, J. Díez, P. Crochet, *Green Chem.* **2009**, *11*, 1681; (b) M. Batuecas, M. A. Esteruelas, C. García-Yebra, E. Oñate, *Organometallics* **2010**, *29*, 2166; (c) B. González, P. Lorenzo-Luis, M. Serrano-Ruíz, E. Papp, M. Fekete, K. Csepke, K. Ösz, A. Kathó, F. Joó, A. Romerosa, *J. Mol. Catal. A: Chem.* **2010**, *326*, 15; (d) A. Azua, S. Sanz, E. Peris, *Organometallics* **2010**, *29*, 3661; (e) A. Pontes da Costa, J. A. Mata, B. Royo, E. Peris, *Organometallics* **2010**, 29, 1832; (f) M. A. Fernández-Zumel, B. Lastra-Barreira, M. Scheele, J. Díez, P. Crochet, J. Gimeno, *Dalton Trans.* **2010**, *39*, 7780; (g) P. N. Liu, K. D. Ju, C. P. Lau, *Adv. Synth. Catal.* **2011**, *353*, 275; (h) J. García-Álvarez, J. Gimeno, F. J. Suárez, *Oganometallics* **2011**, *30*, 2893; (i) E. Putignano, G. Bossi, P. Rigo, W. Baratta, *Organometallics* **2012**, *31*, 1133; (j) R. Wu, M. G. Beauchamps, J. M. Laquidara, J. R. Sowa, *Angew. Chem. Int. Ed.* **2012**, *51*, 2106; (k) V. Bizet, X. Pannecoucke, J.-L. Renaud, D. Cahard, *Angew. Chem. Int. Ed.* **2012**, *51*, 6467; (l) J. Schulz, I. Císařová, P. Štěpnička, *Eur. J. Inorg. Chem.* **2012**, 5000; (m) L. Menéndez-Rodríguez, P. Crochet, V. Cadierno, *J. Mol. Catal. A: Chem.* **2013**, *366*, 390.

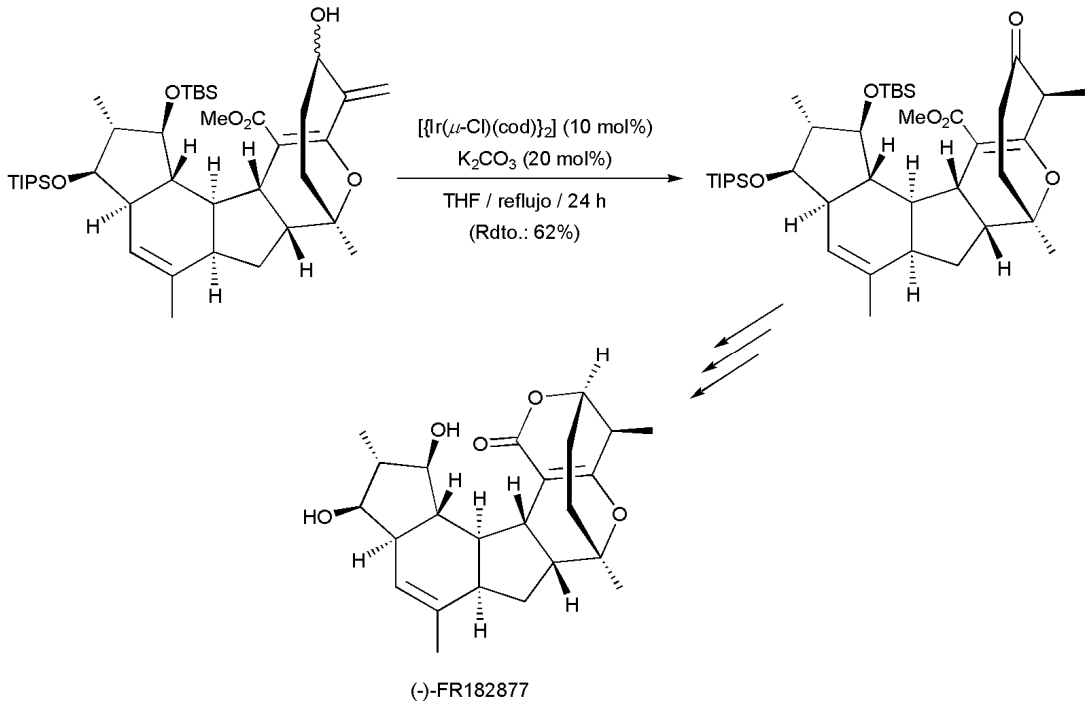
[19] Ejemplos recientes de catalizadores de rodio han sido descritos en: (a) D. H. Leung, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2007**, *129*, 2746; (b) N. Ahlsten, H. Lundberg, B. Martín-Matute, *Green Chem.* **2010**, *12*, 1628; (c) E. G. Corkum, S. Kalapugama, M. J. Hass, S. H. Bergens, *RSC Adv.* **2012**, *2*, 3473; (d) S. Sahoo, H. Lundberg, M. Eden, N. Ahlsten, W. Wan, X. Zou, B. Martín-Matute, *ChemCatChem* **2012**, *4*, 243.

[20] Ejemplos recientes de catalizadores de iridio han sido descritos en: (a) L. Mantilli, C. Mazet, *Chimia* **2009**, *63*, 35; (b) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem. Int. Ed.* **2009**, *48*, 5143; (c) L. Mantilli, C. Mazet, *Tetrahedron Lett.* **2009**, *50*, 4141; (d) L. Mantilli, C. Mazet, *Chem. Commun.* **2010**, *46*, 445; (e) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem. Eur. J.* **2010**, *16*, 12736; (f) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Pure Appl. Chem.* **2010**, *82*, 1461; (g) A. Quintard, A. Alexakis, C. Mazet, *Angew. Chem. Int. Ed.* **2011**, *50*, 2354; (h) J.-Q. Li, B. Peters, P. G. Andersson, *Chem. Eur. J.* **2011**, *17*, 11143; (i) L. Mantilli, D. Gérard, C. Besnard, C. Mazet, *Eur. J. Inorg. Chem.* **2012**, 3320.

[21] Para estudios mecanísticos, ver: (a) W. T. Hendrix, F. G. Cowherd, J. L. von Rosenberg, *Chem. Commun.* **1968**, 97; (b) D. V. McGrath, R. H. Grubbs, *Organometallics* **1994**, *13,* 224; (c) V. Branchadell, C. Crévisy, R. Grée, *Chem. Eur. J.* **2003**, *9,* 2062; (d) V. Cadierno, S. E. García-Garrido, J. Gimeno, A. Varela-Álvarez, J. A. Sordo, *J. Am. Chem. Soc.* **2006**, *128*, 1360; (e) N. Ahlsten, B. Martín-Matute, *Adv. Synth. Catal.* **2009**, *351*, 2657; (f) A. Varela-Álvarez, J. A. Sordo, E. Piedra, N. Nebra, V. Cadierno, J. Gimeno, *Chem. Eur. J.* **2011**, *17*, 10583; (g) L. Bellarosa, J. Díez, J. Gimeno, A. Lledós, F. J. Suárez, G. Ujaque, C. Vicent, *Chem. Eur. J.* **2012**, *18*, 7749; (h) J. Díez, J. Gimeno, A. Lledós, F. J. Suárez, C. Vicent, *ACS Catal.* **2012**, *2*, 2087.

[22] M. Ito, S. Kitahara, T. Ikariya, *J. Am. Chem. Soc.* **2005**, *127*, 6172.

(+)-brevisamida,[24] y en la preparación de la fragancia florhidral®,[25] los analgésicos hidromorfona e hidrocodona,[26] y el agente antitumoral (-)-FR182877 (ver Esquema 3.5).[27]



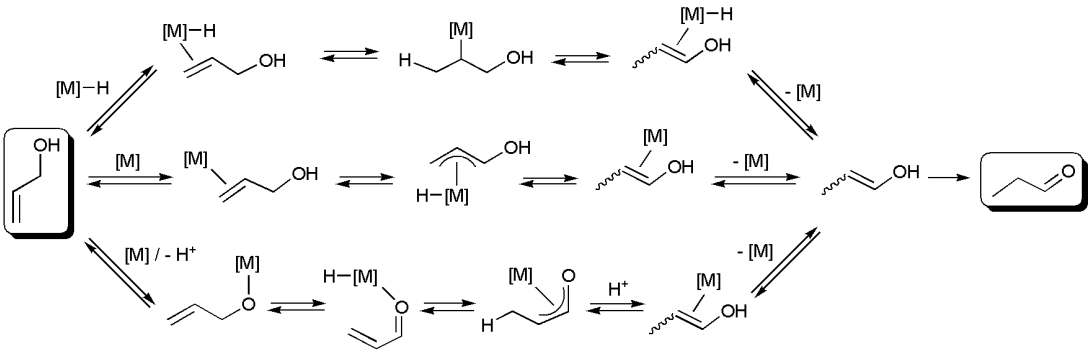
Esquema 3.5: Isomerización redox de un alcohol alílico involucrada en la síntesis del agente antitumoral (-)-FR182877.

Desde un punto de vista mecanístico, la isomerización de alcoholes alílicos en compuestos carbonílicos suele transcurrir a través de uno de los tres caminos de reacción representados de manera simplificada en el Esquema 3.6.[16] Los dos primeros son los mecanísmos clásicos para la isomerización de olefinas (rutas alquílica y alílica),[28] mientras que el tercero es específico para los alcoholes alílicos. Este último, propuesto por B. M.

---

[23] A. Bouziane, T. Régnier, F. Carreaux, B. Carboni, C. Bruneau, J.-L. Renaud, *Synlett* **2010**, 207.
[24] G. Sabitha, S. Nayak, M. Bhikshapathi, J. S. Yadav, *Org. Lett.* **2011**, *13*, 382.
[25] S. Bovo, A. Scrivanti, M. Bertoldini, V. Beghetto, U. Matteoli, *Synthesis* **2008**, 2547.
[26] (a) P. X. Wang, T. Jiang, D. W. Berberich, *PCT Int. Appl.* WO2010118271, **2010**; (b) T. Jiang, P. X. Wang, D. W. Berberich, *PCT Int. Appl.* WO2011137086, **2011**; (c) A. E. Díaz-Álvarez, V. Cadierno, *Recent Patents Catal.* **2012**, *1*, 43.
[27] N. Tanaka, T. Suzuki, T. Matsumura, Y. Hosoya, M. Nakada, *Angew. Chem. Int. Ed.* **2009**, *48*, 2580.
[28] Ver, por ejemplo: R. H. Crabtree, E. Peris, en *Química Organometálica de los Metales de Transición*, Publicaciones de la Universitat Jaume I, Castellón de la Plana, **1997**, pp. 277-279.

Trost y colaboradores,[29] involucra la coordinación inicial del sustrato a través de su forma desprotonada, y la generación de una especie intermedia de tipo *π*-oxoalilo.



Esquema 3.6: Mecanismos propuestos para las reacciones de isomerización de alcoholes alílicos.

Los catalizadores de rutenio activos en la isomerización de alcoholes alílicos suelen operar a través del mecanismo propuesto por B. M. Trost y colaboradores.[16] No es de extrañar, por tanto, que la inmensa mayoría requieran del uso de una base como co-catalizador para que se produzca la desprotonación inicial del grupo hidroxilo del substrato. No obstante, existen excepciones a este comportamiento general, conociéndose complejos de rutenio capaces de promover el proceso en ausencia de una base. Dichos complejos pueden agruparse en los tres grupos siguientes:

- ✓ Los complejos que se activan por reacción con hidrógeno molecular. De esta forma se genera en el medio de reacción una especie hidruro, capaz de operar a través de un mecanismo alquílico clásico (Esquema 3.6).
- ✓ Los complejos capaces de promover la reacción catalítica en agua, ya que la polaridad del medio facilita la ionización del grupo hidroxilo del alcohol alílico.
- ✓ Los complejos que contienen en su estructura ligandos que aportan basicidad y son capaces por si mismos de desprotonar al sustrato (catalizadores bifuncionales), sin necesidad de introducir una base externa.

[29] B. M. Trost, R. J. Kulawiec, *J. Am. Chem. Soc.* **1993**, *115*, 2027.

Durante los últimos años nuestro grupo de investigación ha trabajado activamente en el desarrollo de catalizadores de rutenio para la isomerización de alcoholes alílicos.[16c,g] Así, por ejemplo, se han descrito los catalizadores bis-alilo de rutenio(IV) [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] (**3.9**),[21d] [$RuCl_2$(η^3:η^2:η^3-$C_{12}H_{18}$)] (**3.10**)[30] y [RuCl(OAc)(η^3:η^3-$C_{10}H_{16}$)] (**3.11**)[18h] activos en agua en ausencia de base, y sus análogos bifuncionales [RuCl(η^3:η^3-$C_{10}H_{16}$)(L)] (L = pirazol (**3.12**),[21g] indazol (**3.13**),[21g] benzimidazol (**3.14**)[21h]) (Figura 3.5). Los valores de TOF (*turnover frequency*) y TON (*turnover number*) alcanzados con algunos de ellos, de hasta 62500 h^{-1} y 1500000 respectivamente,[21d] son los más altos descritos hasta la fecha en la bibliografía para esta transformación catalítica.

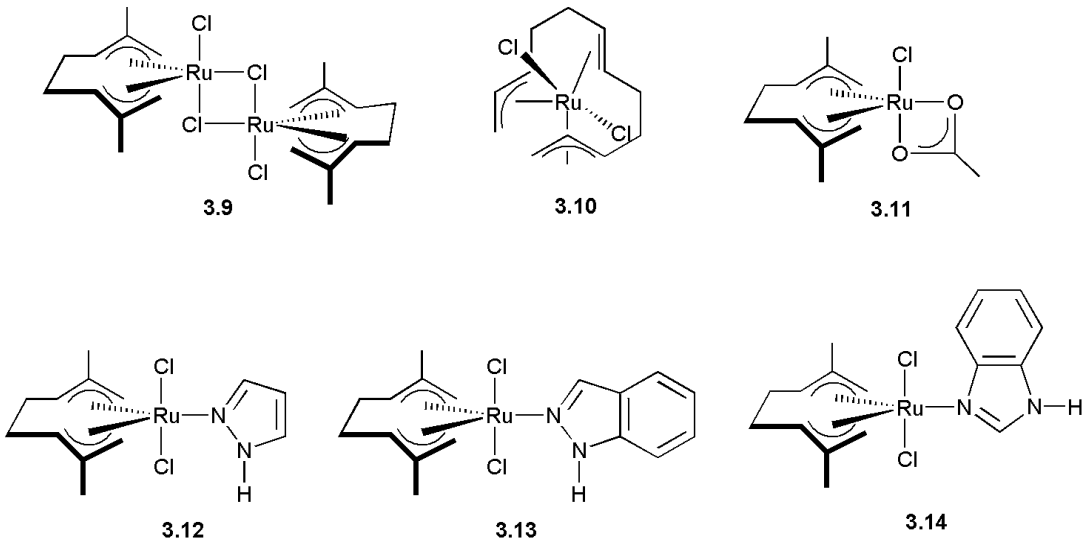


Figura 3.5: Estructura de los catalizadores bis-alilo de rutenio(IV) **3.9-3.14**.

También se han desarrollado en el grupo diferentes catalizadores de tipo rutenio(II)-areno, tales como los complejos **3.15-3.20** representados en la Figura 3.6.[18a,m,31] No obstante, a pesar de que muchos de ellos resultaron activos en agua, por lo general, con estos derivados fue necesaria la introducción de una base en el medio de reacción para obtener buenas actividades catalíticas.

[30] V. Cadierno, S. E. García-Garrido, J. Gimeno, *Chem. Commun.* **2004**, 232.
[31] (a) V. Cadierno, P. Crochet, S. E. García-Garrido, J. Gimeno, *Dalton Trans.* **2004**, 3635; (b) A. E. Díaz-Álvarez, P. Crochet, M. Zablocka, C. Duhayon, V. Cadierno, J. Gimeno, J. P. Majoral, *Adv. Synth. Catal.* **2006**, *348*, 1671; (c) P. Crochet, J. Díez, M. A. Fernández-Zúmel, J. Gimeno, *Adv. Synth. Catal.* **2006**, 348, 93; (d) P. Crochet, M. A. Fernández-Zúmel, J. Gimeno, M. Scheele, *Organometallics* **2006**, *25*, 4846.

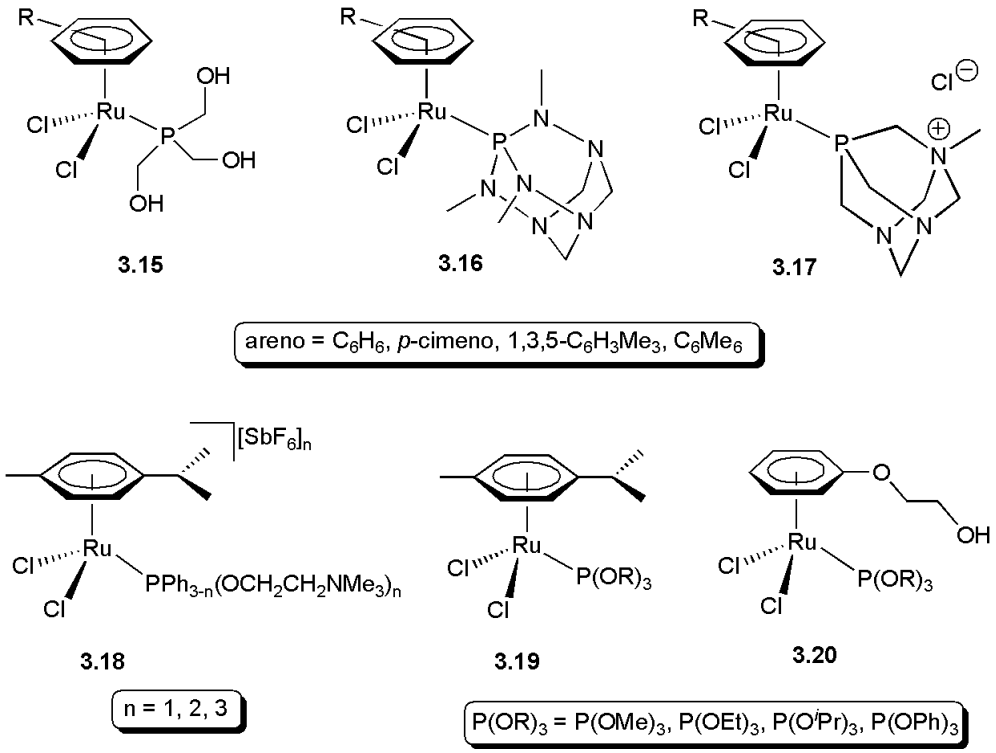
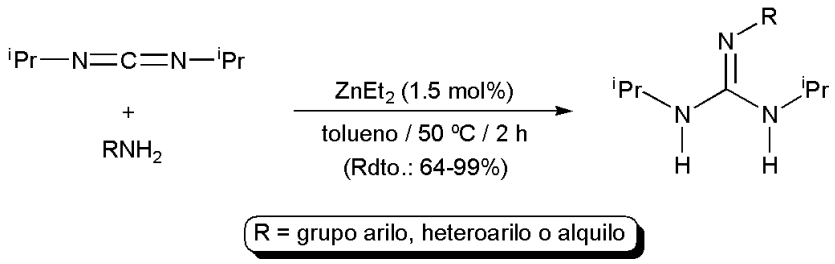


Figura 3.6: Estructura de los catalizadores rutenio(II)-areno **3.15-3.20**.

Objetivos

Los antecedentes que acabamos de comentar ponen de manifiesto el limitado número de complejos rutenio-guanidinato actualmente conocidos, y la ausencia de aplicaciones catalíticas para los mismos. Estos hechos nos animaron, en el marco del Proyecto CONSOLIDER ORFEO (*Development of organometallic moieties for the selective functionalization of organic molecules*) en el que participamos, a iniciar una colaboración con el grupo del Prof. Antonio Antiñolo (Universidad de Castilla-La Mancha) encaminada a la preparación de nuevos complejos rutenio-guanidinato y al estudio de sus propiedades catalíticas. Conviene reseñar que el grupo del Prof. Antonio Antiñolo ha puesto a punto rutas sintéticas eficientes para la síntesis de guanidinas por adición catalítica de aminas a carbodiimidas (un ejemplo representativo se muestra en el Esquema 3.7),[32] y es experto en la química de coordinación de estos ligandos con metales de transición de los Grupos 4 y 5 de la Tabla de Periodos.[7c,i,o]

[32] C. Alonso-Moreno, F. Carrillo-Hermosilla, A. Garcés, A. Otero, I. López-Solera, A. M. Rodríguez, A. Antiñolo, *Organometallics* **2010**, *29*, 2789.



Esquema 3.7: Síntesis de guanidinas por adición de aminas primarias a la *N,N´*-diisopropilcarbodiimida empleando $ZnEt_2$ como catalizador.

Así, en este *Capítulo 3* se describe:

1.- La síntesis y caracterización de una nueva familia de complejos rutenio(II)-areno con ligandos guanidinato de fórmula general [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)], por reacción del precursor dimérico [{RuCl(μ-Cl)(η^6-*p*-cimeno)}$_2$] con las guanidinas (^{i}PrHN)$_2$C=NR (R = ^{i}Pr, 4-$C_6H_4{}^t$Bu, 4-C_6H_4Br, 2,4,6-$C_6H_2Me_3$, 2,6-$C_6H_3{}^i Pr_2$).[33]

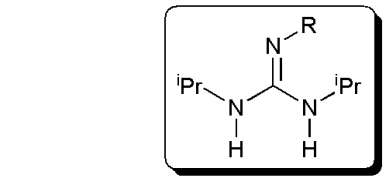
2.- La evaluación de la actividad catalítica de estos nuevos complejos en la isomerización redox de alcoholes alílicos.

[33] Debemos hacer notar que, con nuestro trabajo en el campo ya iniciado, el grupo de N. Thirupathi y colaboradores describió la preparación de una serie de complejos de tipo [RuCl{κ^2-*N,N´*-C(NAr)$_2$NHAr}(η^6-*p*-cimeno)] y [RuN$_3${κ^2-*N,N´*-C(NAr)$_2$NHAr}(η^6-*p*-cimeno)] a partir de *N,N´,N´´*-triarilguanidinas simétricas, y estudió la reactividad de los complejos azido frente a alquinos activados (reacciones de cicloadición [3+2]): T. Singh, R. Kishan, M. Nethaji, N. Thirupathi, *Inorg. Chem.* **2012**, *51*, 157.

CAPÍTULO 3

3.2.- DISCUSIÓN DE RESULTADOS

Como se acaba de comentar en la *Introducción* del presente *Capítulo*, el objetivo de nuestro trabajo ha sido la preparación de nuevos complejos rutenio(II)-areno con ligandos de tipo guanidinato, y el estudio de su actividad catalítica en la isomerización redox de alcoholes alílicos. Para tales fines, se realizó una estancia en los laboratorios del Prof. Antonio Antiñolo y, siguiendo la ruta sintética recogida en el Esquema 3.7, se prepararon las guanidinas **3.21a-e** (Figura 3.7),[32] cuya reactividad frente al precursor dimérico [{RuCl(μ-Cl)(η^6-*p*-cimeno)}$_2$] fue estudiada posteriormente en Oviedo.

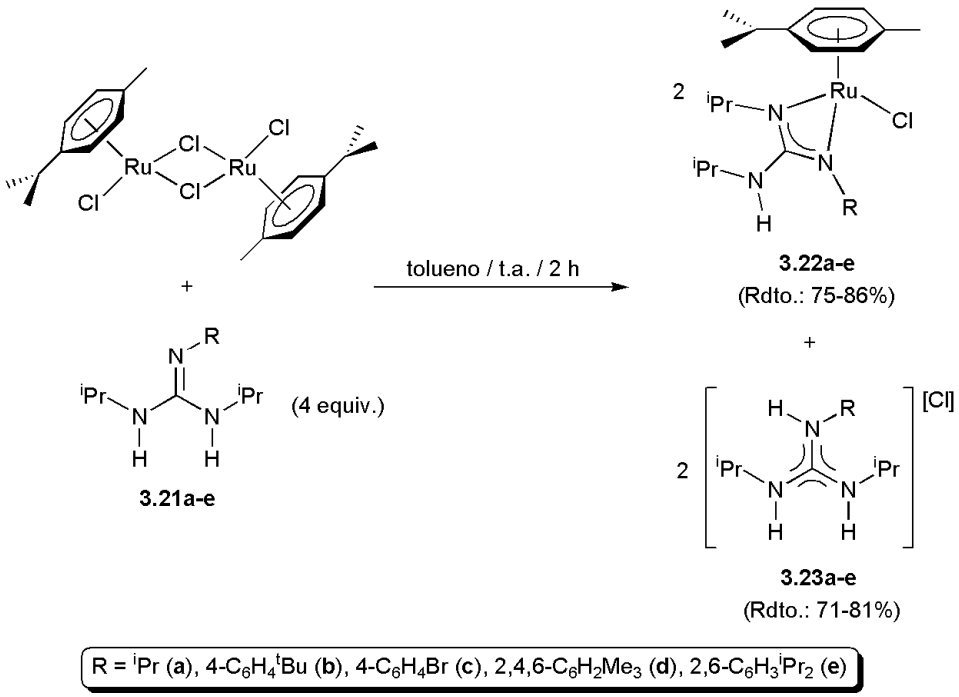


R = ^{i}Pr (**3.21a**), 4-C$_6$H$_4$^{t}Bu (**3.21b**), 4-C$_6$H$_4$Br (**3.21c**), 2,4,6-C$_6$H$_2$Me$_3$ (**3.21d**), 2,6-C$_6$H$_3$^{i}Pr$_2$ (**3.21e**)

Figura 3.7: Estructura de las guanidinas empleadas en este trabajo.

3.2.1.- Síntesis y caracterización de los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (R = ^{i}Pr (3.22a), 4-C$_6$H$_4$^{t}Bu (3.22b), 4-C$_6$H$_4$Br (3.22c), 2,4,6-C$_6$H$_2$Me$_3$ (3.22d), 2,6-C$_6$H$_3$^{i}Pr$_2$ (3.22e)).

La coordinación de las guanidinas (^{i}PrHN)$_2$C=NR (**3.21a-e**) al fragmento rutenio(II)-*p*-cimeno se llevó a cabo siguiendo el procedimiento descrito por P. J. Bailey y colaboradores para la síntesis del derivado [RuCl{κ^2-(*N,N*)-C(NPh)$_2$NHPh}(η^6-*p*-cimeno)] (**3.2**) (Esquema 3.2).[8] De esta forma, encontramos que el tratamiento del dímero [{RuCl(μ-Cl)(η^6-*p*-cimeno)}$_2$] con 4 equivalentes de la guanidina **3.21a-e** correspondiente, en tolueno y a temperatura ambiente, conduce a la formación de los complejos guanidinato mononucleares [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**) (Esquema 3.8).



Esquema 3.8: Síntesis de los complejos mononucleares de rutenio(II) [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**).

Como era de esperar, en las reacciones se forman también las correspondientes sales de guanidinio [(^{i}PrHN)$_2$C(NHR)][Cl] (**3.23a-e**), que precipitan en el medio de reacción y pueden ser fácilmente separadas y aisladas (71-81%) a través de un simple proceso de filtración. Una vez filtradas las disoluciones, la concentración y enfriamiento de las mismas (a -20 ºC durante 1-2 días) nos permitió aislar los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**) por cristalización con buenos rendimientos (75-86%). Cabe destacar en este punto que los derivados [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (R = 4-C$_6$H$_4$^{t}Bu (**3.22b**), 4-C$_6$H$_4$Br (**3.22c**), 2,4,6-C$_6$H$_2$Me$_3$ (**3.22d**), 2,6-C$_6$H$_3$^{i}Pr$_2$ (**3.22e**)) representan los primeros ejemplos de complejos de rutenio con ligandos guanidinato no-simétricos descritos hasta la fecha en la bibliografía.

Tanto los complejos **3.22a-e** como las sales de guanidinio **3.23a-e** fueron caracterizados empleando las técnicas analíticas y espectroscópicas habituales (IR y RMN de ^{1}H y ^{13}C{^{1}H}), encontrándose los datos obtenidos recogidos en la correspondiente publicación adjunta. No obstante, merece la pena reseñar aquí que, para los derivados **3.22a-e**, la coordinación no-simétrica de los ligandos guanidinato quedó claramente confirmada en sus espectros de RMN ^{1}H y ^{13}C{^{1}H} por la aparición de cuatro señales bien

diferenciadas para los protones y carbonos de las unidades CH aromáticas del anillo *p*-cimeno, situación típica en complejos (η^6-*p*-cimeno)-rutenio(II) donde el metal es un centro estereogénico. A modo ilustrativo, los espectros obtenidos para el derivado **3.22b** se muestran en la Figura 3.8.

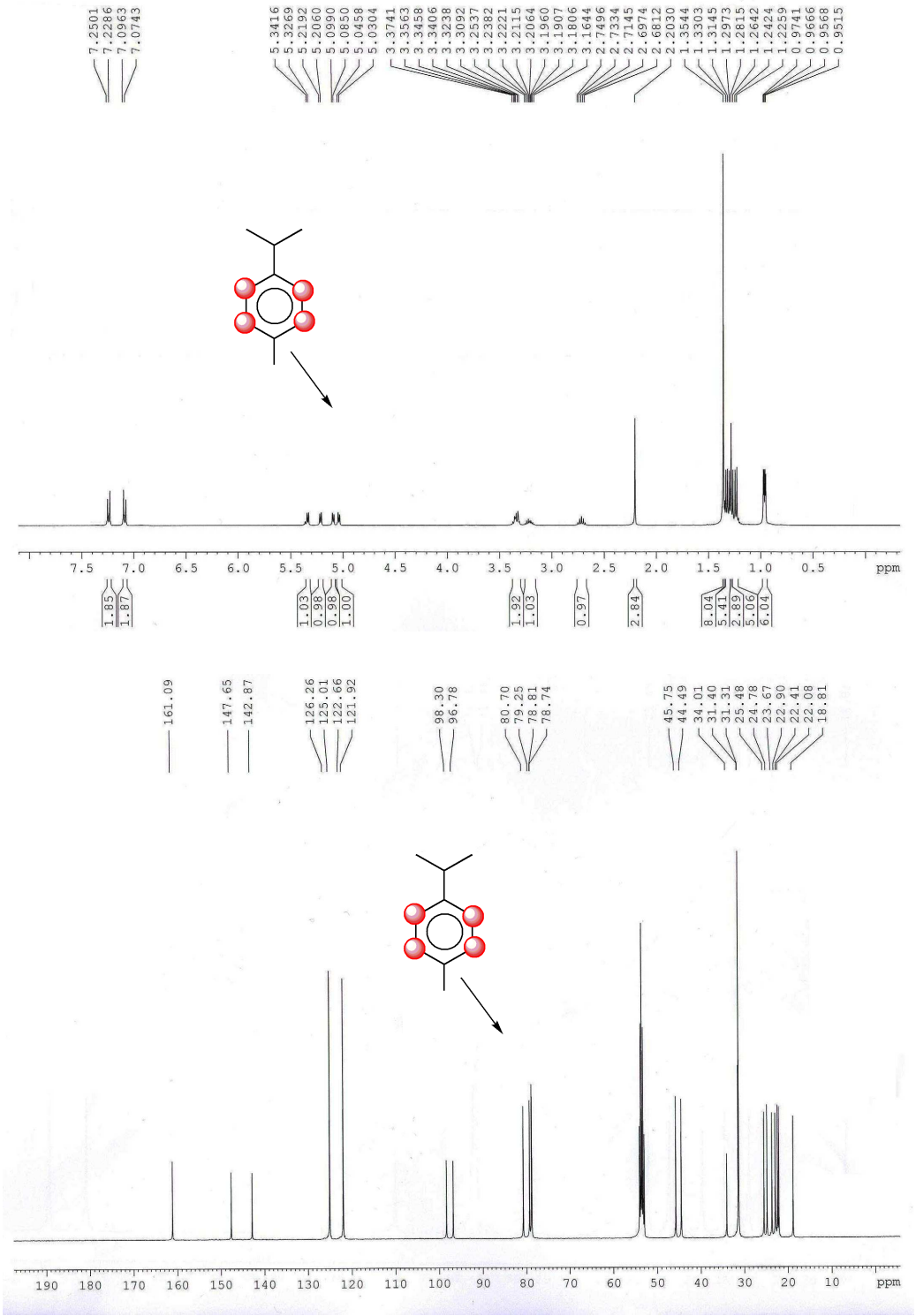


Figura 3.8: Espectros de RMN de ^{1}H y ^{13}C{^{1}H} (CD_2Cl_2) obtenidos para el complejo [RuCl{κ^2-*N,N´*-C(N-4-$C_6H_4{}^t$Bu)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22b**).

En el caso del complejo simétrico [RuCl{κ^2-*N,N´*-C(N^{i}Pr)$_2$NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a**), estas unidades CH del anillo *p*-cimeno son equivalentes dos a dos, de modo que para ellas sólo se observan dos señales en los espectros de RMN de ^{1}H y de ^{13}C{^{1}H} de este derivado. Las estructuras propuestas para los complejos [RuCl{κ^2-*N,N´*-C(N^{i}Pr)$_2$NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a**) y [RuCl{κ^2-*N,N´*-C(N-4-C$_6$H$_4$^{t}Bu)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22b**) pudieron ser posteriormente corroboradas de manera inequívoca mediante la técnica de difracción de rayos-X de monocristal (ver detalles y discusión de las estructuras en la publicación adjunta).

Cabe destacar también que, para los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (R = 2,4,6-C$_6$H$_2$Me$_3$ (**3.22d**), 2,6-C$_6$H$_3$^{i}Pr$_2$ (**3.22e**)) que contienen sustituyentes arilo muy voluminosos, la rotación alrededor del enlace N-Ar parece estar impedida. Este hecho se refleja en los espectros de RMN de ^{1}H y ^{13}C{^{1}H} de estos derivados por la inequivalencia observada para los grupos Me e ^{i}Pr situados en las posiciones *orto* de los anillos aromáticos (Figura 3.9).

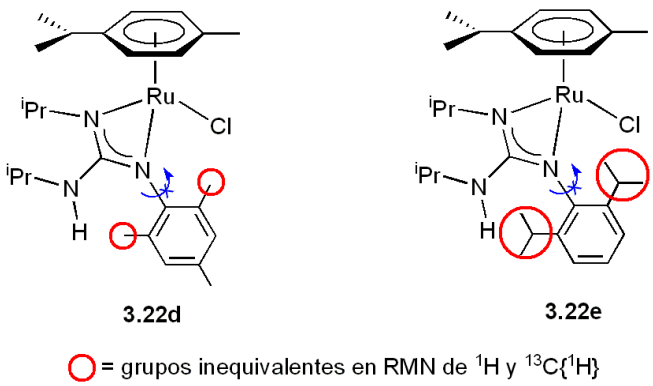
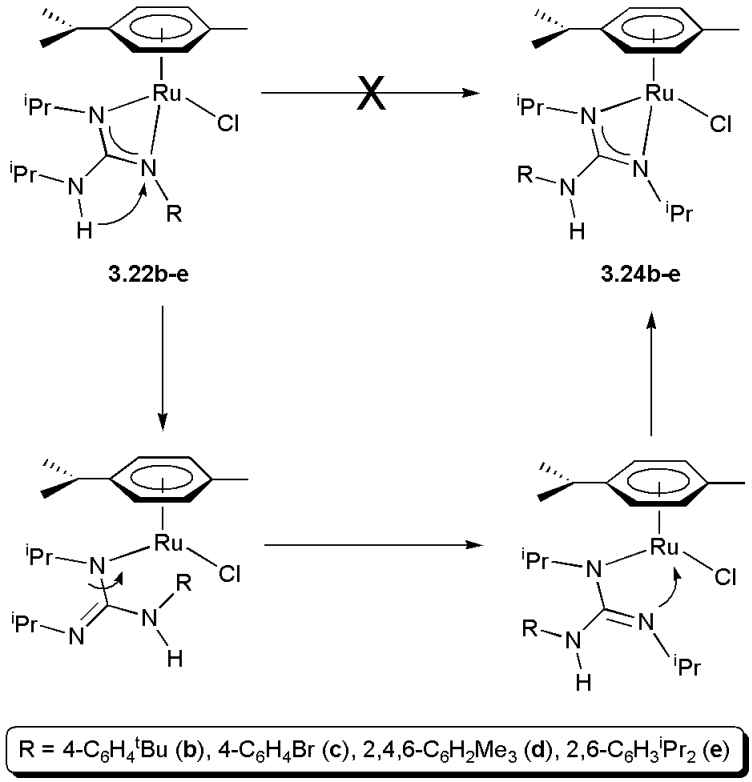


Figura 3.9: Rotación restringida de los enlaces N-arilo en los complejos **3.22d** y **3.22e**.

La repulsión estérica entre estos grupos y los sustituyentes ^{i}Pr y/o Me del ligando η^6-*p*-cimeno explicaría la ausencia de rotación libre alrededor de los enlaces N-Ar observada en los espectros de resonancia magnética nuclear. No obstante, a pesar de los impedimentos estéricos existentes alrededor del centro metálico, en ningún momento hemos observado el reordenamiento de los complejos **3.22d-e**, o el de sus análogos no-simétricos **3.22b-c**, en los correspondientes isómeros [RuCl{κ^2-*N,N´*-C(N^{i}Pr)$_2$NHR}(η^6-*p*-cimeno)] (R = 4-C$_6$H$_4$^{t}Bu (**3.24b**), 4-C$_6$H$_4$Br

(**3.24c**), 2,4,6-$C_6H_2Me_3$ (**3.24d**), 2,6-$C_6H_3{}^iPr_2$ (**3.24e**)) donde la coordinación simétrica de los ligandos guanidinato estaría menos impedida estéricamente (Esquema 3.9).[34]



Esquema 3.9: Reordenamiento potencial de los complejos **3.22d-e** en sus isómeros **3.24d-e**.

Para explicar la preferencia observada por la coordinación no-simétrica de los aniones guanidinato en los complejos **3.22b-e** se estudió la estabilidad relativa de los mismos frente a sus isómeros **3.24b-e** mediante cálculos DFT (ver detalles en la publicación correspondiente adjunta). Los resultados obtenidos pusieron de manifiesto que los derivados no-simétricos **3.22b-e** son termodinámicamente más estables que sus isómeros simétricos **3.24b-e**, con diferencias de energías comprendidas en el intervalo 3.1-5.9 kcal/mol. La diferencia más pequeña se observó para la pareja [RuCl{κ^2-*N,N´*-C(N-2,6-$C_6H_3{}^iPr_2$)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22e**) /

[34] Este tipo de reordenamientos, que involucran una migración formal 1,3 de hidrógeno, están bien documentados en la bibliografía, tanto en complejos guanidinato como en las propias guanidinas libres. Ver, por ejemplo, la referencia 33 y: (a) S. M. Mullins, A. P. Duncan, R. G. Bergman, J. Arnold, *Inorg. Chem.* **2001**, *40*, 6952; (b) J. Zhang, R. Cai, L. Weng, X. Zhuo, *Organometallics* **2004**, *23*, 3303; (c) C. Qian, X. Zhang, J. Li, F. Xu, Y. Zhang, Q. Shen, *Organometallics* **2009**, *28*, 3856; (d) X. Zhang, C. Wang, C. Qian, F. Han, F. Xu, Q. Shen, *Tetrahedron* **2011**, *67*, 8790.

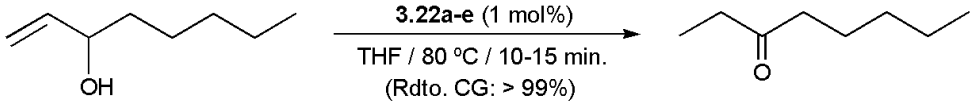
[RuCl{κ^2-*N,N´*-C(N^{i}Pr)$_2$NH(N-2,6-C$_6$H$_3$^{i}Pr$_2$)}(η^6-*p*-cimeno)] (**3.24e**), donde existe una mayor demanda estérica debido a la presencia del sustituyente 2,6-diisopropilfenil. Estas predicciones teóricas, que se encuentran en total sintonía con los resultados obtenidos experimentalmente, sugieren que los factores electrónicos prevalecen sobre los estéricos. De esta forma, la estabilización asociada a la conjugación electrónica de los electrones π deslocalizados de la unidad N-C-N con los anillos aromáticos podría ser la responsable de la mayor estabilidad termodinámica de **3.22b-e** *vs* **3.24b-e**.

3.2.2.- Estudio de la actividad catalítica de los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (R = ^{i}Pr (3.22a), 4-C$_6$H$_4$^{t}Bu (3.22b), 4-C$_6$H$_4$Br (3.22c), 2,4,6-C$_6$H$_2$Me$_3$ (3.22d), 2,6-C$_6$H$_3$^{i}Pr$_2$ (3.22e)) en la isomerización redox de alcoholes alílicos.

Una vez sintetizados y caracterizados, decidimos explorar el potencial catalítico de los derivados [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**), ya que, como se ha comentado anteriormente, no existen precedentes en la bibliografía sobre la aplicación de complejos rutenio-guanidinato en catálisis homogénea. En este sentido, nuestros esfuerzos iniciales se centraron en la reacción de hidratación de nitrilos. Desafortunadamente, las actividades catalíticas mostradas por los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**) en la hidratación del sustrato modelo, *i.e.* la benzamida, bajo diferentes condiciones de reacción, fueron prácticamente nulas. Estos resultados negativos son debidos a la inestabilidad de los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**) frente al agua, que produce la rápida descomposición de los mismos. Dicho proceso de descomposición es apreciable a simple vista por el cambio de color de las correspondientes disoluciones (de naranja a negro).

La necesidad de trabajar en medios de reacción anhidros nos orientó hacia las reacciones de isomerización de alcoholes alílicos, procesos bien conocidos en el grupo y que no requieren de la presencia de agua.[16c,g,18a,f,h,m,21d,fg,h,30,31] Para evaluar la actividad catalítica de los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**) en este tipo de procesos se eligió como reacción modelo la isomerización de 1-

octen-3-ol en 3-octanona. De forma general, las reacciones se llevaron a cabo bajo atmósfera de nitrógeno, en tubo sellado, añadiendo el precursor de catalizador (1 mol%) sobre una disolución del sustrato en THF (0.2 M), y calentando la mezcla resultante a 80 °C. Como se puede observar en el Esquema 3.10, todos los complejos sintetizados mostraron ser catalizadores activos y selectivos en el proceso, generando la 3-octanona deseada con rendimientos prácticamente cuantitativos por CG y en tiempos de reacción muy cortos (10-15 min).



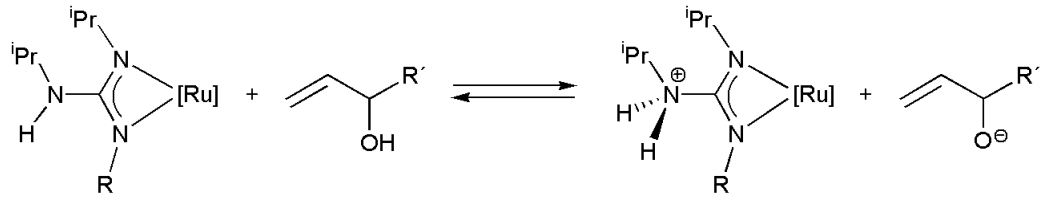
Esquema 3.10: Isomerización del 1-octen-3-ol en 3-octanona empleando los complejos **3.22a-e** como catalizadores.

Estudios adicionales empleando el complejo [RuCl{κ^2-*N,N´*-C(N-4-C_6H_4Br)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22c**) mostraron que la alta actividad de estos derivados se mantiene al emplear cargas de catalizador más bajas. Así, por ejemplo, usando tan sólo un 0.1 mol% de **3.22c** se puede transformar cuantitativamente el 1-octen-3-ol en 3-octanona tras 1 h de calentamiento a 80 °C, lo que se traduce en un valor de TOF de 1000 h^{-1}. Aunque dicho valor está lejos del máximo alcanzado para esta transformación catalítica, *i.e.* 62500 h^{-1} empleando el complejo bis(alilo) de rutenio(IV) [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] (**3.9** en la Figura 3.5),[21d] es muy superior al descrito para otros sistemas catalíticos de tipo rutenio(II)-areno activos en ausencia de base descritos en la bibliografía.[16] Cabe mencionar también que, llevando a cabo la reacción en presencia de 20 equivalentes (por Ru) de *p*-cimeno libre, la actividad catalítica del complejo **3.22c** se reduce significativamente (empleando 1 mol% de **3.22c**, se necesitan dos horas de calentamiento para que la reacción termine). Este hecho parece indicar que las vacantes de coordinación requeridas para la coordinación del sustrato al metal se generan por disociación del ligando η^6-areno, proceso que vendría motivado por los impedimentos estéricos existentes entre los sustituyentes del ligando guanidinato y los del anillo de *p*-cimeno.

La generalidad del proceso fue confirmada empleando el complejo [RuCl{κ^2-*N,N´*-C(N-4-C_6H_4Br)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22c**) y una familia variada de alcoholes alílicos R-CH(OH)-CH=CH_2 (R = Me, Et, ^{n}Pr, ^{n}Bu, Ph,

4-C_6H_4F, 4-C_6H_4Cl, 4-C_6H_4OMe). Así, utilizando 1 mol% del complejo **3.22c** y una temperatura de trabajo de 80 ºC, todos los alcoholes ensayados pudieron ser transformados en las correspondientes cetonas saturadas con rendimientos superiores al 80% (determinados por CG). No obstante, debemos hacer notar que, en el caso de los sustratos aromáticos, se requieren tiempos de reacción más largos que en el caso de los sustratos alifáticos (3-24 h *vs* 10-30 min) para obtener buenas conversiones. Esto es debido, muy probablemente, a los impedimentos estéricos relacionados con la presencia de grupos voluminosos en posición α con respecto al alcohol, que desfavorecen su coordinación al centro metálico.[35] Empleando **3.22c**, confirmamos que el proceso no está restringido a alcoholes alílicos con dobles enlaces C=C monosustituidos, pudiendo llevarse a cabo también la isomerización de alcoholes alílicos disustituidos, tales como el 3-penten-2-ol (rendimiento cuantitativo de la 2-pentanona tras 1 h de calentamiento).

Como acabamos de ver, a diferencia de la mayoría de catalizadores de rutenio activos en medio orgánico,[16] los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**) son capaces de promover la isomerización redox de alcoholes alílicos de manera eficiente en ausencia de base. Este hecho hace pensar en un posible efecto cooperativo por parte del grupo amino NH^{i}Pr del ligando guanidinato durante la reacción catalítica. Este grupo podría facilitar la formación del alcoholato correspondiente por desprotonación del alcohol alílico (Esquema 3.11), favoreciendo así la coordinación del sustrato al centro metálico.



Esquema 3.11: Posible efecto cooperativo de los ligandos guanidinato.

Para esclarecer esta cuestión decidimos preparar el complejo amidinato [RuCl{κ^2-*N,N´*-C(N^{i}Pr)$_2$Me}(η^6-*p*-cimeno)], que contiene un grupo metilo en lugar del isopropilamino (NH^{i}Pr), y estudiar su comportamiento

[35] Estudios previos ya han puesto de manifiesto este efecto. Ver, por ejemplo, las referencias 31b-d y: (a) V. Cadierno, J. Francos, J. Gimeno, N. Nebra, *Chem. Commun.* **2007**, 2536; (b) V. Cadierno, P. Crochet, J. Francos, S. E. García-Garrido, J. Gimeno, N. Nebra, *Green Chem.* **2009**, *11*, 1992.

en la isomerización del sustrato modelo 1-octen-3-ol empleando las mismas condiciones de reacción que las recogidas en el Esquema 3.10. La actividad catalítica mostrada por este derivado amidinato fue muy inferior a la de los complejos guanidinato **3.22a-e** (conversión por CG del 96% tras 6 h *vs* > 99% tras 10-15 min), lo que parece corroborar nuestra hipótesis. Otro hecho que también apoya el efecto cooperativo de los ligandos guanidinato es que, cuando se llevan a cabo las reacciones catalíticas en presencia de ácido, la actividad de los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**) disminuye drásticamente.

CAPÍTULO 3

3.3.- PUBLICACIONES

Los resultados obtenidos en este capítulo han dado lugar a la publicación que se adjunta:

"Ruthenium(II) arene complexes with asymmetrical guanidinate ligands: Synthesis, characterization, and application in the base-free catalytic isomerization of allylic alcohols". Rocío García-Álvarez, Francisco J. Suárez, Josefina Díez, Pascale Crochet, Victorio Cadierno, Antonio Antiñolo, Rafael Fernández-Galán, Fernando Carrillo-Hermosilla. *Organometallics* **2012**, *31*, 8301-8311.

ORGANOMETALLICS

Article

pubs.acs.org/Organometallics

Ruthenium(II) Arene Complexes with Asymmetrical Guanidinate Ligands: Synthesis, Characterization, and Application in the Base-Free Catalytic Isomerization of Allylic Alcohols

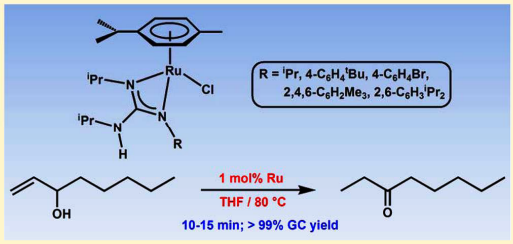
Rocío García-Álvarez,[†] Francisco J. Suárez,[†] Josefina Díez,[†] Pascale Crochet,*[,†] Victorio Cadierno,*[,†] Antonio Antiñolo,*[,‡] Rafael Fernández-Galán,[‡] and Fernando Carrillo-Hermosilla[‡]

[†]Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles", Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain

[‡]Departamento de Química Inorgánica, Orgánica y Bioquímica, Facultad de Ciencias Químicas, Campus de Ciudad Real, Universidad de Castilla-La Mancha, Campus Universitario, E-13071 Ciudad Real, Spain

Supporting Information

ABSTRACT: The ruthenium(II) arene dimer [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] readily reacted with 4 equiv of guanidines (^{i}PrHN)$_2$C=NR (R = ^{i}Pr (**1a**), 4-C$_6$H$_4$^{t}Bu (**1b**), 4-C$_6$H$_4$Br (**1c**), 2,4,6-C$_6$H$_2$Me$_3$ (**1d**), 2,6-C$_6$H$_3$^{i}Pr$_2$ (**1e**)) in toluene at room temperature to generate the mononuclear complexes [RuCl{κ^2*N*,*N*′-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (**2a**–**e**) and the easily separable guanidinium chloride salts [(^{i}PrHN)$_2$C(NHR)][Cl] (**3a**–**e**). Compounds **2a**–**e** and **3a**–**e** were fully characterized by elemental analysis and IR and NMR spectroscopy. The structures of [RuCl{κ^2*N*,*N*′-C(N^{i}Pr)$_2$NH^{i}Pr}(η^6-*p*-cymene)] (**2a**) and [RuCl{κ^2*N*,*N*′-C(N-4-C$_6$H$_4$^{t}Bu)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (**2b**) were also determined by X-ray diffraction analysis. Regardless of the steric requirements of the aromatic substituents, a nonsymmetric coordination of the guanidinate anions in **2b**–**e** was observed, in complete accord with theoretical calculations (DFT) on the corresponding [RuCl{κ^2*N*,*N*′-C(NR)(N^{i}Pr)-NH^{i}Pr}(η^6-*p*-cymene)] and [RuCl{κ^2*N*,*N*′-C(N^{i}Pr)$_2$NHR}(η^6-*p*-cymene)] models. Remarkably, complexes **2a**–**e** were active catalysts for the redox isomerization of allylic alcohols in the absence of base, which represents the first catalytic application known for ruthenium guanidinate species.



INTRODUCTION

Guanidinate monoanions of the general formula [(RN)$_2$CNR$_2$]$^-$ are closely related to the well-known amidinates, differing only in that they contain an amino (R$_2$N) substituent on the ligand's central carbon which results in a higher steric and electronic tunability. Since the preparation of the first transition-metal guanidinate complex by Lappert and co-workers in 1970,[1] a huge number of coordination complexes involving metals from across the periodic table have been described.[2,3] In these, the guanidinate anions have exhibited many coordination modes, but by far the two most common are when they act as delocalized N,N′-chelating or bridging ligands (Figure 1).

Remarkably, despite the great variety of transition-metal guanidinates reported to date in the literature, ruthenium derivatives remain surprisingly rare. Thus, in addition to a series of diruthenium complexes bridged by the *N*,*N*′,*N*″-triphenylguanidinate monoanion described by Berry and co-workers,[4] at the beginning of our work in the field, only the following mononuclear derivatives were known: (i) the octahedral species [Ru{κ^2*N*,*N*′-C(NPh)$_2$NHPh}$_2$(CO)(PPh$_3$)],[5] [RuH{κ^2*N*,*N*′-C(NPh)$_2$NHPh}(CO)(PPh$_3$)$_2$],[6] and [Ru{κ^2*N*,*N*′-C(NPh)$_2$NHPh}$_3$][7] and (ii) the half-sandwich ruthenium(II) arene complex [RuCl{κ^2*N*,*N*′-C(NPh)$_2$NHPh}(η^6-*p*-cymene)].[8,9] Very recently, with our work already in progress, a family of related chloride and azide (η^6-*p*-cymene)Ru^{II} derivatives bearing *N*,*N*′,*N*″-triarylguanidinates has been described by Thirupathi and co-workers, along with a thorough structural characterization in both solution and the solid state, and reactivity studies of the azido complexes with activated alkynes ([3 + 2] cycloaddition reactions).[10] As in the preceding cases, guanidinate monoanions generated from guanidines with the symmetric substitution pattern (ArHN)$_2$C=NAr were employed by Thirupathi. It is also worthy of note that, despite the burgeoning role of ruthenium in catalytic organic synthesis,[11] none of the ruthenium guanidinate complexes reported so far have been explored in homogeneous catalysis. This fact contrasts with the chemistry of related ruthenium amidinate systems, which have found application in different catalytic transformations.[12]

Received: September 26, 2012
Published: November 5, 2012

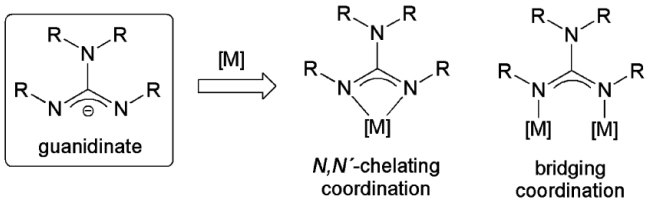


Figure 1. Guanidinate monoanions and their most common coordination modes.

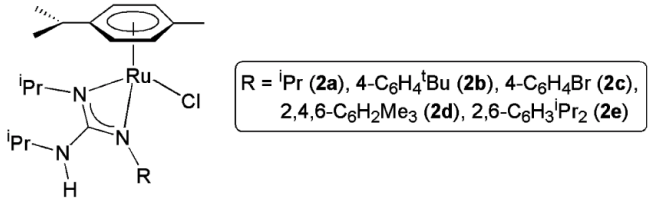
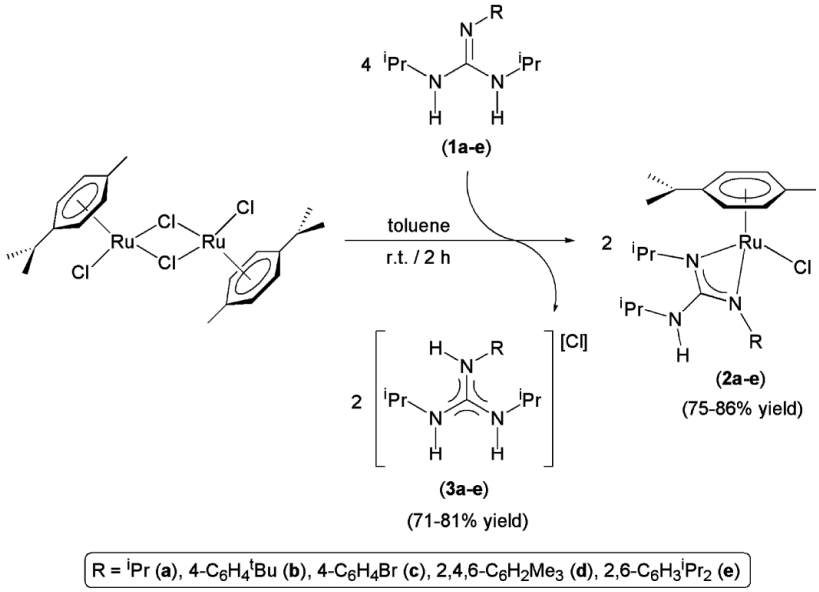


Figure 2. Structure of the ruthenium(II) arene complexes synthesized in this work.

Scheme 1. Synthesis of the Mononuclear Ru(II) Complexes [RuCl{κ^2*N,N*′-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (2a−e)



To bridge this gap, herein we describe the preparation of the novel ruthenium(II) arene complexes **2a−e** (Figure 2), generated from the reactions of the readily available guanidines (^{i}PrHN)$_2$C═NR (R = ^{i}Pr (**1a**), 4-C$_6$H$_4$^{t}Bu (**1b**), 4-C$_6$H$_4$Br (**1c**), 2,4,6-C$_6$H$_2$Me$_3$ (**1d**), 2,6-C$_6$H$_3$^{i}Pr$_2$ (**1e**))[13] with the dimeric precursor [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$],[14] and their application in the catalytic isomerization of allylic alcohols to carbonyl compounds.[15] The present paper brings novelty since (i) compounds **2b−e** represent the first examples of ruthenium complexes containing asymmetrical monoanionic guanidinate ligands and (ii) unlike the majority of ruthenium catalysts previously described for redox isomerizations of allylic alcohols, complexes **2a−e** operate without the assistance of base.[15]

RESULTS AND DISCUSSION

Synthesis and Characterization of Complexes [RuCl{κ^2*N,N*′-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (2a−e). The novel ruthenium-guanidinate complexes [RuCl{κ^2*N,N*′-C(NR)(N^{i}Pr)-NH^{i}Pr}(η^6-*p*-cymene)] (R = ^{i}Pr (**2a**), 4-C$_6$H$_4$^{t}Bu (**2b**), 4-C$_6$H$_4$Br (**2c**), 2,4,6-C$_6$H$_2$Me$_3$ (**2d**), 2,6-C$_6$H$_3$^{i}Pr$_2$ (**2e**)) were synthesized by following the same procedure reported by Bailey and Thirupathi for the preparation of related symmetrical [RuCl{κ^2*N,N*′-C(NAr)$_2$NHAr}(η^6-*p*-cymene)] species.[8,10] Thus, as shown in Scheme 1, treatment of [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] with 4 equiv of guanidines (^{i}PrHN)$_2$C═NR (**1a−e**), in toluene at room temperature, led to the precipitation of the corresponding guanidinium chloride salts [(^{i}PrHN)$_2$C(NHR)]-

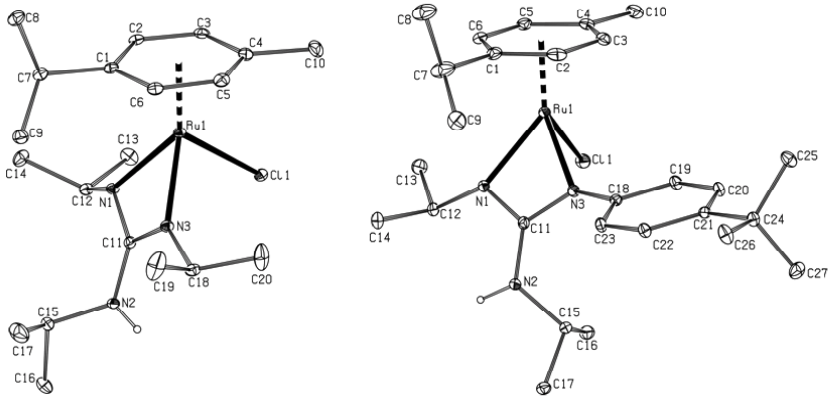


Figure 3. ORTEP-type views of the structures of the ruthenium complexes **2a** (left) and **2b** (right) with the crystallographic labeling schemes. Hydrogen atoms, except that on N(2), have been omitted for clarity in both structures. Thermal ellipsoids are drawn at the 10% probability level.

[Cl] (**3a−e**) and the clean formation of the mononuclear complexes **2a−e**, which were crystallized from the solution by concentration, filtration of **3a−e**, and cooling. Both complexes **2a−e** and the guanidinium salts **3a−e** were isolated as air-stable solids in high yields (75−86% and 71−81%, respectively) and characterized by elemental analysis and IR and NMR (^{1}H and ^{13}C{^{1}H}) spectroscopy (details are given in the Experimental Section). The asymmetric coordination of the guanidinate anions in complexes **2b−e** was clearly reflected in their ^{1}H and ^{13}C{^{1}H} NMR spectra by the appearance of four well-differentiated signals for the aromatic CH protons and carbons of the η^6-coordinated cymene ring, a typical situation in (η^6-*p*-cymene)ruthenium(II) complexes where the metal is a stereogenic center.[16] In the case of the symmetric complex **2a**, these CH units are two-by-two equivalent, leading only to two signals in the spectra. The expected resonances for the guanidinate ligands were also observed in the ^{1}H and ^{13}C{^{1}H} NMR spectra of **2a−e**, with a downfield singlet for the central CN_3 carbon at δ_C 160.8−165.4 ppm being their most characteristic hallmark (for the guanidinium salts **3a−e** this carbon resonates at slightly higher fields (δ_C 153.6−156.1 ppm)). It is also worthy of note that for complexes **2d,e**, containing the bulky aryl substituents mesityl and 2,6-diisopropylphenyl, restricted rotation around the N−Ar bond takes place in solution, as clearly evidenced in their ^{1}H and ^{13}C{^{1}H} NMR spectra by the chemical inequivalence of the Me and ^{i}Pr groups located in the ortho positions of the aromatic rings. This fact clearly reflects the high steric hindrance between these aryl groups and the *p*-cymene ligand.

The structures of the symmetrical complex [RuCl{κ^2*N*,*N*′-C(N^{i}Pr)$_2$NH^{i}Pr}(η^6-*p*-cymene)] (**2a**) and the unsymmetrical complex [RuCl{κ^2*N*,*N*′-C(N-4-C$_6$H$_4$^{t}Bu)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (**2b**) were fully confirmed by means of X-ray diffraction methods. Single crystals suitable for X-ray analysis were obtained by slow diffusion of *n*-pentane into saturated solutions of these compounds in diethyl ether. ORTEP views of the molecules are shown in Figure 3, and selected structural parameters are collected in Table 1.

A typical three-legged piano-stool geometry, with the ruthenium atom surrounded by the η^6-bonded *p*-cymene ligand, a terminal chloride, and the corresponding chelating guanidinate anion, is observed in both cases. The Ru−N(1) and Ru−N(3) bond lengths, in the range 2.076(2)−2.1196(19) Å, are comparable to those previously found in the crystal structures of [RuCl{κ^2*N*,*N*′-C(NAr)$_2$-NHAr}(η^6-*p*-cymene)] (Ar = Ph,[8] 4-C$_6$H$_4$Me,[10] 2-C$_6$H$_4$Me,[10] 2-C$_6$H$_4$OMe,[10] 2,4-C$_6$H$_3$Me$_2$[10]) (2.086(3)−2.149(3) Å). As observed for these complexes, the CN_3 cores of the guanidinate skeletons in **2a,b** are perfectly planar, as indicated by the sum of angles around the central C(11) carbons of 359.9° (**2a**) and 360° (**2b**). Concerning the bonding of the guanidinate anions to ruthenium, it is best

Table 1. Selected Bond Distances (Å) and Bond Angles (deg) for 2a,b[a]

	2a	2b
Bond Distances		
Ru−C*	1.66433(17)	1.6655(2)
Ru−Cl(1)	2.4284(6)	2.4147(9)
Ru−N(1)	2.1196(19)	2.108(3)
Ru−N(3)	2.076(2)	2.085(3)
C(11)−N(1)	1.340(3)	1.319(4)
C(11)−N(2)	1.385(3)	1.375(4)
C(11)−N(3)	1.322(3)	1.338(4)
N(1)−C(12)	1.458(3)	1.469(4)
N(2)−C(15)	1.454(3)	1.477(4)
N(3)−C(18)	1.460(3)	1.396(4)
Bond Angles		
C*−Ru−Cl(1)	126.800(17)	129.42(2)
C*−Ru−N(1)	134.97(5)	135.12(8)
C*−Ru−N(3)	136.83(6)	135.68(8)
Cl(1)−Ru−N(1)	87.86(6)	85.33(8)
Cl(1)−Ru−N(3)	85.66(6)	84.92(9)
N(1)−Ru−N(3)	62.19(8)	62.3(1)
Ru−N(1)−C(11)	92.41(14)	93.7(2)
Ru−N(1)−C(12)	135.56(16)	136.4(2)
Ru−N(3)−C(11)	94.87(15)	94.2(2)
Ru−N(3)−C(18)	138.85(17)	132.0(2)
N(1)−C(11)−N(3)	109.0(2)	109.3(3)
N(1)−C(11)−N(2)	124.4(2)	125.0(3)
N(2)−C(11)−N(3)	126.5(2)	125.7(3)
C(11)−N(1)−C(12)	123.4(2)	122.3(3)
C(11)−N(2)−C(15)	121.8(2)	121.4(3)
C(11)−N(3)−C(18)	125.6(2)	129.7(3)

[a]C* denotes the centroid of the *p*-cymene ring (C(1), C(2), C(3), C(4), C(5), and C(6)).

dx.doi.org/10.1021/om3009124 | *Organometallics* 2012, 31, 8301−8311

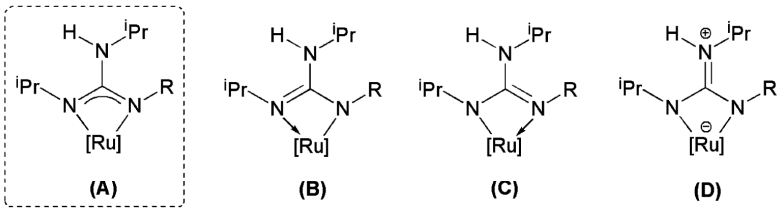


Figure 4. Resonance forms of the guanidinate ligands in complexes **2a–e**.

described through the diazaallyl resonance form **A** (Figure 4). The C–N bond distances between the metal-coordinated nitrogen atoms N(1) and N(3) and the central carbon C(11) of the ligand, very similar in both structures (1.319(4)-1.340(3) Å) and significantly shorter than that of the C(11)–N(2) bond (1.385(3) Å (**2a**) and 1.375(4) Å (**2b**)), are in complete accord with the higher contribution of the delocalized form **A** over the alternative resonance forms **B–D** to the bonding.

It is also worthy of note that the crystal packings of the two molecules are different. Thus, while in the case of [RuCl{κ^2*N*,*N*′-C(N-4-$C_6H_4{}^tBu$)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (**2b**) no intermolecular interactions were found in the crystal lattice, the N(2)–H unit of [RuCl{κ^2*N*,*N*′-C(N^{i}Pr)$_2$NH^{i}Pr}(η^6-*p*-cymene)] (**2a**) is involved in a hydrogen bond with the chloride ligand of a neighboring molecule, thus leading to the formation of dimeric aggregates in the solid state (see Figure 5).[17] According

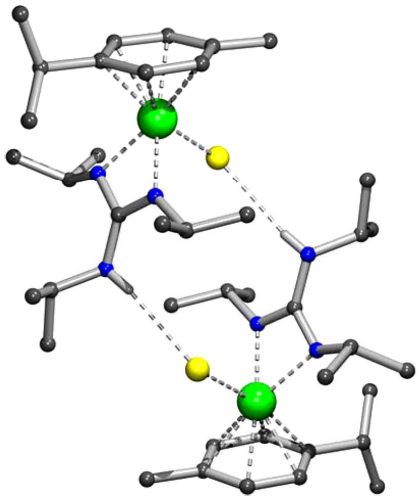


Figure 5. Hydrogen-bonding scheme for complex **2a**. Hydrogen atoms, except that on N(2), have been omitted for clarity. Distances (Å) and angle (deg) for the intermolecular N(2)-H···Cl(1) hydrogen bond are as follows: N(2)–H = 0.81; H–Cl(1) = 2.58; N(2)–Cl(1) = 3.354; N(2)–H–Cl(1) = 161.64.

to the classification of Jeffrey,[18] the distance and angle of the N–H···Cl contact of 2.58 Å and 161.64°, respectively, allow it to be classified as "weak" among the H bonds considered most common in chemical systems. The absence of this weak intermolecular interaction in the structure of **2b** is probably associated with the higher steric demand of the 4-$C_6H_4{}^tBu$ group in comparison to the ^{i}Pr group, which leads to a less compact crystal packing.

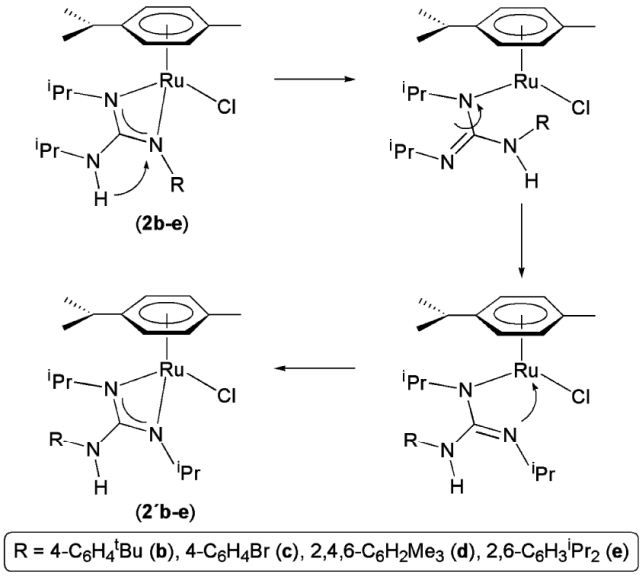
As noted above, restricted rotation of the N–aryl bond in complexes **2d,e** was observed by NMR spectroscopy as a result of the steric crowding in the metal environment. Despite this, guanidinate rearrangement from the asymmetrical (complexes **2b–e**) to the less congested symmetrical coordination (complexes **2′b–e**), via a formal 1,3-hydrogen shift, was not observed in solution (Scheme 2).[19] In order to account for the preferred asymmetric coordination of the guanidinate anions, the relative stability of complexes **2b–e** vs **2′b–e** was studied by means of DFT calculations at the B3LYP/6-31G(d)+LANL2DZ level of theory. For comparative purposes, the free anions **4b–e** and **4′b–e** were also investigated (Figure 6).

The optimized structures of **2b–e**, **2′b–e**, **4b–e**, and **4′b–e**, and their most relevant geometrical parameters, are given in the Supporting Information.[20] All of them were characterized as minima on the potential energy surface, and their absolute and relative energies are given in Table 2. According to our calculations, the unsymmetrical complexes **2b–e** are more stable than the symmetrical complexes **2′b–e** by 3.1–5.9 kcal/mol. The smallest energy difference was observed for the **2e**/**2′e** couple, in which the most sterically demanding 2,6-diisopropylphenyl group is present (3.1 kcal/mol). Concerning the free guanidinate anions **4b–e** and **4′b–e**, the former was much more stable than the latter, with energy differences ranging from 10.3 to 14.9 kcal/mol. In contrast to what is observed in the complexes, the presence of the bulkiest 2,6-diisopropylphenyl group results now in a marked preference for the nonsymmetric structure **4e**. All these theoretical predictions, which are in complete accord with the experimental results, suggest that electronic factors prevail over the steric factors to rationalize the observed structures. The stabilization associated with the electronic conjugation of the delocalized π electrons of the N–C–N linkages with the aromatic rings may be evoked to explain the higher thermodynamic stability of **2b–e** vs **2′b–e** and **4b–e** vs **4′b–e**.

Catalytic Isomerization of Allylic Alcohols. The redox isomerization of allylic alcohols represents an efficient, selective, and atom-economical approach for the preparation of saturated carbonyl compounds. The process involves the one-pot migration of the C=C bond of the allylic alcohol and subsequent tautomerization of the resulting enol (Scheme 3). This catalytic transformation has been extensively studied in academic laboratories during the last two decades, as it conveniently replaces the classical routes involving two-step sequential oxidation and reduction reactions,[15] and has found utility in the pharmaceutical industry for the transformation of the naturally occurring opiates morphine and codeine into the more commonly prescribed narcotic analgesics hydromorphone and hydrocodone.[21]

dx.doi.org/10.1021/om3009124 | *Organometallics* 2012, 31, 8301–8311

Scheme 2. Potential Isomerization of the Unsymmetrical Complexes 2b−e into the Symmetrical Complexes 2′b−e



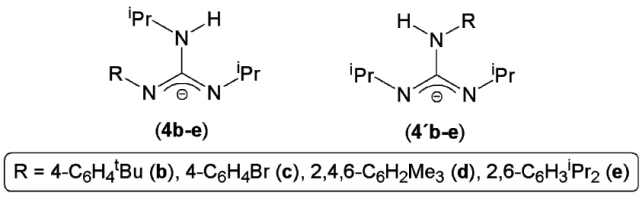


Figure 6. Structure of the guanidinate anions **4b−e** and **4′b−e**.

Table 2. Calculated Total (hartree) and Relative (kcal/mol) Energies for Ruthenium Complexes 2b−e and 2′b−e and Guanidinate Anions 4b−e and 4′b−e[a]

2b	−1 772.588 602 12 (0.0)	**4b**	−828.939 055 043 (0.0)
2′b	−1 772.579 963 55 (5.4)	**4′b**	−828.922 596 635 (10.3)
2c	−4 186.140 932 31 (0.0)	**4c**	−3 242.500 517 74 (0.0)
2′c	−4 186.131 577 88 (5.9)	**4′c**	−3 242.480 911 75 (12.3)
2d	−1 733.281 334 09 (0.0)	**4d**	−789.633 654 411 (0.0)
2′d	−1 733.272 761 79 (5.4)	**4′d**	−789.614 214 617 (12.2)
2e	−1 851.206 685 05 (0.0)	**4e**	−907.565 605 016 (0.0)
2′e	−1 851.201 805 35 (3.1)	**4′e**	−907.541 868 079 (14.9)

[a]B3LYP/6-31G(d)+LANL2DZ-optimized geometries.

The most effective catalysts presently available for the redox isomerization of allylic alcohols are based on ruthenium, rhodium, and iridium complexes,[15] with the first group being particularly attractive due to their lower cost. In this context, a huge number of ruthenium-based catalytic systems for this relevant transformation have been described in recent years.[22] Worthy of note, fast conversions are usually achieved in the presence of a base, since deprotonation of the hydroxyl group of the allylic alcohol is needed to enhance its coordinating ability.[23] In marked contrast to this common trend, we have found that the ruthenium guanidinate complexes [RuCl{κ^2N,N'-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (R = ^{i}Pr (**2a**), 4-C$_6$H$_4$^{t}Bu (**2b**), 4-C$_6$H$_4$Br (**2c**), 2,4,6-C$_6$H$_2$Me$_3$ (**2d**), 2,6-C$_6$H$_3$^{i}Pr$_2$ (**2e**)) are able to promote the redox isomerization of allylic alcohols under base-free conditions. In this sense, all of them were able to convert selectively and almost quantitatively 1-octen-3-ol into octan-3-one, in remarkably short times (10−15 min), with the catalytic reactions being performed in THF (0.2 M solutions of the allylic

Scheme 3. Catalytic Redox Isomerization of Allylic Alcohols

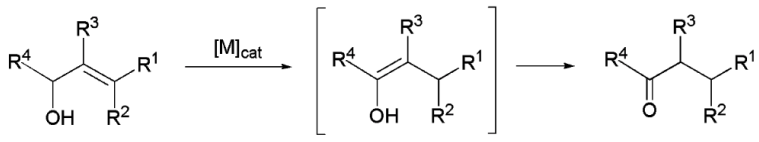
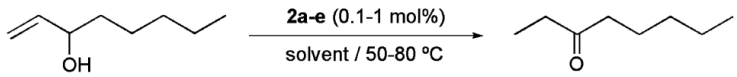


Table 3. Catalytic Isomerization of 1-Octen-3-ol into Octan-3-one using [RuCl{κ^2*N*,*N*′-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (2a−e) as Catalysts[a]



entry	cat.	amt of Ru, mol %	solvent	temp, °C	time	yield, %[b]
1	**2a**	1	THF	80	15 min	>99
2	**2b**	1	THF	80	15 min	>99
3	**2c**	1	THF	80	10 min	>99
4	**2d**	1	THF	80	10 min	>99
5	**2e**	1	THF	80	10 min	>99
6	**2c**	0.5	THF	80	20 min	>99
7	**2c**	0.1	THF	80	1 h	>99
8	**2c**	1	toluene	80	2 h	99
9	**2c**	1	1,2-dichloroethane	80	20 min	99
10	**2c**	1	MeOH	80	3 h	52
11	**2c**	1	H_2O	80	3 h	15
12	**2c**	1	THF	50	24 h	92
13[c]	**2c**	1	THF	80	2 h	>99

[a]Reactions performed under an N_2 atmosphere using 4 mmol of 1-octen-3-ol (0.2 M solutions). [b]Yields determined by GC. [c]Reaction performed in the presence of 20 equiv (per Ru) of free *p*-cymene.

alcohol) at 80 °C with a metal loading of 1 mol % (entries 1−5 in Table 3). Turnover frequencies of up to 540 h^{-1} were reached under these conditions (entries 3−5). As shown in entries 6 and 7, lower catalyst loadings were tolerated without a drastic increase in the reaction times. For example, using only 0.1 mol % of [RuCl{κ^2*N*,*N*′-C(N-4-C_6H_4Br)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (**2c**), complete formation of octan-3-one took place in 1 h (TOF = 1000 h^{-1}; entry 7). The isomerization of 1-octen-3-ol into octan-3-one by means of complex **2c** (1 mol %) was also studied in other organic solvents (toluene, 1,2-dichloroethane, and methanol), as well as in water, but none of them allowed us to improve the result previously obtained in THF (entries 8−11 vs entry 3). The use of protic solvents (H_2O and MeOH) turned out to be particularly harmful due to the partial decomposition of **2c**, a process clearly appreciable to the naked eye by a color change of the solution from orange to black. Poorer results were also obtained on lowering the reaction temperature (e.g., at 50 °C in THF, 24 h of heating was needed to attain a 92% conversion; see entry 12). It is also important to note that, when the isomerization of 1-octen-3-ol with complex **2c** (1 mol %, THF, 80 °C) was performed in the presence of 20 equiv of free *p*-cymene, the performance shown by this catalyst was significantly reduced (entry 13 vs 3). This fact seems to indicate that the required vacant sites for coordination of the substrate may be generated by release of the arene ligand, possibly as a result of the steric hindrance between the bulky guanidinate substituents and the coordinated *p*-cymene unit.

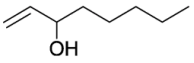
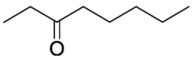
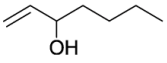
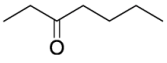
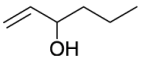
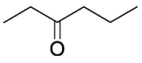
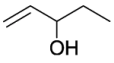
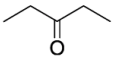
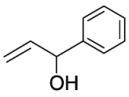
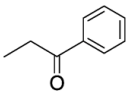
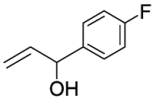
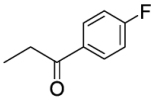
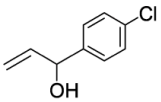
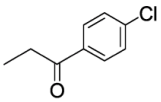
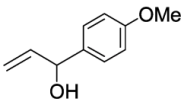
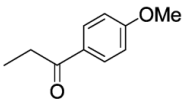
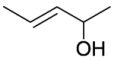
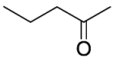
To define the scope of this catalytic transformation, other allylic alcohols were subjected to the action of [RuCl{κ^2*N*,*N*′-C(N-4-C_6H_4Br)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (**2c**) (Table 4). This complex was chosen because it could be easily crystallized on a large scale. Reactions were performed in all cases in THF (0.2 M solutions) at 80 °C using a Ru loading of 1 mol %. Thus, as observed for 1-octen-3-ol (entry 1), related aliphatic substrates AlkCH(OH)CH=CH_2 could also be efficiently converted into the corresponding ketones after only 10−30 min of heating (entries 2−5).

Complex **2c** proved also effective in the isomerization of aromatic allylic alcohols ArCH(OH)CH=CH_2, thus confirming the generality of this base-free catalytic transformation (entries 6−9). However, due probably to the steric congestion associated with the presence a bulky Ar group in an α position with respect to the alcohol unit, which disfavors their coordination to the metal, longer reaction times (3−24 h) were in these cases required to attain good conversions.[24] In addition, a marked influence of the electronic properties of the aryl rings on the reaction rates was observed, with those substrates bearing electron-withdrawing groups showing a remarkably lower reactivity (entries 7 and 8 vs 9). Finally, it is also worthy of note that the process is not restricted to allylic alcohols with a monosubstituted carbon−carbon double bond, since the isomerization of the disubstituted 3-penten-2-ol into pentan-2-one also took place efficiently after a short heating period (1 h; entry 10).

The effectiveness shown by [RuCl{κ^2*N*,*N*′-C(NR)(N^{i}Pr)-NH^{i}Pr}(η^6-*p*-cymene)] (**2a−e**) under base-free conditions raised the question of a possible cooperative effect of the pendant amino NH^{i}Pr group of the guanidinate ligands during catalysis. This group could facilitate the generation of the more coordinating oxo-allyl anion by deprotonation of the allylic alcohol. To answer this question, we decided to prepare the related amidinate complex [RuCl{κ^2*N*,*N*′-C(N^{i}Pr)$_2$Me}(η^6-*p*-cymene)] (**5**), by reacting [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] with the lithium amidinate salt Li[(N^{i}Pr)$_2$CMe][25] (details are given in the Experimental Section), and explore its catalytic behavior (Scheme 4).[26] The remarkably lower catalytic activity shown by this complex in the redox isomerization of the model substrate 1-octen-3-ol seems to corroborate our hypothesis. More evidence supporting the direct participation of the pendant amino NH^{i}Pr group during the catalytic events is the fact that the activity of [RuCl{κ^2*N*,*N*′-C(N-4-C_6H_4Br)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cymene)] (**2c**) is drastically reduced in the presence of an acid. Thus, when the catalytic isomerization of 1-octen-3-ol into octan-3-one by means of **2c** (1 mol %) was performed with 1 equiv of HCl (Et_2O solution) per Ru in the medium, 6.5 h of heating was needed to achieve a quantitative conversion (13% after 1 h) of the substrate, instead of the 10 min required under acid-free conditions (entry 1 in Table 4).

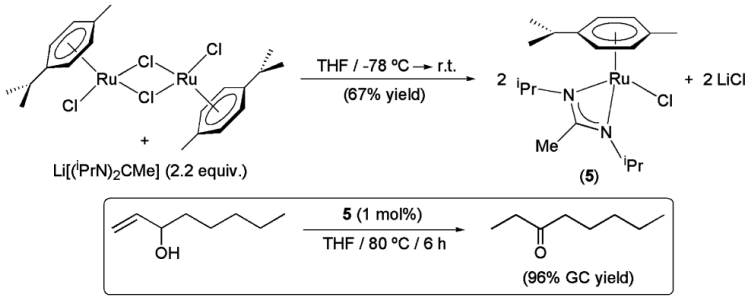
dx.doi.org/10.1021/om3009124 | *Organometallics* 2012, 31, 8301−8311

Table 4. Catalytic Isomerization of Allylic Alcohols Using [RuCl{κ^2*N*,*N*′-C(N-4-C_6H_4Br)(N^iPr)NH^iPr}(η^6-*p*-cymene)] (**2c**) as Catalyst[a]

Entry	Substrate	Product	Time	Yield[b]
1			10 min	> 99%
2			30 min	96%
3			30 min	97%
4			20 min	> 99%
5			10 min	> 99%
6			12 h	83%
7			24 h	88%
8			24 h	80%
9			3 h	99%
10			1 h	99%

[a]Reactions performed at 80 °C under N_2 atmosphere using 4 mmol of the corresponding allylic alcohol (0.2 M solutions in THF). [substrate]:[Ru] = 100:1. [b]Yields determined by GC.

Scheme 4. Synthesis and Catalytic Behavior of the Ruthenium(II) Amidinate Complex **5**



■ CONCLUSION

In summary, the novel ruthenium(II) guanidinate complexes [RuCl{κ^2*N*,*N*′-C(NR)(N^iPr)NH^iPr}(η^6-*p*-cymene)] (R = ^{i}Pr (**2a**), 4-$C_6H_4{}^t$Bu (**2b**), 4-C_6H_4Br (**2c**), 2,4,6-$C_6H_2Me_3$ (**2d**), 2,6-$C_6H_3{}^i Pr_2$ (**2e**)) have been synthesized in high yields from the reaction of the dimer [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] with an excess of the corresponding guanidines (^{i}PrHN)$_2$C═NR, and two of them, namely [RuCl{κ^2*N*,*N*′-C(N^iPr)$_2$$NH^i$Pr}($\eta^6$-*p*-cymene)] (**2a**) and [RuCl{κ^2*N*,*N*′-C(N-4-$C_6H_4{}^t$Bu)(N^iPr)-NH^iPr}(η^6-*p*-cymene)] (**2b**), were structurally characterized by

dx.doi.org/10.1021/om3009124 | *Organometallics* 2012, 31, 8301−8311

means of single-crystal X-ray diffraction techniques. Compounds **2b−e** represent the first examples of ruthenium complexes containing asymmetrical monoanionic guanidinate ligands reported to date in the literature. In addition, we have also demonstrated that complexes **2a−e** are efficient catalysts in the redox isomerization of allylic alcohols into the corresponding saturated ketones and that, unlike the majority of ruthenium catalysts previously described for this catalytic transformation, they are able to operate under base-free conditions. To the best of our knowledge, this is the first catalytic application known for ruthenium guanidinate species.

EXPERIMENTAL SECTION

Synthetic procedures were performed under an atmosphere of dry nitrogen using vacuum-line and standard Schlenk techniques. Solvents were dried by standard methods and distilled under nitrogen before use. All reagents were obtained from commercial suppliers and used without further purification, with the exception of the ruthenium(II) arene dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$,[14] guanidines $(^iPrHN)_2C{=}NR$ (**1a−e**),[13] the lithium amidinate salt $Li[(^iPrN)_2CMe]$,[25] and the allylic alcohols 1-(4-fluorophenyl)-2-propen-1-ol,[27] 1-(4-chlorophenyl)-2-propen-1-ol,[28] and 1-(4-methoxyphenyl)-2-propen-1-ol,[29] which were prepared by following the methods reported in the literature. Infrared spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. The C, H, and N analyses were carried out with a Perkin-Elmer 2400 microanalyzer. NMR spectra were recorded on Bruker DPX300 and AV400 instruments. Chemical shifts are given in ppm, relative to internal tetramethylsilane. DEPT experiments have been carried out for all the compounds reported in this paper. GC and GC/MSD measurements were made on a Hewlett-Packard HP6890 apparatus (Supelco Beta-DexTM 120 column, 30 m length, 250 μm diameter) and an Agilent 6890N apparatus coupled to a 5973 mass detector (HP-1MS column, 30 m length, 250 μm diameter), respectively.

Reactions of the Dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$ with Guanidines $(^iPrHN)_2C{=}NR$ (R = ^{i}Pr (1a), 4-$C_6H_4{}^t$Bu (1b), 4-C_6H_4Br (1c), 2,4,6-$C_6H_2Me_3$ (1d), 2,6-$C_6H_3{}^iPr_2$ (1e)). A solution of $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$ (0.306 g, 0.5 mmol) in 30 mL of toluene was treated with the appropriate guanidine **1a−e** (2 mmol) at room temperature for 2 h. The gradual appearance of a white solid precipitate of the guanidinium chloride salts $[(^iPrHN)_2C(NHR)][Cl]$ (**3a−e**) was observed. The resulting suspension was then concentrated to ca. 10 mL and filtered using a cannula. The white solid was washed with hexanes (2 × 10 mL) and diethyl ether (5 mL) to afford **3a−e** in pure form. The filtrate was stored in a freezer at −20 °C for 24−48 h, leading to complexes $[RuCl\{\kappa^2N,N'\text{-}C(NR)(N^iPr)NH^iPr\}(\eta^6\text{-}p\text{-cymene})]$ (**2a−e**) as yellow-orange crystals, which were separated, washed with hexanes (2 × 5 mL), and vacuum-dried. Characterization data for **2a−e** are as follows. **2a**: yield 0.364 g (80%); IR (KBr, cm^{-1}) ν 3289 (N−H); ^{1}H NMR (CD_2Cl_2) δ 5.42 and 5.18 (d, 2H each, $^3J_{HH}$ = 5.9 Hz, CH of cym), 3.50−3.32 (m, 3H, NC*H*Me$_2$), 2.87 (d, 1H, $^3J_{HH}$ = 10.8 Hz, NH), 2.80 (sept, 1H, $^3J_{HH}$ = 7.0 Hz, C*H*Me$_2$ of cym), 2.18 (s, 3H, Me of cym), 1.30, 1.20, and 1.11 (d, 6H each, $^3J_{HH}$ = 6.4 Hz, NCH*Me*$_2$), 1.27 (d, 6H, $^3J_{HH}$ = 7.0 Hz, CH*Me*$_2$ of cym) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 163.6 (s, CN_3), 97.9 and 96.7 (s, C of cym), 79.0 and 78.9 (s, CH of cym), 46.7 and 46.6 (s, NCHMe$_2$), 31.9 (s, CHMe$_2$ of cym), 26.0, 25.0, 23.8, and 22.3 (s, NCH*Me*$_2$ and CH*Me*$_2$ of cym), 15.1 (s, Me of cym) ppm. Anal. Calcd for $RuC_{20}H_{36}N_3Cl$: C, 52.79; H, 7.97; N, 9.23. Found: C, 52.66; H, 8.10; N, 9.17. **2b**: yield 0.409 g (75%); IR (KBr, cm^{-1}) ν 3338 (N−H); ^{1}H NMR (CD_2Cl_2) δ 7.24 and 7.09 (d, 2H each, $^3J_{HH}$ = 8.7 Hz, CH_{arom}), 5.33 and 5.04 (d, 1H each, $^3J_{HH}$ = 6.1 Hz, CH of cym), 5.21 and 5.09 (d, 1H each, $^3J_{HH}$ = 5.5 Hz, CH of cym), 3.34 (m, 2H, NC*H*Me$_2$ and NH), 3.21 (m, 1H, NC*H*Me$_2$), 2.71 (m, 1H, C*H*Me$_2$ of cym), 2.20 (s, 3H, Me of cym), 1.35 (s, 9H, C*M*e$_3$), 1.32 and 1.29 (d, 3H each, $^3J_{HH}$ = 6.3 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym), 1.27 and 0.97 (d, 3H each, $^3J_{HH}$ = 6.9 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym), 1.23 (d, 3H, $^3J_{HH}$ = 6.6 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym), 0.96 (d, 3H, $^3J_{HH}$ = 6.0 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 161.1 (s, CN_3), 147.7 and 142.9 (s, C_{arom}), 125.0 and 121.9 (s, CH_{arom}), 98.3 and 96.8 (s, C of cym), 80.7, 79.3, 78.8, and 78.7 (s, CH of cym), 45.8 and 44.5 (s, NCHMe$_2$), 34.0 (s, C*M*e$_3$), 31.4 (s, CHMe$_2$ of cym), 31.3 (s, C*M*e$_3$), 25.5, 24.8, 23.7, 22.9, 22.4, and 22.1 (s, NCH*Me*$_2$ and CH*Me*$_2$ of cym), 18.8 (s, Me of cym) ppm. Anal. Calcd for $RuC_{27}H_{42}N_3Cl$: C, 59.48; H, 7.77; N, 7.71. Found: C, 59.60; H, 7.68; N, 7.83. **2c**: yield 0.488 g (86%); IR (KBr, cm^{-1}) ν 3355 (N−H); ^{1}H NMR ($CDCl_3$) δ 7.29 and 7.04 (d, 2H each, $^3J_{HH}$ = 8.5 Hz, CH_{arom}), 5.31 and 5.01 (d, 1H each, $^3J_{HH}$ = 5.5 Hz, CH of cym), 5.13 and 5.06 (d, 1H each, $^3J_{HH}$ = 5.7 Hz, CH of cym), 3.37−3.13 (m, 3H, NC*H*Me$_2$ and NH), 2.65 (m, 1H, C*H*Me$_2$ of cym), 2.19 (s, 3H, Me of cym), 1.31, 1.29, 0.97, and 0.94 (d, 3H each, $^3J_{HH}$ = 6.0 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym), 1.24 and 1.20 (d, 3H each, $^3J_{HH}$ = 7.0 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym) ppm; $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 160.8 (s, CN_3), 149.9 and 111.6 (s, C_{arom}), 131.0 and 123.7 (s, CH_{arom}), 98.5 and 97.3 (s, C of cym), 80.6, 79.3, 79.0, and 78.6 (s, CH of cym), 45.7 and 44.8 (s, NCHMe$_2$), 31.4 (s, CHMe$_2$ of cym), 25.3, 24.7, 23.8, 22.7, 22.4, 22.0, and 18.8 (s, NCH*Me*$_2$, CH*Me*$_2$ of cym and Me of cym) ppm. Anal. Calcd for $RuC_{23}H_{33}N_3BrCl$: C, 48.64; H, 5.86; N, 7.40. Found: C, 48.82; H, 5.79; N, 7.29. **2d**: yield 0.435 g (82%); IR (KBr, cm^{-1}) ν 3343 (N−H); ^{1}H NMR (CD_2Cl_2) δ 6.89 and 6.82 (s, 1H each, CH_{arom}), 5.04, 5.03, 4.99, and 4.82 (d, 1H each, $^3J_{HH}$ = 5.5 Hz, CH of cym), 3.45 (d, 1H, $^3J_{HH}$ = 10.2 Hz, NH), 3.20 and 2.82 (m, 1H each, NC*H*Me$_2$), 2.72 (m, 1H, C*H*Me$_2$ of cym), 2.32, 2.28, and 2.27 (s, 3H each, Ar*Me*), 2.10 (s, 3H, Me of cym), 1.39, 1.26, and 0.91 (d, 3H each, $^3J_{HH}$ = 6.4 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym), 1.31 (d, 3H, $^3J_{HH}$ = 6.8 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym), 1.29 (d, 3H, $^3J_{HH}$ = 7.5 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym), 0.74 (d, 3H, $^3J_{HH}$ = 5.3 Hz, NCH*Me*$_2$ or CH*Me*$_2$ of cym) ppm; $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 163.0 (s, CN_3), 144.6, 133.4, 132.2, and 131.3 (s, C_{arom}), 121.9 and 128.6 (s, CH_{arom}), 101.5 and 92.4 (s, C of cym), 80.0, 79.4, 78.4, and 77.9 (s, CH of cym), 45.4 and 44.0 (s, NCHMe$_2$), 31.2 (s, CHMe$_2$ of cym), 26.0, 25.4, 24.4, 22.9, 22.7, 22.1, 20.5, 20.2, 18.7, and 18.6 (s, NCH*Me*$_2$, CH*Me*$_2$ of cym, Me of cym and Ar*Me*) ppm. Anal. Calcd for $RuC_{26}H_{40}N_3Cl$: C, 58.79; H, 7.59; N, 7.91. Found: C, 58.65; H, 7.62; N, 7.78. **2e**: yield 0.441 g (77%); IR (KBr, cm^{-1}) ν 3321 (N−H); ^{1}H NMR (CD_2Cl_2) δ 7.15−7.09 (m, 3H, CH_{arom}), 5.23 and 5.12 (d, 1H each, $^3J_{HH}$ = 5.6 Hz, CH of cym), 5.03 and 4.96 (d, 1H each, $^3J_{HH}$ = 6.2 Hz, CH of cym), 4.00, 2.84, and 2.69 (m, 1H each, NC*H*Me$_2$, C*H*Me$_2$ of cym or C*H*Me$_2$ of Ar), 3.25 (m, 2H, NC*H*Me$_2$, C*H*Me$_2$ of cym or C*H*Me$_2$ of Ar), 3.07 (d, 1H, $^3J_{HH}$ = 10.8 Hz, NH), 2.15 (s, 3H, Me of cym), 1.42 (d, 3H, $^3J_{HH}$ = 7.4 Hz, NCH*Me*$_2$, CH*Me*$_2$ of cym or CH*Me*$_2$ of Ar), 1.36, 1.34, and 1.33 (d, 3H, $^3J_{HH}$ = 6.7 Hz, NCH*Me*$_2$, CH*Me*$_2$ of cym or CH*Me*$_2$ of Ar), 1.31 (d, 3H, $^3J_{HH}$ = 7.0 Hz, NCH*Me*$_2$, CH*Me*$_2$ of cym or CH*Me*$_2$ of Ar), 1.26 (d, 6H, $^3J_{HH}$ = 6.4 Hz, NCH*Me*$_2$, CH*Me*$_2$ of cym or CH*Me*$_2$ of Ar), 1.05 (d, 3H, $^3J_{HH}$ = 7.1 Hz, NCH*Me*$_2$, CH*Me*$_2$ of cym or CH*Me*$_2$ of Ar), 0.95 (d, 3H, $^3J_{HH}$ = 6.0 Hz, NCH*Me*$_2$, CH*Me*$_2$ of cym or CH*Me*$_2$ of Ar), 0.60 (d, 3H, $^3J_{HH}$ = 5.8 Hz, NCH*Me*$_2$, CH*Me*$_2$ of cym or CH*Me*$_2$ of Ar) ppm; $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 165.4 (s, CN_3), 147.3, 145.3, and 144.5 (s, C_{arom}), 123.9, 123.8, and 123.7 (s, CH_{arom}), 102.0 and 92.9 (s, C of cym), 80.2, 79.4, 78.2, and 76.1 (s, CH of cym), 45.7 and 44.3 (s, NCHMe$_2$), 31.4 (s, CHMe$_2$ of cym), 27.6 and 27.8 (s, C*H*Me$_2$ of Ar), 26.9, 26.7, 26.4, 25.5, 25.4, 25.0, 24.1, 22.9, 22.5, and 22.3 (s, NCH*Me*$_2$, CH*Me*$_2$ of cym and CH*Me*$_2$ of Ar), 18.2 (s, Me of cym). Anal. Calcd for $RuC_{29}H_{46}N_3Cl$: C, 60.76; H, 8.09; N, 7.33. Found: C, 60.69; H, 8.16; N, 7.21.

Characterization data for the guanidinium chloride salts **3a−e** are as follows. **3a**:[30] yield 0.175 g (79%); IR (KBr, cm^{-1}) ν 3312 (N−H); ^{1}H NMR ($CDCl_3$) δ 7.03 (broad s, 3H, NH), 3.97 (broad s, 3H, C*H*Me$_2$), 1.39 (broad s, 18H, CH*Me*$_2$) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 156.1 (s, CN_3), 46.9 (s, CHMe$_2$), 23.9 (s, CH*Me*$_2$) ppm. Anal. Calcd for $C_{10}H_{24}N_3Cl$: C, 54.16; H, 10.91; N, 18.95. Found: C, 54.01; H, 11.05; N, 18.85. **3b**: yield 0.252 g (81%); IR (KBr, cm^{-1}) ν 3411 (N−H), 3182 (N−H); ^{1}H NMR (CD_2Cl_2) δ 10.05 (broad s, 1H, NH), 7.65 (broad s, 2H, NH), 7.41 and 7.21 (broad d, 2H each, $^3J_{HH}$ = 7.5 Hz, CH_{arom}), 4.05 (broad s, 2H, C*H*Me$_2$), 1.34 (s, 9H, C*M*e$_3$), 1.20 (d, 12H, $^3J_{HH}$ = 6.0 Hz, CH*Me*$_2$) ppm; $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 154.9 (s, CN_3), 149.0 and 134.5 (s, C_{arom}), 126.4 and 122.8 (s, CH_{arom}), 45.7 (s, CHMe$_2$), 34.4 (s, C*M*e$_3$), 31.0 (s, C*M*e$_3$), 22.4 (s, CH*Me*$_2$) ppm. Anal. Calcd for $C_{17}H_{30}N_3Cl$: C, 65.47; H, 9.70; N, 13.47. Found: C, 65.59; H, 9.87; N, 13.19. **3c**: yield 0.251 g (75%); IR (KBr, cm^{-1}) ν 3402 (N−H), 3221 (N−H); ^{1}H NMR (CD_2Cl_2) δ 10.04 (broad s, 1H, NH), 7.74 (broad, 2H, NH), 7.41 and 7.13 (broad d, 2H each, $^3J_{HH}$ = 7.7 Hz, CH_{arom}), 3.94

dx.doi.org/10.1021/om3009124 | *Organometallics* 2012, 31, 8301−8311

(broad s, 2H, CHMe$_2$), 1.17 (broad s, 12H, CHMe$_2$) ppm; ^{13}C{^{1}H} NMR (CD_2Cl_2) δ 154.7 (s, CN_3), 136.1 and 119.0 (s, C$_{arom}$), 132.6 and 124.0 (s, CH$_{arom}$), 46.3 (s, CHMe$_2$), 22.6 (s, CHMe$_2$) ppm. Anal. Calcd for $C_{13}H_{21}N_3BrCl$: C, 46.65; H, 6.32; N, 12.55. Found: C, 46.54; H, 6.48; N, 12.69. **3d**: yield 0.229 g (77%); IR (KBr, cm^{-1}) ν 3393 (N−H), 3176 (N−H); ^{1}H NMR ($CDCl_3$) δ 9.37 (broad s, 1H, NH), 6.86 (s, 2H, CH$_{arom}$), 4.17 (broad s, 2H, CHMe$_2$), 2.26 (s, 3H, ArMe), 2.17 (s, 6H, ArMe), 1.15 (broad s, 12H, CHMe$_2$) ppm; NH^{i}Pr signals not observed; ^{13}C{^{1}H} NMR ($CDCl_3$) δ 153.6 (s, CN_3), 141.1, 138.1, and 136.0 (s, C$_{arom}$), 129.8 (s, CH$_{arom}$), 45.4 (s, CHMe$_2$), 23.0 (s, CHMe$_2$), 21.0 and 18.4 (s, ArMe) ppm. Anal. Calcd for $C_{16}H_{28}N_3Cl$: C, 64.52; H, 9.47; N, 14.11. Found: C, 64.64; H, 9.38; N, 14.34. **3e**: yield 0.241 g (71%); IR (KBr, cm^{-1}) ν 3391 (N−H), 3227 (N−H); ^{1}H NMR ($CDCl_3$) δ 9.57 (broad s, 1H, NH), 7.89 (broad s, 2H, NH), 7.32 (t, 1H, $^3J_{HH}$ = 7.3 Hz, CH$_{arom}$), 7.17 (d, 2H, $^3J_{HH}$ = 7.3 Hz, CH$_{arom}$), 4.43 (broad s, 2H, NCHMe$_2$), 3.00 (broad s, 2H, CHMe$_2$), 1.16 (d, 12H, $^3J_{HH}$ = 6.0 Hz, CHMe$_2$), 1.14 (broad s, 12H, NCHMe$_2$) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$) δ 155.8 (s, CN_3), 147.4 and 129.0 (s, C$_{arom}$), 129.6 and 124.6 (s, CH$_{arom}$), 45.1 (broad s, NCHMe$_2$), 28.3 (s, CHMe$_2$), 24.5 (broad s, NCHMe$_2$), 22.9 (s, CHMe$_2$) ppm. Anal. Calcd for $C_{19}H_{34}N_3Cl$: C, 67.13; H, 10.08; N, 12.36. Found: C, 67.24; H, 9.90; N, 12.43.

Preparation of the Amidinate Complex [RuCl{κ^2*N*,*N*′-C(N^{i}Pr)$_2$Me}(η^6-*p*-cymene)] (5).[26] The dimeric precursor [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] (0.122 g, 0.2 mmol) and the lithium amidinate salt Li[(^{i}PrN)$_2$CMe] (0.067 g, 0.45 mmol) were dissolved in 10 mL of dry tetrahydrofuran at −78 °C, and the resulting mixture was warmed to room temperature. The solvent was then removed under vacuum, the crude product extracted with hexanes (ca. 30 mL), and the extract filtered over Kieselguhr. Concentration of the resulting solution to ca. 5 mL resulted in the precipitation of a red solid, which was separated and vacuum-dried. Yield: 0.110 g (67%). ^{1}H NMR (C_6D_6): δ 5.08 and 4.81 (d, 2H each, $^3J_{HH}$ = 5.7 Hz, CH of cym), 3.41 (sept, 2H, $^3J_{HH}$ = 6.3 Hz, NCHMe$_2$), 2.74 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, CHMe$_2$ of cym), 2.16 (s, 3H, Me of cym), 1.52 (s, 3H, N$_2$CMe), 1.25 (d, 12H, $^3J_{HH}$ = 6.3 Hz, NCHMe$_2$), 1.20 (d, 6H, $^3J_{HH}$ = 6.9 Hz, CHMe$_2$ of cym) ppm. ^{13}C{^{1}H} NMR (C_6D_6): δ 151.5 (s, NCN), 98.0 and 97.3 (s, C of cym), 78.9 and 78.3 (s, CH of cym), 47.8 (s, NCHMe$_2$), 32.1 (s, CHMe$_2$ of cym), 25.6 (s, NCHMe$_2$), 22.5 (s, CHMe$_2$ of cym), 19.0 (s, Me of cym), 13.1 (s, N$_2$CMe) ppm. Anal. Calcd for $RuC_{18}H_{31}N_2Cl$: C, 52.48; H, 7.58; N, 6.80. Found: C, 52.59; H, 7.52; N, 6.95.

General Procedure for the Catalytic Isomerization of Allylic Alcohols. In a sealed tube under a nitrogen atmosphere, the corresponding ruthenium complex **2a−e** (0.004−0.04 mmol; 0.1−1 mol % of Ru) was added to a solution of the corresponding allylic alcohol (4 mmol) in tetrahydrofuran (20 mL), and the resulting mixture was stirred at 80 °C for the indicated time (see Tables 3 and 4). The course of the reaction was monitored by regularly taking samples of ca. 10 μL, which after dilution with THF (3 mL) were analyzed by GC. The identity of the resulting carbonyl compounds was assessed by comparison with commercially available pure samples (Aldrich Chemical Co. or Acros Organics) and by their fragmentation in GC/MS.

Computational Details. All theoretical calculations were performed with the program package Gaussian03,[31] at the density functional theory (DFT) level by means of the hybrid B3LYP functional.[32] The molecular geometries were optimized, without any molecular symmetry constraint, using Pople's 6-31G(d) split valence basis set for C, H, N, Cl, and Br elements[33] and LANL2DZ for Ru, which combines quasi-relativistic effective core potentials with a valence double-basis set.[34] Frequency calculations were performed to determine whether the optimized geometries were minima on the potential energy surface. Optimized geometries and Cartesian coordinates for all the compounds studied can be found in the Supporting Information.

X-ray Crystal Structure Determination of Complexes 2a,b. Crystals suitable for X-ray diffraction analysis were in both cases obtained by slow diffusion of *n*-pentane into a saturated solution of the complex in diethyl ether. The most relevant crystal and refinement data are collected in Table S1 (Supporting Information). For both crystals, data collection was performed on a Oxford Diffraction Xcalibur Nova single-crystal diffractometer, using Cu Kα radiation (λ = 1.5418 Å). Images were collected at a 75 (**2a**) or 63 mm (**2b**) fixed crystal−detector distance, using the oscillation method, with 1° oscillation and variable exposure time per image (6−10 s for **2a** and 1.5−5 s for **2b**). Data collection strategy was calculated with the program CrysAlis^{Pro} CCD.[35] Data reduction and cell refinement was performed with the program CrysAlis^{Pro} RED.[35] An empirical absorption correction was applied using the SCALE3 ABSPACK algorithm as implemented in the program CrysAlis^{Pro} RED.[35] The software package WINGX[36] was used for space group determination, structure solution, and refinement. The structures were solved by Patterson interpretation and phase expansion using SIR92.[37]

Isotropic least-squares refinement on F^2 using SHELXL97[38] was performed. During the final stages of the refinements, all the positional parameters and the anisotropic temperature factors of all the non-H atoms were refined. The H atoms were geometrically located, and their coordinates were refined riding on their parent atoms (except that on N(2), which in both complexes was found from different Fourier maps and included in a refinement with isotropic parameters). The function minimized was $[\sum w(F_o^2 - F_c^2)/\sum w(F_o^2)]^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ (a and b values are given in Table S1) with $\sigma(F_o^2)$ from counting statistics and $P = (\mathrm{Max}(F_o^2,0) + 2F_c^2)/3$. The maximum residual electron density is in both cases located near heavier atoms. Atomic scattering factors were taken from ref 39. Geometrical calculations were made with PARST.[40] The crystallographic plots were made with PLATON.[41]

■ ASSOCIATED CONTENT

Supporting Information

A CIF file and a table giving crystallographic data for compounds **2a,b** and figures and tables giving optimized geometries and Cartesian coordinates for **2b−e**, **2′b−e**, **4b−e**, and **4′b−e**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: crochetpascale@uniovi.es (P.C.); vcm@uniovi.es (V.C.); Antonio.Antinolo@uclm.es (A.A.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Spanish Ministry of Science and Innovation (projects CTQ2010-14796/BQU, CTQ2009-09214, and CSD2007-00006).

■ REFERENCES

(1) Chandra, G.; Jenkins, A. D.; Lappert, M. F.; Srivastava, R. C. *J. Chem. Soc. A* **1970**, 2550−2558.

(2) For reviews, see: (a) Bailey, P. J.; Pace, S. *Coord. Chem. Rev.* **2001**, *214*, 91−141. (b) Piers, W. E.; Emslie, D. J. H. *Coord. Chem. Rev.* **2002**, 233−234, 131−155. (c) Edelmann, F. T. *Adv. Organomet. Chem.* **2008**, *57*, 183−352. (d) Edelmann, F. T. *Chem. Soc. Rev.* **2009**, *38*, 2253−2268. (e) Jones, C. *Coord. Chem. Rev.* **2010**, *254*, 1273−1289. (f) Trifonov, A. A. *Coord. Chem. Rev.* **2010**, *254*, 1327−1347. (g) Collins, S. *Coord. Chem. Rev.* **2011**, *255*, 118−138.

(3) For very recent examples, see: (a) Kelley, M. R.; Rohde, J.-U. *Chem. Commun.* **2012**, *48*, 2876−2878. (b) Yonke, B. L.; Keane, A. J.; Zavalij, P. Y.; Sita, L. R. *Organometallics* **2012**, *31*, 345−355. (c) Elorriaga, D.; Carrillo-Hermosilla, F.; Antiñolo, A.; López-Solera, I.; Menot, B.; Fernández-Galán, R.; Villaseñor, E.; Otero, A. *Organometallics* **2012**, *31*, 1840−1848. (d) Chlupatý, T.; Padělkova, Z.; DeProft, F.; Willem, R.; Růžička, A. *Organometallics* **2012**, *31*, 2203−2211. (e) Chen, S.-J.; Dougan, B. A.; Chen, X.-T.; Xue, Z.-L. *Organometallics* **2012**, *31*, 3443−3446. (f) Willcocks, A. M.; Robinson, T. P.; Roche, C.; Pugh, T.; Richards, S. P.; Kingsley, A. J.; Lowe, J. P.; Johnson, A. L. *Inorg. Chem.*

2012, *51*, 246−257. (g) Rai, V. K.; Nishiura, M.; Takimoto, M.; Zhao, S.; Liu, Y.; Hou, Z. *Inorg. Chem.* **2012**, *51*, 822−835. (h) Chiarella, G. M.; Cotton, F. A.; Dalal, N. S.; Murillo, C. A.; Wang, Z.; Young, M. D. *Inorg. Chem.* **2012**, *51*, 5257−5263. (i) Fernández-Galán, R.; Antiñolo, A.; Carrillo-Hermosilla, F.; López-Solera, I.; Otero, A.; Serrano-Laguna, A.; Villaseñor, E. *J. Organomet. Chem.* **2012**, *711*, 35−42. (j) Zhang, X.; Qian, C.; Wang, C.; Zhang, Y.; Wang, Y.; Yao, Y.; Shen, Q. *Eur. J. Inorg. Chem.* **2012**, 847−858. (k) Neuhäuser, C.; Reinmuth, M.; Kaifer, E.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2012**, 1250−1260. (l) Zelga, K.; Leszczyński, M.; Justyniak, I.; Kornowicz, A.; Cabaj, M.; Wheatley, A. E. H.; Lewiński, J. *Dalton Trans.* **2012**, *41*, 5934−5938. (m) Wang, Y.; Luo, Y.; Chen, J.; Xue, H.; Liang, H. *New J. Chem.* **2012**, *36*, 933−940. (n) Chiarella, G. M.; Melgarejo, D. Y.; Fackler, J. P., Jr. *Inorg. Chim. Acta* **2012**, *386*, 13−16.

(4) Pap, J. S.; Snyder, J. L.; Piccoli, P. M. B.; Berry, J. F. *Inorg. Chem.* **2009**, *48*, 9846−9852.

(5) Holman, K. T.; Robinson, S. D.; Sahajpal, A.; Steed, J. W. *J. Chem. Soc., Dalton Trans.* **1999**, 15−18.

(6) Robinson, S. D.; Sahajpal, A.; Steed, J. *Inorg. Chim. Acta* **2000**, *303*, 265−270.

(7) Bailey, P. J.; Grant, K. J.; Mitchell, L. A.; Pace, S.; Parkin, A.; Parsons, S. *Dalton Trans.* **2000**, 1887−1891.

(8) Bailey, P. J.; Mitchell, L. A.; Parsons, S. *J. Chem. Soc., Dalton Trans.* **1996**, 2839−2841.

(9) An isolated example of a ruthenium complex containing a coordinated guanidinate dianion, namely [Ru{κ^2-(*N*,*N*′)-C(NAc)$_2$=NAc}(η^6-*p*-cymene)(PPh$_3$)], has also been described: Dinger, M. B.; Henderson, W.; Nicholson, B. K. *J. Organomet. Chem.* **1998**, *556*, 75−88.

(10) Singh, T.; Kishan, R.; Nethaji, M.; Thirupathi, N. *Inorg. Chem.* **2012**, *51*, 157−169.

(11) For selected reviews, accounts, and books on the field, see: (a) Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1997**, 507−512. (b) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599−2660. (c) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770. (f) *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (g) *Ruthenium Catalysts and Fine Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer: Berlin, 2004. (h) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630−6666. (i) Bruneau, C.; Dérien, S.; Dixneuf, P. H. *Top. Organomet. Chem.* **2006**, *19*, 295−326. (j) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176−2203. (k) Cadierno, V.; Crochet, P.; García-Garrido, S. E.; Gimeno, J. *Curr. Org. Chem* **2006**, *10*, 165−183. (l) Cadierno, V.; Crochet, P. *Curr. Org. Synth.* **2008**, *5*, 343−364. (m) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490−1501. (n) Bruneau, C.; Renaud, J.-L.; Demerseman, B. *Pure Appl. Chem.* **2008**, *80*, 861−871. (o) Kondo, T. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 441−458. (p) Bruneau, C.; Achard, M. *Coord. Chem. Rev.* **2012**, *256*, 525−536.

(12) For a review on the catalytic applications of ruthenium-amidinates, see: Nagashima, H.; Kondo, H.; Hayashida, T.; Yamaguchi, Y.; Gondo, M.; Masuda, S.; Miyazaki, K.; Matsubara, K.; Kirchner, K. *Coord. Chem. Rev.* **2003**, *245*, 177−190.

(13) Alonso-Moreno, C.; Carrillo-Hermosilla, F.; Garcés, A.; Otero, A.; López-Solera, I.; Rodríguez, A. M.; Antiñolo, A. *Organometallics* **2010**, *29*, 2789−2795.

(14) Bennett, M. A.; Huang, T.-N.; Matheson, T. W.; Smith, A. K. *Inorg. Synth.* **1982**, *21*, 74−78.

(15) For reviews and accounts on this catalytic transformation, see: (a) Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, *103*, 27−51. (b) van der Drift, R. C.; Bouwman, E.; Drent, E. *J. Organomet. Chem.* **2002**, *650*, 1−24. (c) Cadierno, V.; Crochet, P.; Gimeno, J. *Synlett* **2008**, 1105−1124. (d) Mantilli, L.; Mazet, C. *Chem. Lett.* **2011**, *40*, 341−344. (e) Mazet, C. *Chimia* **2011**, *65*, 802−805. (f) Ahlsten, N.; Bartoszewicz, A.; Martín-Matute, B. *Dalton Trans.* **2012**, *41*, 1660−1670. (g) Lorenzo-Luis, P.; Romerosa, A.; Serrano-Ruiz, M. *ACS Catal.* **2012**, *2*, 1079−1086.

(16) See, for example: (a) Cadierno, V.; Crochet, P.; Díez, J.; García-Álvarez, J.; García-Garrido, S. E.; Gimeno, J.; García-Granda, S.; Rodríguez, M. A. *Inorg. Chem.* **2003**, *42*, 3293−3307. (b) Cadierno, V.; Crochet, P.; Díez, J.; García-Álvarez, J.; García-Garrido, S. E.; García-Granda, S.; Gimeno, J.; Rodríguez, M. A. *Dalton Trans.* **2003**, 3240−3249. (c) Cadierno, V.; Díez, J.; García-Álvarez, J.; Gimeno, J.; Calhorda, M. J.; Veiros, L. F. *Organometallics* **2004**, *23*, 2421−2433. (d) Cadierno, V.; Díez, J.; García-Álvarez, J.; Gimeno, J. *Organometallics* **2004**, *23*, 3425−3436. (e) Cadierno, V.; Díez, J.; García-Álvarez, J.; Gimeno, J. *Organometallics* **2005**, *24*, 2801−2810. (f) Cadierno, V.; Díez, J.; García-Álvarez, J.; Gimeno, J. *J. Organomet. Chem.* **2005**, *690*, 2087−2096. (g) Cadierno, V.; García-Álvarez, J.; Gimeno, J.; Rubio-García, J. *J. Organomet. Chem.* **2005**, *690*, 5856−5862. (h) Díaz-Álvarez, A. E.; Crochet, P.; Zablocka, M.; Cadierno, V.; Duhayon, C.; Gimeno, J.; Majoral, J.-P. *New J. Chem.* **2006**, *30*, 1295−1306. (i) Díaz-Álvarez, A. E.; Crochet, P.; Zablocka, M.; Cadierno, V.; Vendier, L.; Gimeno, J.; Majoral, J.-P. *Polyhedron* **2007**, *26*, 933−940. (j) Cadierno, V.; Díez, J.; García-Álvarez, J.; Gimeno, J.; Rubio-García, J. *Dalton Trans.* **2008**, 5737−5748. (k) Cadierno, V.; Díez, J.; García-Álvarez, J.; Gimeno, J. *Organometallics* **2008**, *27*, 1809−1822. (l) Cadierno, V.; Díez, J.; García-Álvarez, J.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 941−956.

(17) Metal-bound chlorine atoms are well-known hydrogen-bond acceptors: Aullón, G.; Bellamy, D.; Brammer, L.; Bruton, E. A.; Orpen, A. G. *Chem. Commun.* **1998**, 653−654.

(18) (a) Jeffrey, G. A. In *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, U.K., 1997. (b) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48−76.

(19) Related rearrangements in both free guanidines and guanidinate complexes have been described. See ref 10 and: (a) Mullins, S. M.; Duncan, A. P.; Bergman, R. G.; Arnold, J. *Inorg. Chem.* **2001**, *40*, 6952−6963. (b) Zhang, J.; Cai, R.; Weng, L.; Zhuo, X. *Organometallics* **2004**, *23*, 3303−3308. (c) Qian, C.; Zhang, X.; Li, J.; Xu, F.; Zhang, Y.; Shen, Q. *Organometallics* **2009**, *28*, 3856−3862. (d) Zhang, X.; Wang, C.; Qian, C.; Han, F.; Xu, F.; Shen, Q. *Tetrahedron* **2011**, *67*, 8790−8799.

(20) The optimized bond distances for **2b** are in good agreement with those experimentally obtained by X-ray diffraction (Table 1), deviating only ca. ±0.5 Å (e.g., Ru−N(1) = 2.147 Å, Ru−N(3) = 2.095 Å, C(11)−N(1) = 1.337 Å, C(11)−N(2) = 1.381 Å, C(11)−N(3) = 1.340 Å). The calculated bond angles are also in complete accord with those found experimentally (e.g., N(1)−C(11)−N(3) = 109.37°, N(1)−Ru−N(3) = 61.99°).

(21) Díaz-Álvarez, A. E.; Cadierno, V. *Recent Patents Catal.* **2012**, *1*, 43−50 and patents cited therein.

(22) See, for example: (a) Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* **2005**, *127*, 6172−6173. (b) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Varela-Álvarez, A.; Sordo, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 1360−1370. (c) Crochet, P.; Fernández-Zúmel, M. A.; Gimeno, J.; Scheele, M. *Organometallics* **2006**, *25*, 4846−4849. (d) Bouziane, A.; Carboni, B.; Bruneau, C.; Carreaux, F.; Renaud, J.-L. *Tetrahedron* **2008**, *64*, 11745−11750. (e) Lastra-Barreira, B.; Díez, J.; Crochet, P. *Green Chem.* **2009**, *11*, 1681−1686. (f) Servin, P.; Laurent, R.; Gonsalvi, L.; Tristany, M.; Peruzzini, M.; Majoral, J.-P.; Caminade, A. M. *Dalton Trans.* **2009**, 4432−4434. (g) González, B.; Lorenzo-Luis, P.; Serrano-Ruiz, M.; Papp, É.; Fekete, M.; Csépke, K.; Ősz, K.; Joó, F.; Romerosa, A. *J. Mol. Catal. A: Chem.* **2010**, *326*, 15−20. (h) Pontes da Costa, A.; Mata, J. A.; Royo, B.; Peris, E. *Organometallics* **2010**, *29*, 1832−1838. (i) Azua, A.; Sanz, S.; Peris, E. *Organometallics* **2010**, *29*, 3661−3664. (j) Fernández-Zumel, M. A.; Lastra-Barreira, B.; Scheele, M.; Díez, J.; Crochet, P.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 7780−7785. (k) Liu, P. N.; Ju, K. D.; Lau, C. P. *Adv. Synth. Catal.* **2011**, *353*, 275−280. (l) Brown, C. J.; Miller, G. M.; Johnson, M. W.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 11964−11966. (m) García-Álvarez, J.; Gimeno, J.; Suárez, F. J. *Organometallics* **2011**, *30*, 2893−2896. (n) Putignano, E.; Bossi, G.; Rigo, P.; Baratta, W. *Organometallics* **2012**, *31*, 1133−1142. (o) Bizet, V.; Pannecoucke, X.; Renaud, J.-L.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 6467−6470. (p) Bellarosa, L.; Díez, J.; Gimeno, J.; Lledós, A.; Suárez, F. J.; Ujaque, G.; Vicent, C. *Chem. Eur. J.* **2012**, *18*, 7749−7765. (q) Udvardy, A.; Bényei, A. C.; Kathó, Á. *J. Organomet. Chem.* **2012**, *717*, 116−122. (r) Díez, J.; Gimeno, J.; Lledós, A.; Suárez, F. J.; Vicent, C. *ACS Catal.*

2012, *2*, 2087−2099. (s) Schulz, J.; Císařová, I.; Štěpnička, P. *Eur. J. Inorg. Chem.* **2012**, 5000−5010.
(23) The use of water as solvent has allowed, in some cases, the reactions to be carried out in the absence of base. The high polarity of this medium favors the deprotonation of the alcohol to form the corresponding oxo-allyl anion. See, for example, refs 22b,f,i,m,p,r.
(24) Previous studies have already pointed out this effect. See, for example, ref 22c and: (a) Crochet, P.; Díez, J.; Fernández-Zumel, M. A.; Gimeno, J. *Adv. Synth. Catal.* **2006**, *348*, 93−100. (b) Díaz-Álvarez, A. E.; Crochet, P.; Zablocka, M.; Duhayon, C.; Cadierno, V.; Gimeno, J.; Majoral, J. P. *Adv. Synth. Catal.* **2006**, *348*, 1671−1679. (c) Cadierno, V.; Francos, J.; Gimeno, J.; Nebra, N. *Chem. Commun.* **2007**, 2536−2538. (d) Cadierno, V.; Crochet, P.; Francos, J.; García-Garrido, S. E.; Gimeno, J.; Nebra, N. *Green Chem.* **2009**, *11*, 1992−2000.
(25) Coles, M. P.; Swenson, D. C.; Jordan, R. F.; Young, V. G., Jr. *Organometallics* **1997**, *16*, 5183−5194.
(26) The amidinate complex **5** has been previously mentioned in a patent. However, neither details on its isolation nor characterization data were given in the document: Shenai-Khatkhate, D. V.; Wang, Q. M. *U.S. Pat. Appl. Publ.* US 20080026578, 2008.
(27) Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653−2656.
(28) Brown, R. C. D.; Fisher, M. L.; Brown, L. J. *Org. Biomol. Chem.* **2003**, *1*, 2699−2709.
(29) Laabs, S.; Münch, W.; Bats, J. W.; Nubbemeyer, U. *Tetrahedron* **2002**, *58*, 1317−1334.
(30) Said, F. F.; Ong, T.-G.; Yap, G. P. A.; Richeson, D. *Cryst. Growth Des.* **2005**, *5*, 1881−1888.
(31) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. *Gaussian 03, Revision C.01*; Gaussian, Inc., Wallingford, CT, 2004.
(32) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (c) Lee, C.; Parr, R. G.; Yang, W. *Phys. Rev. B* **1988**, *37*, 785−789. (d) Stephens, P. J.; Devlin, J. F.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627.
(33) Henre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. In *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
(34) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270−283. (b) Ehlers, A. W.; Boehme, M.; Dapprich, S.; Gobbi, A.; Hoellwarth, A.; Jonas, V.; Koehler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett.* **1993**, *208*, 111−114.
(35) *CrysAlis^{Pro} CCD & CrysAlis^{Pro} RED*; Oxford Diffraction Ltd., Oxford, U.K., 2008.
(36) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837−838.
(37) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435−436.
(38) Sheldrick, G. M. *SHELXL97: Program for the Refinement of Crystal Structures*; University of Göttingen, Göttingen, Germany, 1997.
(39) *International Tables for X-Ray Crystallography*; Kynoch Press: Birminghan, U.K., 1974; Vol. *IV* (present distributor: Kluwer Academic Publishers, Dordrecht, The Netherlands)
(40) Nardelli, M. *Comput. Chem.* **1983**, *7*, 95−97.
(41) Spek, A. L. *PLATON: A Multipurpose Crystallographic Tool*; University of Utrecht, Utrecht, The Netherlands, 2007.

CAPÍTULO 3

3.4.- CONCLUSIONES

De los resultados descritos en el presente *Capítulo 3* pueden extraerse las siguientes conclusiones:

- ✓ Se ha sintetizado y caracterizado una nueva familia de complejos rutenio(II)-areno con ligandos guanidinato de fórmula general [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**), por reacción del precursor dimérico [{RuCl(μ-Cl)(η^6-*p*-cimeno)}$_2$] con un exceso de las guanidinas (^{i}PrHN)$_2$C=NR correspondientes (R = ^{i}Pr (**3.21a**), 4-C$_6$H$_4$^{t}Bu (**3.21b**), 4-C$_6$H$_4$Br (**3.21c**), 2,4,6-C$_6$H$_2$Me$_3$ (**3.21d**), 2,6-C$_6$H$_3$^{i}Pr$_2$ (**3.21e**)). Independientemente de los requerimientos estéricos del sustituyente aromático, y en concordancia con los cálculos teóricos DFT llevados a cabo en los modelos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] y [RuCl{κ^2-*N,N´*-C(N^{i}Pr)$_2$NR}(η^6-*p*-cimeno)], hemos encontrado que los aniones guanidinato adoptan una coordinación no-simétrica en los complejos **3.22b-e**. Cabe destacar que estos derivados representan los primeros ejemplos de complejos de rutenio con ligandos guanidinato no-simétricos descritos hasta la fecha en la literatura.

- ✓ Los complejos [RuCl{κ^2-*N,N´*-C(NR)(N^{i}Pr)NH^{i}Pr}(η^6-*p*-cimeno)] (**3.22a-e**) han mostrado ser catalizadores activos en reacciones de isomerización redox de alcoholes alílicos, conduciendo a las cetonas correspondientes de manera selectiva, y con altos rendimientos, al emplear tetrahidrofurano como disolvente. Es de destacar que, a diferencia de la mayoría de catalizadores de rutenio activos en medio orgánico previamente descritos en la literatura, los complejos **3.22a-e** son capaces de promover estas transformaciones en ausencia de base. En nuestro conocimiento, esta es la primera aplicación conocida de especies de tipo rutenio-guanidinato en catálisis homogénea.

ANEXO

ANEXO

Además de las publicaciones recogidas en los *Capítulos 1-3*, como *Anexo* se adjuntan un artículo de revisión y un capítulo de libro, cuyo contenido está íntimamente relacionado con los aspectos discutidos en los *Capítulos 1* y *2* de esta *Tesis Doctoral*:

"Metal-catalyzed amide bond forming reactions in an environmentally friendly aqueous medium: Nitrile hydrations and beyond". Rocío García-Álvarez, Pascale Crochet, Victorio Cadierno. *Green Chemistry* **2013**, *15*, 46-66.

"Ruthenium-catalyzed nitrile hydration reactions using glycerol as solvent". Alba E. Díaz-Álvarez, Rocío García-Álvarez, Pascale Crochet, Victorio Cadierno. *Glycerol: Production, Structure and Applications* (eds. M. de Santos Silva, P. Costa Ferreira), Nova Science Publishers, New York, **2012**, 249-261.

Green Chemistry

RSC Publishing

TUTORIAL REVIEW

Metal-catalyzed amide bond forming reactions in an environmentally friendly aqueous medium: nitrile hydrations and beyond

Cite this: *Green Chem.*, 2013, **15**, 46

Rocío García-Álvarez, Pascale Crochet* and Victorio Cadierno*

Received 28th September 2012,
Accepted 24th October 2012

DOI: 10.1039/c2gc36534k

www.rsc.org/greenchem

Amides are versatile building blocks in synthetic organic chemistry, presenting a wide range of pharmacological applications, and are used as raw materials in industry for the large-scale production of engineering plastics, detergents and lubricants. The development of green procedures for the synthesis of this relevant class of compounds from various starting materials, which replace antiquated methods using carboxylic acid derivatives and amines, is therefore of prime interest in modern chemistry. In this review article, a survey of metal-catalyzed synthetic approaches of amides conducted in an environmentally friendly aqueous medium is given.

Introduction

Amides are one of the most important functional groups in nature (amide linkages are the key chemical connections of proteins), they constitute versatile building blocks in synthetic organic chemistry, and also exhibit a wide range of industrial applications and pharmacological interest.[1] Chemical reactions for their formation are among the most executed transformations in organic chemistry. As a representative example, an analysis of drug candidate molecules manufactured by the leading pharmaceutical companies GlaxoSmithKline, AstraZeneca and Pfizer showed that amide bond formation was utilized in the synthesis of 66% of the candidates surveyed.[2] Amides are typically prepared from the union of carboxylic acids and derivatives (halides, anhydrides or esters) with amines.[1–3] However, although they are remarkably general, these methods present several drawbacks such as the use of toxic, corrosive and/or expensive materials, highly

Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Departamento de Química Orgánica e Inorgánica. Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, Julián Clavería 8, 33006 Oviedo, Spain. E-mail: crochetpascale@uniovi.es, vcm@uniovi.es; Fax: +(34) 985103446; Tel: +(34) 985103453

Rocío García-Álvarez

Rocío García-Álvarez received her BSc in Chemistry from the University of Oviedo (Spain) in 2007. In 2008 she started her PhD thesis under the supervision of Drs P. Crochet and V. Cadierno at the University of Oviedo, with research on novel ruthenium catalysts for amide syntheses in water.

Pascale Crochet

Pascale Crochet studied chemistry at the University of Rennes I (France) and obtained her PhD in 1996 under the supervision of Prof. P. H. Dixneuf and B. Demerseman. After a two-year post-doctoral stay in the group of Prof. M. A. Esteruelas (University of Zaragoza, Spain) and one year as Assistant Professor at the "National High School of Physics and Chemistry" of Bordeaux (France), she moved in 1999 to the University of Oviedo where she is currently Associate Professor of Inorganic Chemistry. Her research interest deals with the design and synthetic applications of organometallic complexes, with a particular focus on hydrosoluble ruthenium catalysts.

exothermic reactions, low tolerance to sensitive functional groups, complex reaction conditions and wasteful procedures. As a matter of fact, in 2005, the ACS GCIPR (American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable) identified amide formation as one of the most problematic syntheses in the pharmaceutical industry, and labelled it as a high priority research field.[4] In the search for improved synthetic methods, metal-catalyzed transformations have emerged in recent years as the most promising alternatives for the atom-economical and cost effective synthesis of amides, opening also previously unavailable routes that start from substrates other than carboxylic acids and their derivatives.[5] A couple of reviews covering these innovative approaches have recently appeared in the literature.[6]

On the other hand, over the past two decades, increasing environmental concerns have stimulated the development of new synthetic protocols that minimize the generation of waste to the maximum. Solvents account for 80–90% of mass utilization in a typical pharmaceutical/fine chemical operational process.[7] Consequently, they are responsible for most of the waste generated in the chemical industries and laboratories. With the ultimate goal of solving this environmental problem, remarkable research efforts have focused on the replacement of traditional organic solvents by water, since water is the most convenient solvent that one can imagine in terms of cost, availability, safety, and environmental impact.[8] Besides its inherent advantages, which fit perfectly with the requirements of the Green Chemistry principles,[9] the use of water as a solvent can also provide a notable difference in reactivity, enhancing in some cases the rate or changing the selectivity of a given reaction. Several books, reviews and accounts illustrating the enormous potential of water in developing new organic transformations are currently available, and they are recommended to those readers seeking a broader introduction to the topic.[10] In the context of homogeneous catalysis, the use of water as a solvent is also usually associated with an easy catalyst/product separation, thus allowing in some cases the effective recycling of the catalytically active species, which is another crucial factor in realizing a "green" process.[11] In addition, it is also worthy of note that the discovery of new techniques in nanofiltration and recovery of metal ions from water are, during water purification and recycling, no longer a barrier for large-scale chemical processes.[12]

The aim of the present review article is to provide a comprehensive account of metal-catalyzed synthetic approaches of amides in an environmentally friendly aqueous medium. Only those reactions conducted in pure water, without requirement of an organic cosolvent, will be discussed. Aqueous transformations in which the amide functionality already exists in the molecule, and a metal catalyst is employed to promote further structural modifications, are also considered to be out of the scope of this review. Literature published up to September 2012 is covered.

Victorio Cadierno

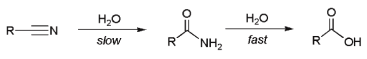
Victorio Cadierno received his PhD degree from the University of Oviedo (Spain) in 1996 under the supervision of Prof. J. Gimeno. He then joined the group of Dr J. P. Majoral at the Laboratoire de Chimie de Coordination (LCC-CNRS) in Toulouse (France) for a two-year postdoctoral stay. Thereafter, he returned to the University of Oviedo where he is currently Associate Professor of Inorganic Chemistry. In 2002 he received from the Spanish Royal Society of Chemistry (RSEQ) the Young Investigator Award. His current research involves the use of transition metal complexes for catalytic organic synthesis, with special focus on metal-catalyzed reactions in water.

Catalytic synthesis of primary amides in water

In this section the formation of primary amides RC(=O)NH_2 promoted by homogeneous and heterogeneous metal compounds in an aqueous medium is discussed. The field is clearly dominated by the catalytic hydration of nitriles. However, as the reader will see, several synthetic methods that make use of alternative starting materials (aldoximes, aldehydes, amines, azides, alcohols or methylarenes) have also appeared in recent years.

From nitriles

Ideally, the hydration of nitriles is the most atom-economical reaction and a sustainable method for the preparation of primary amides. However, traditional protocols for hydrating nitriles involve the use of strong bases or acids under harsh conditions, methods which are not compatible with many sensitive functional groups. In addition, the base-catalyzed reactions usually cause over-hydrolysis of the amides into the corresponding carboxylic acids, a kinetically favoured reaction compared to the hydration one (Scheme 1).[1,3] Although under acidic conditions it is possible to stop the process at the amide stage, in these cases it is necessary to control carefully the temperature and stoichiometry employed in order to avoid the formation of polymeric side products.[13] It is also important to note that, from an industrial perspective, the final neutralization step required either in the acid- or base-catalyzed reactions leads to extensive salt formation with inconvenient product contamination and pollution effects.

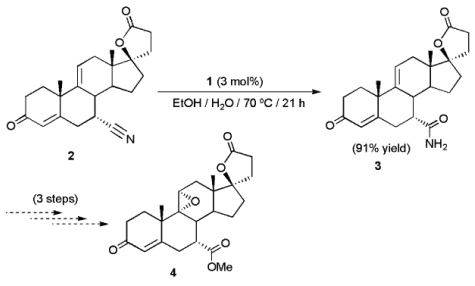


Scheme 1 Nitrile hydration and amide hydrolysis reactions.

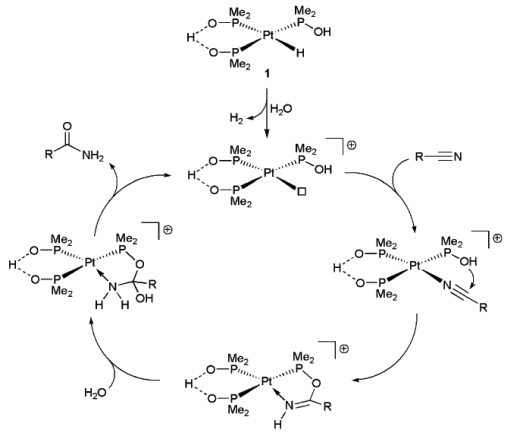
Nitrile hydrations using enzymatic catalysis allow us to circumvent most of these problems, offering cleaner, safer and more selective protocols for the preparation of primary amides.[14] In fact, some *nitrile hydratases* are currently employed for the industrial production of acrylamide, nicotinamide and 5-cyanovaleramide by hydration of the corresponding nitriles.[15] However, despite the significant progress made in the field and its commercial success, the isolation costs and the narrow substrate specificity of the current available enzymes severely limit their practical use. Given their greater scope, catalytic methods based on the use of metal compounds represent a more attractive alternative than enzymes. In this context, a great variety of homogeneous and heterogeneous systems have been developed during the last two decades.[16] Most of them operate in organic media in the presence of only small amounts of water, but, owing to practical and environmental concerns, current research has focused on the search for catalytic systems able to operate directly in water. The advances reached in the field are summarized in the following lines.

The platinum(II) complex $[PtH\{(PMe_2O)_2H\}(PMe_2OH)]$ **1**, synthesized by Parkins and co-workers in 1995,[17] is probably the most versatile catalyst presently available for the hydration of C≡N bonds. Its remarkable activity under relatively mild conditions (70–100 °C), along with its exquisite functional group tolerance, has allowed the implementation of this catalyst in the synthesis of a huge number of biologically active molecules and natural products.[18] As a representative example, the preparation of the steroidal compound 7α-carbamoyl-9(11)$^{\Delta}$-canrenone **3**, an advanced intermediate in the production of the orally-active aldosterone antagonist eplerenone **4** used for the treatment of hypertension and congestive heart failure, could be performed in excellent yield by catalytic hydration of 7α-cyano-9(11)$^{\Delta}$-canrenone **2** using this complex (Scheme 2).[18e]

The presence of a phosphinito ligand in **1**, which incorporates a tethered hydroxyl group, eliminates the need for a base in the reactions, the proposed mechanism of action involving the direct participation of this group in the hydration step (Scheme 3).[17] Although in the initial work by Parkins' group the hydration of model acetonitrile and 3-cyanopyridine



Scheme 2 Pt-catalyzed hydration of 7α-cyano-9(11)$^{\Delta}$-canrenone **2**.



Scheme 3 Suggested mechanism for the catalytic hydration of nitriles by complex **1**.

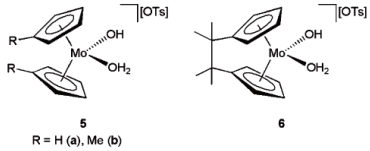
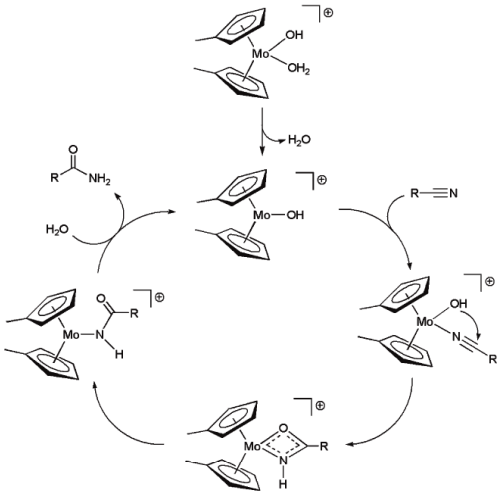


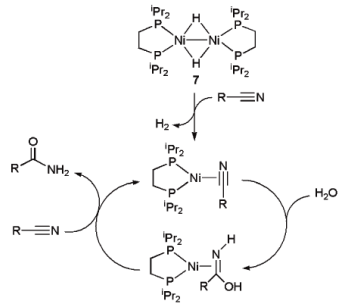
Fig. 1 Structure of the water-soluble molybdocene catalysts **5** and **6**.

substrates with **1** could be performed directly in water (yields up to 91%, TOF up to 450 h^{-1} and TON up to 50 000 using 0.004–0.1 mol% of **1** at 100 °C),[17] in all the later studies water/organic solvent (ethanol, methanol, tetrahydrofuran or 1,4-dioxane) mixtures were systematically employed as the reaction media (as in the example of Scheme 1).[18] Only recently, a pure aqueous medium was used to study the catalytic behaviour of $[PtH\{(PMe_2O)_2H\}(PMe_2OH)]$ **1** towards cyanohydrins (α-hydroxynitriles).[19] Unfortunately, the hydration rates for these substrates were very slow in comparison to those observed with other nitriles, and only a few turnovers could be achieved. The low reactivity was ascribed to the liberation of HCN by partial degradation of the cyanohydrin substrate, the coordination of the cyanide anion leading to the deactivation of the catalyst.

Like the platinum–phosphinito complex **1**, the molybdocene derivatives $[(\eta^5\text{-}C_5H_4R)_2Mo(OH)(H_2O)][OTs]$ (R = **H 5a**, Me **5b**) and $[\{C_2Me_4(\eta^5\text{-}C_5H_4)_2\}Mo(OH)(H_2O)][OTs]$ **6** (OTs = *p*-toluenesulfonate) developed by Tyler and co-workers (Fig. 1) are also slightly soluble in water and effective towards the selective hydration of nitriles, affording the amides without further hydrolysis to the carboxylic acids.[20] A wide range of aromatic, aliphatic and α,β-unsaturated nitriles were successfully transformed performing the catalytic reactions in D_2O at 80 °C with 0.1–5 mol% of these molybdocene complexes (TOF values



Scheme 4 Catalytic cycle for the hydration of nitriles with complex **5b**.



Scheme 5 Suggested mechanism for the hydration of nitriles by the Ni dimer **7**.

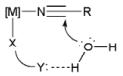


Fig. 2 Cooperative effect of the ligand during nitrile hydration.

up to 4077 h^{-1}). However, we must note that challenging cyanohydrin substrates could not be hydrated despite the rapid conversion observed for β-hydroxynitriles.[19] In addition, complexes **5**–**6** were also intolerant to ether- and ester-containing nitriles (*e.g.* 2-methylcyanoacetate or 2-methoxyacetonitrile) due to the facile hydrolysis of those groups.[20a]

On the basis of kinetic data and H/D exchange experiments a reaction mechanism for the hydration process involving the intramolecular attack of the hydroxo ligand on the metal-coordinated nitrile was proposed for **5b** (Scheme 4).[20a] In addition, it was also observed that increasing the electron-withdrawing ability of the nitrile enhanced the rate of the reaction. This result suggested that the intramolecular attack of OH^- is the rate-limiting step of the catalytic cycle. All these facts were later confirmed by Tyler[19] and López[21] through density functional theory (DFT) calculations on the $[Cp_2Mo(OH)(H_2O)]^+$ system **5a**.

The nickel(I) dimer $[\{Ni(dippe)(\mu\text{-}H)\}_2]$ **7** (dippe = 1,2-bis(diisopropylphosphino)ethane) is another relevant example of a homogeneous metal catalyst active in a pure aqueous medium. For example, hydration of benzonitrile and acetonitrile at 180 °C with this complex led to TON and TOF values of up to 984 and 14 h^{-1}, respectively, using a nickel loading of only 0.04 mol%.[22] From a mechanistic point of view (Scheme 5), an initial reduction of Ni(I) to Ni(0) *via* H_2 release was proposed, followed by η^2-coordination of the nitrile to the metal. Then, intermolecular nucleophilic attack of water on the η^2-nitrile takes place to generate a hydroxy-imine, which decoordinates from the Ni(0) center giving the final amide. In accord with this proposal, isolated complexes $[Ni(dippe)(\eta^2\text{-NCR})]$ proved to be catalytically active.[22] In addition to benzonitrile and acetonitrile, hydration of 1,2-, 1,3- and 1,4-dicyanobenzenes,[23] as well as a variety of *N*-heterocyclic nitriles, such as 2- and 3-cyanoquinolines, 2-, 3- and 4-cyanopyridines or 2,6-dicyanopyridine,[24] with the aid of complex **7** was also demonstrated. For the latter, selective entries to the mixed cyano/amide and fully hydrated dicarboxamide could be established.[24b] Moreover, this Ni-based methodology was further optimized for alkyl-nitriles and aliphatic dinitriles of variable chain length making use of *p*-toluenesulfonic acid (PTSA) as a co-catalyst.[25]

A catalytic system of superior simplicity for the hydration of aryl, benzyl and both sterically hindered and unhindered alkyl nitriles in water, consisting of cheap, commercially available and environmentally friendly compounds (a ZnX_2/ketoxime combination), was described by Kukushkin and Pombeiro.[26] The nature of the X^- anion in the zinc salt (X^- = NO_3^-, Cl^-, $CF_3SO_3^-$) or that of the ketoxime ($Me_2C{=}NOH$, $c\text{-}C_4H_8C{=}NOH$, $c\text{-}C_5H_{10}C{=}NOH$) does not affect strongly the catalytic properties of the system, but the best results were obtained so far with the $Zn(NO_3)_2{\cdot}6H_2O$ (0.7 mol%)/$Me_2C{=}NOH$ (2.8 mol%) combination. TOF and TON values of up to 45 h^{-1} and 450, respectively, could be reached with this system performing the catalytic reactions in air under refluxing conditions. Interestingly, the presence of both components is imperative as the hydration process does not proceed at all with either the zinc compound or the ketoxime taken alone. Addition of the ketoxime ($R_2C{=}NOH$) to the ligated nitrile (R′C≡N), to give an imino intermediate [Zn]–NH=C(R′)-ON=CR_2 which by hydrolysis furnishes the amide and regenerates the Zn(II)/ketoxime catalyst, was proposed to explain these experimental observations.

On the other hand, recent work has demonstrated that catalytic nitrile hydration can be facilitated by the presence of functionalized ligands able to activate the nucleophilic water molecule through a hydrogen-bond interaction (Fig. 2).[27] Such a cooperative effect of the ligand represents a typical example

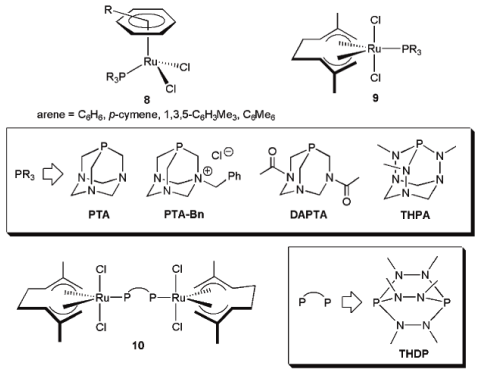
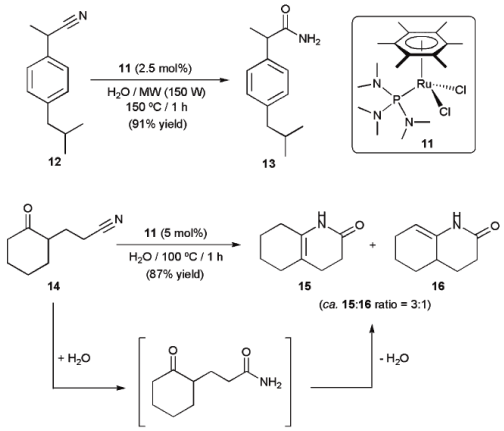


Fig. 3 Structure of some ruthenium catalysts with cooperative phosphine ligands.



Scheme 6 Catalytic synthesis of ibuprofenamide and ene-lactams using complex **11**.

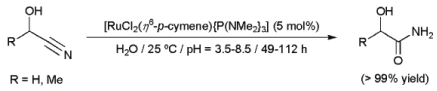
of the so-called "bifunctional catalysis"; that is, the metal ion acts as a Lewis acid and the ligand as a Lewis base, a concept largely exploited in homogeneous catalysis during the last few years.[28]

In this context, a series of arene–ruthenium(II) **8**[29] and bis(allyl)–ruthenium(IV) complexes **9**–**10**,[30] containing "cage-like" water-soluble phosphines, have been found to operate through this bifunctional catalysis mechanism (Fig. 3). Thus, once the nitrile is coordinated to ruthenium, *via* dissociation of one of the chloride ligands, its hydration is favoured by H-bonding of the incoming water molecule with the nitrogen atoms of the phosphines. This fact was supported by the remarkably lower effectiveness shown by related complexes bearing the sulphonated phosphine TPPMS ((*meta*-sulfonatophenyl)-diphenylphosphine sodium salt), in which such an interaction cannot be established.[29,30] Complexes **8**–**10** are all active in pure water, within the temperature regime 100–150 °C (classical or MW heating), without requirement of any acidic or basic co-catalyst. Best results in terms of activity (TOF and TON up to 127 h^{-1} and 100, respectively) were found with the mononuclear compounds $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ and $[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(THPA)]$, and the dinuclear one $[\{RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})\}_2(\mu\text{-}THDP)]$ (**10**). Almost quantitative conversions of a wide variety of aromatic, heteroaromatic, α,β-unsaturated and aliphatic nitriles were observed with these systems within 1–15 h, and the reactions tolerated common functional groups such as halides, nitro, hydroxy, ethers, thioethers, amino, ketones, aldehyde, esters or alkynes. After crystallization of the amide, recycling of the aqueous phase containing the active species was also demonstrated for $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$.[29,31]

A superior recycling (up to 7 consecutive runs) after amide crystallization was observed with the octahedral ruthenium(II) derivative $[RuCl_2(PTA)_4]$.[32] TOF and TON values of up to 30 h^{-1} and 22 000, respectively, could be reached with this complex performing the catalytic reactions at 100 °C. Other commendable aspects of $[RuCl_2(PTA)_4]$ are its tolerance to the presence of air (no inert atmosphere required) and its high functional group compatibility.

The Ru(II) complexes $[RuCl_2(\eta^6\text{-arene})\{P(NMe_2)_3\}]$ (arene = C_6H_6, *p*-cymene, 1,3,5-$C_6H_3Me_3$, C_6Me_6), incorporating the commercially available, inexpensive and H-bond accepting ligand tris(dimethylamino)phosphine, have also shown to be highly effective for nitrile hydration in pure water under neutral conditions.[33] Within this family of catalysts, best results were obtained with the hexamethylbenzene derivative $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ **11**, which selectively provided the desired amides from a wide range of organonitriles in excellent yields and short times (TOF values up to 11 400 h^{-1} could be reached at 150 °C under MW irradiation). Taking advantage of the remarkable activity of this catalyst, an efficient and practical synthesis of the non-steroidal anti-inflammatory drug ibuprofenamide **13** by catalytic hydration of 2-(4-isobutylphenyl)-propionitrile **12** could be developed (Scheme 6). In addition, complex **11** proved to be also effective for the one-pot conversion of δ-ketonitrile **14** into the isomeric ene-lactams **15** and **16**, *via* a tandem hydration/condensation sequence.[34] The only drawback of these methodologies is the impossibility to recycle **11** due to its progressive decomposition into the less active dimethylamine–ruthenium(II) complex $[RuCl_2(\eta^6\text{-}C_6Me_6)(NHMe_2)]$ by hydrolysis of the coordinated $P(NMe_2)_3$ ligand.[33b]

Further studies revealed an unprecedented reactivity of $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(NMe_2)_3\}]$ in the challenging hydration of cyanohydrins to the corresponding α-hydroxyamides.[35] Thus, running the catalytic reactions within the pH range 3.5–8.5 to avoid the decomposition of the substrates into the corresponding aldehydes and HCN, complete conversion of glycolonitrile (R = H) and lactonitrile (R = Me) could be achieved at room temperature (Scheme 7). Complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(NMe_2)_3\}]$ was also able to hydrate acetone cyanohydrin, but a lower conversion (15%) to the amide



Scheme 7 Cyanohydrins hydration with complex [$RuCl_2(\eta^6$-*p*-cymene)-{$P(NMe_2)_3$}].

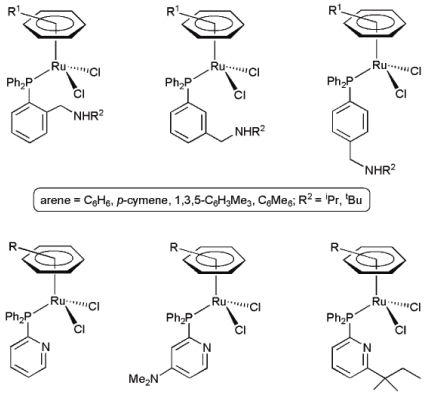
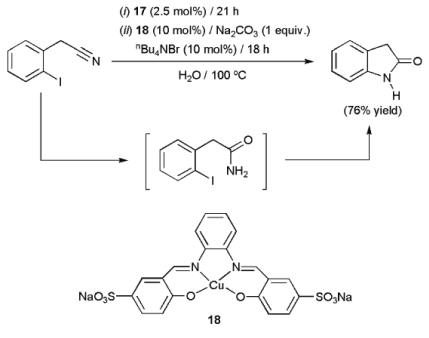


Fig. 4 Structure of arene–ruthenium(II) catalysts containing amino-phosphine and pyridyl-phosphine ligands.

product was in this case observed. Overall, these results represent a benchmark for future studies on cyanohydrins hydration using metallic catalysts.

In the search for cooperative effects of the ligands, other arene–ruthenium(II) complexes with potentially H-bond accepting amino-phosphines[36] and pyridyl-phosphines[37] were also investigated (Fig. 4). However, in contrast to the previous examples, they showed only modest activities. The results obtained with the amino-phosphine derivatives indicated that the pendant amino group of the ligands acts as a Brønsted base, generating the real nucleophile of the hydration process, *i.e.* the OH^- group. In the case of the pyridyl-phosphine derivatives, bifunctional pathways during the catalytic events were totally ruled out. In fact, the high tendency of PPh_2py and PPh_2(py-4-NMe_2) to adopt a κ^2-*P*,*N*-chelating coordination results in the formation of very low active species, while in the case of PPh_2(py-6-*tert*-amyl) the presence of the bulky *tert*-amyl substituent seems to prevent the approach of the substrate to the Lewis acid metal center, leading also to poor results in catalysis.[38]

Quite recently, the cuprous complex $[Cu_4(\mu_3\text{-}I)(H_2O)_4]$ **17** (2.5 mol%) has been successfully applied in the selective hydration of several benzonitriles, cinnamonitriles and arylacetonitriles in pure water at 100 °C (yields up to 98% after 21 h).[39] After completion of the reactions, the mixtures were cooled to *ca.* 5 °C and crystals of the amides selectively appeared. This fact allowed, once again, the easy separation of the products by simple filtration, and also the recycling of the aqueous solution containing the catalyst (up to 5 consecutive



Scheme 8 Copper-catalyzed one-pot synthesis of 2-oxotetrahydroindole in water.

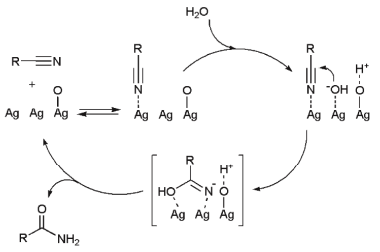
runs). In addition, using a combination of complex **17** and the C–N coupling Cu(II) catalyst **18**, 2-oxotetrahydroindole could be prepared in good yields from 2-iodophenylacetonitrile through the one-pot domino protocol depicted in Scheme 8.

In addition to the above-discussed systems, other examples of transition-metal complexes operative in nitrile hydration processes, without the requirement of an organic co-solvent, reported in the literature include: (i) the hydroxo-palladium(II) and -rhodium(I) derivatives [PdCl(OH)(bipy)] (bipy = 2,2′-bipyridine)[40] and *trans*-$[Rh(OH)(CO)(PPh_3)_2]$,[41] (ii) the hydride-iridium(I) and ruthenium(II) complexes $[IrH(CO)(TPPTS)_3]$ (TPPTS = $P(m\text{-}C_6H_4SO_3Na)_3 \cdot xH_2O$)[42] and $[RuH(\eta^5\text{-}C_9H_7)(dppm)]$ (C_9H_7 = indenyl; dppm = bis(diphenylphosphino)methane),[43] (iii) the recyclable (up to five cycles) Rh(I) system $[\{Rh(\mu\text{-}Cl)(cod)\}_2]$/TPPTS (cod = 1,5-cyclooctadiene),[44] (iv) the peroxo-iridium(III) derivative $[Ir(O_2)(PMe_3)_4][Cl]$,[45] (v) the osmium(II) complex $[\{OsCl(\mu\text{-}Cl)(CO)_3\}_2]$,[46] and (vi) the dicationic octahedral ruthenium(II) derivative $[Ru(H_2O)(NCMe)_4(P^iPr_3)][BF_4]_2$.[47] However, they were in general less active and/or selective than the examples discussed above, and their scope was not always demonstrated. In line with this latter point, several Os(II) and Ru(II) complexes have been exclusively studied in the catalytic hydration of chloroacetonitriles ($Cl_{3-n}CH_nC{\equiv}N$) into the corresponding chloroacetamides ($Cl_{3-n}CH_nC(=O)NH_2$), a particular class of compounds that exhibit a wide range of biological properties and are widely used as building blocks in preparative organic chemistry.[48] Among them, the best results were obtained with the osmium(II) derivative *cis*,*fac*-$[OsCl_2(Hbzim)(dmso)_3]$ (Hbzim = benzimidazole) which reached TON values up to 412 for trichloroacetamide (n = 0) and 578 for dichloroacetamide (n = 1) at 75 °C.[48a]

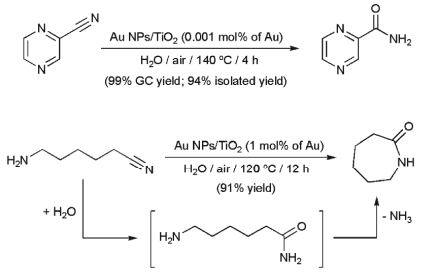
On the other hand, over the last decade, the use of nanoparticles (NPs) in catalysis has expanded considerably and has led to many interesting applications.[49] The nano-sized particles increase the exposed surface area of the active component of the catalyst, thereby enhancing the contact between reactants and catalyst dramatically and mimicking the homogeneous systems. However, their insolubility in reaction solvents renders them easily separable from the reaction mixture

like heterogeneous catalysts, which in turn minimizes the effort of the product isolation stage. This bridge between homogeneous and heterogeneous catalysis tended by NPs gives unique opportunities towards the development of efficient reactions under environmentally benign conditions. In this context, colloidal dispersions of Cu/Pd bimetallic nanoclusters proved to be selective and recyclable catalysts for the hydration of acrylonitrile to acrylamide in pure water at 80 °C (up to 95% yield after 8 h), showing much higher activities than those of pure Cu colloids and other Cu-based systems.[50,51] PVP-stabilized Pd nanoparticles (PVP = poly-(*N*-vinyl-2-pyrrolidone)) in combination with $Cu(acac)_2$ or CuO acted also as catalysts for the hydration of various nitriles without requiring the preparation of an alloy.[52] As an example, more than 99% yield on benzonitrile hydration was achieved with the Pd NP–$Cu(acac)_2$ system (5 mol% of Pd and 10 mol% of Cu) at 180 °C for 16 h.

Studies by Kaneda[53a] and Park[53b] have demonstrated the utility of hydroxyapatite-supported and PVP-stabilized silver NPs, respectively, as recyclable catalysts for the selective hydration of nitriles in pure water. Reactions performed with Ag loadings of 0.3–3 mol% delivered the desired amides in high yields (>80%) after 1–6 h of heating at 140–180 °C when starting from aromatic or heteroaromatic nitriles, but proved to be much less effective with aliphatic substrates. The Ag NPs were in both cases readily separated by centrifugation and could be reused 4–5 times without loss of their catalytic activity and selectivity. A mechanism of action involving the initial coordination of water and the nitrile on the silver NP surface was proposed. Subsequently, an OH^- anion generated from a proximal silver-coordinated H_2O molecule attacks the nitrile carbon atom to form the corresponding amide through an iminol intermediate.[53a] Further recent studies by Shimizu and co-workers using SiO_2-supported Ag NPs pointed out the key role played by the oxygen atoms adsorbed on the silver surface, which seem to act as Brønsted bases facilitating the dissociation of water and the generation of the nucleophilic OH^- (Scheme 9).[54] Notably, unlike the previous examples, the less reactive aliphatic nitriles could be effectively hydrated with this new Ag-based system (70–90% yield after 24–48 h of heating at 160 °C with a silver loading of 9 mol%).



Scheme 9 Proposed mechanism for the Ag/SiO_2-catalyzed hydration of nitriles.



Scheme 10 Catalytic synthesis of pyrazinecarboxamide and ε-caprolactam in water using Au NPs supported on TiO_2.

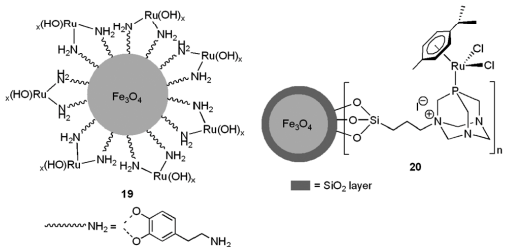
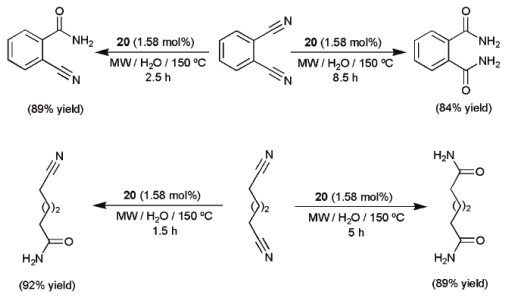


Fig. 5 Structure of the nano-catalysts **19** and **20**.

Gold NPs supported on TiO_2 proved to be more efficient and general than the Ag-based systems described above.[55] For example, an impressive TOF value of 25 000 h^{-1} was reached in the hydration of pyrazinecarbonitrile to produce pyrazinecarboxamide, an antibacterial agent used for the treatment of tuberculosis (Scheme 10). The reaction cleanly took place in neat water, under air, with a gold loading of only 0.001 mol%. In addition, after recycling the catalyst 10 times by simple filtration, an unprecedented cumulative TON of 1 000 000 could be realized. The high-yield synthesis of ε-caprolactam by hydration/cyclization of 6-aminocapronitrile is another example of the synthetic usefulness of this heterogeneous system (Scheme 10).[55,56]

Nanoferrites-supported ruthenium hydroxide **19** (0.003 mol% of Ru)[57] and the bifunctional arene–ruthenium(II) complex **20** (1.58 mol% of Ru)[58] have also been employed to promote nitrile hydration reactions in pure water under neutral conditions, using microwave irradiation as the heating source (Fig. 5).

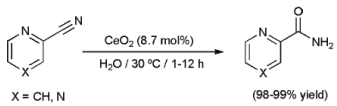
Both nano-catalysts showed excellent activities (TOFs up to 30 000 h^{-1}) and selectivities for a broad range of aromatic, heteroaromatic, aliphatic and α,β-unsaturated nitriles, leading to the desired primary amides in high yields (70–95%) after 0.5–7 h of MW irradiation at 130–150 °C. Several functional groups, *i.e.* halide, ether, thioether, amino, nitro, ketone, aldehyde, ester or alkyne, were tolerated and no overhydrolysis to carboxylic acids was observed. Noteworthily, the selective mono and dihydration of dicyano derivatives could also be conveniently achieved using **20** just by controlling the time of



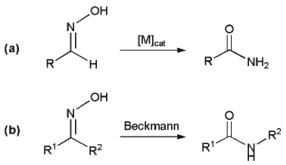
Scheme 11 Selective hydration of dinitriles in water using nano-catalyst **20**.

MW irradiation (representative examples are given in Scheme 11).[58] After completion of the hydration reactions, the magnetic nanocatalysts **19**–**20** could be easily separated from the reaction mixtures with the help of an external magnet and recycled up to three (**19**) or six (**20**) times. In addition, after separation of the nanoparticles, the aqueous solutions were cooled and crystals of the amides with acceptable purity precipitated, thus avoiding the use of organic solvents also in the work-up steps. Overall, the use of relatively low metal concentrations, environmentally friendly water as the reaction medium (with no use of single drop of organic solvent during or after the reactions) and low-energy-consuming microwave heating, along with an easy recycling procedure, makes these protocols "truly" green and sustainable. In a related recent study, the utility of ruthenium hydroxide nanoparticles immobilized on magnetic silica (Fe_3O_4@SiO_2) for aqueous hydration of nitriles under neutral conditions was also demonstrated.[59]

In addition to the discussed nanocatalysts, several insoluble metal oxides have been explored as potential heterogeneous catalysts for the hydration of C≡N bonds in an aqueous medium.[60] In general, they exhibited poor activities and, in some cases, low selectivities towards the desired amides. The most relevant results in this field are: (i) the selective generation of nicotinamide from aqueous 3-cyanopyridine over MnO_2 (>99% yield after 8 h of heating at 100 °C using 13 mol% of MnO_2),[60e] (ii) the selective hydration of different aromatic and heteroaromatic nitriles by means of the recyclable spinel cobalt oxide Co_3O_4 (75–99% yield after 7–24 h of heating at 140 °C using 17 mol% of Co_3O_4),[60f] and (iii) the remarkable substrate-specificity shown by CeO_2.[60g] This latter oxide proved to be only effective for the hydration of nitriles that contain a heteroatom (N or O) adjacent to the α carbon of the CN group. Such substrates were cleanly converted into the corresponding amides even at 30 °C (as representative examples, the hydrations of 2-cyanopyridine and pyrazinecarbonitrile at this remarkably low temperature are given in Scheme 12). A mechanism involving initial H_2O dissociation on CeO_2, subsequent adsorption of the nitrile on the solid surface, and final nucleophilic attack of a hydroxyl species on the adsorbed nitrile was proposed, with the latter being the rate-limiting



Scheme 12 Hydration of 2-cyanopyridine and pyrazinecarboxamide with CeO_2.



Scheme 13 Rearrangements of oximes to amides.

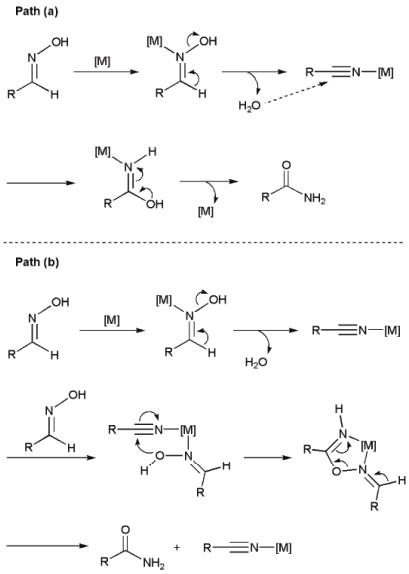
step of the process as determined by kinetic analyses. Favoured adsorption nitriles containing heteroatoms adjacent to the α carbon of the CN group account for the substrate-specificity observed.

Ruthenium hydroxide supported on alumina ($Ru(OH)_x/Al_2O_3$),[61] ruthenium-substituted hydroxyapatite ($\{RuCl\}_2Ca_8\{PO_4\}_6\{OH\}_2$)[62] and a Nafion-Ru solid resin[63] proved to be also useful heterogeneous and recyclable catalysts for the hydration of various kinds of nitriles in water at 140–175 °C. Worthy of note, using $Ru(OH)_x/Al_2O_3$, a totally organic solvent free process was developed since the solid catalyst can be easily separated from the reaction mixture by hot filtration at 90 °C, and the amides crystallize in a pure form from the filtrate upon cooling at 0 °C.

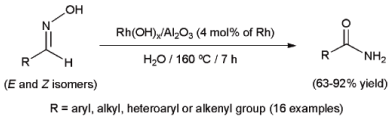
From aldoximes

The metal-catalyzed rearrangement of aldoximes represents an alternative atom efficient method for forming primary amides (Scheme 13(a)). Despite the similitude of this process with the classical Beckmann rearrangement in which N-substituted amides are generated by the acid-catalyzed rearrangement of ketoximes (Scheme 13(b)),[64] it is important to note that the reaction of aldoximes in the presence of acid catalysts usually gives the corresponding nitriles due to the propensity of the H atom to act as a leaving group. In fact, the synthesis of primary amides from aldoximes is a specially exigent reaction that traditionally requires harsh conditions.[65]

In recent years, several Ni-,[66] Pd-,[66a,b,67] Cu-,[68] Au-,[69] Ru-,[70] Rh-,[71] Ir-,[72] Zn-[73] and In-based[73b] systems able to promote efficiently this atom-economical transformation in organic media have been developed, thus expanding its synthetic potential. From a mechanistic point of view, two different reaction pathways have been proposed. The first one involves the initial dehydration of the aldoxime into a nitrile intermediate,[74] which is subsequently hydrated by the water released in the previous step to generate the final amide (path (a) in Scheme 14).



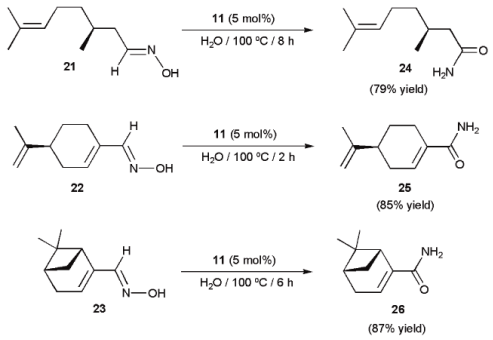
Scheme 14 Proposed mechanisms for the catalytic rearrangement of aldoximes to amides.



Scheme 15 $Rh(OH)_x/Al_2O_3$-catalyzed synthesis of amides from aldoximes.

In the second one, metal-promoted dehydration of the aldoxime to form a nitrile also takes place initially, but the nitrile now evolves into the final amide with the aid of a second molecule of aldoxime which acts as a water surrogate (path (b) in Scheme 14).[75] Thus, intramolecular attack on the nitrile by a coordinate aldoxime leads to a five-membered cyclic intermediate, which decomposes into the final amide product and another coordinated nitrile which continues with the catalytic cycle. Remarkably, despite the dehydration/rehydration pathway involving water (a) has been the generally accepted mechanism for the rearrangement of aldoximes to amides, a recent study by Williams and co-workers using ^{18}O labelled substrates has pointed out that most of the homogeneous catalysts described so far in the literature for this reaction really operate through the pathway (b).[76]

To date, little attention has been paid to this rearrangement in aqueous media. In fact, the first approach was made by Mizuno and co-workers only in 2007 employing supported rhodium hydroxide ($Rh(OH)_x/Al_2O_3$) as catalyst (Scheme 15).[77] The reactions, performed in pure water with a rhodium loading of 4 mol%, delivered the desired amides in high yields



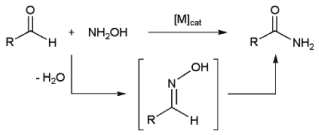
Scheme 16 Ruthenium-catalyzed rearrangement of the optically active aldoximes **21–23** in water.

after 7 h of heating at 160 °C. Both aromatic, heteroaromatic, aliphatic and α,β-unsaturated aldoximes were tolerated, and the heterogeneous catalyst could be recovered by filtration and reused with retention of its activity. Remarkably, in contrast to the transformations in water, nitriles were formed as the major products when the same reactions were performed in common organic solvents. This fact, along with the ability of $Rh(OH)_x/Al_2O_3$ to catalyze the hydration of nitriles under the same experimental conditions, seems to indicate that this heterogeneous system operates through pathway (a) in which the nitrile intermediates are hydrated by water (Scheme 14).

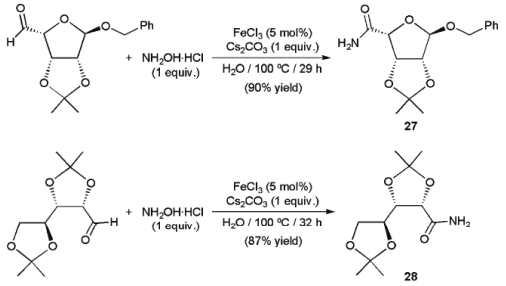
More recently, the arene–ruthenium(II) complex $[RuCl_2\{\eta^6\text{-}C_6Me_6\}\{P(NMe_2)_3\}]$ **11** (5 mol%) proved to be also effective in water.[78] The reactions proceeded cleanly at 100 °C without the assistance of any co-catalyst, affording the desired amides in high yields (70–90%) after short reaction periods (1–7 h). Again, the process was operative with both aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldoximes, and tolerated several functional groups. The synthetic utility of this homogeneous system was fully demonstrated in the preparation of the chiral amides **24–26** (Scheme 16), which were isolated in high yields by rearrangement of the optically pure aldoximes **21–23** derived from the naturally occurring aldehydes (*S*)-(−)-citronellal, (*S*)-(−)-perillaldehyde and (1*R*)-(−)-myrtenal, respectively. Reaction profiles, kinetic analyses, and experiments using ^{18}O-labelled water supported in this case the involvement of both dehydration/rehydration pathways depicted in Scheme 14, with that involving the hydration of the corresponding nitrile intermediates by a second molecule of aldoxime (b) being predominant.

From aldehydes

Aldoximes are generally synthesized by condensation of aldehydes with hydroxylamine. Consequently, significant efforts have been devoted in recent years to the development of one-pot processes enabling the direct formation of primary amides from aldehydes and hydroxylamine derivatives, *via* rearrangement of the *in situ* formed aldoximes (Scheme 17). This



Scheme 17 Catalytic synthesis of primary amides from aldehydes and hydroxylamine.

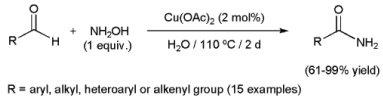


Scheme 18 $FeCl_3$-catalyzed synthesis of amides **27** and **28**.

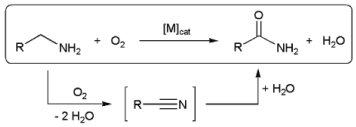
protocol is an attractive alternative to the more classical oxidative amidations of aldehydes (see below).[79]

Several catalytic systems based on copper,[68c,80] scandium,[81] zinc,[73b] iron,[82] ruthenium,[70b,c,83] rhodium,[77] iridium,[72] palladium,[84] and indium[73b] compounds able to effect efficiently this sequential transformation have already been discovered, some of them operating in aqueous media. In particular, using catalytic amounts of $Rh(OH)_x/Al_2O_3$ (4 mol% of Rh)[77] and $FeCl_3$ (5 mol%),[82] a large variety of aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes were converted into the corresponding primary amides in high yields performing the reactions in pure water at 100–160 °C for 6–32 h with the hydroxylammonium salts $(NH_2OH)_2{\cdot}H_2SO_4$ or $NH_2OH{\cdot}HCl$. Remarkably, while heterogeneous $Rh(OH)_x/Al_2O_3$ could be reused without a significant loss of its activity, the homogeneous one $FeCl_3$ proved to be useful for the preparation of biologically relevant compounds, such as the β-D-ribofuranose derivatives **27** and **28** (Scheme 18).

Faster transformations of any type of aldehydes were described by Singh and co-workers employing scandium(III) triflate (10 mol%) under controlled MW irradiation (300 W).[81] The reactions, performed in water at 135 °C with stoichiometric amounts of $NH_2OH{\cdot}HCl$ and Na_2CO_3, selectively delivered the desired amides in excellent yields (82–95%) after very short irradiation periods (15–35 min). More recently, a protocol involving recyclable (up to ten times) copper(II) acetate and hydroxylamine has been described by Ramón and co-workers (Scheme 19).[68c] The direct use of hydroxylamine instead of hydroxylammonium salts avoids in this case the introduction of a base in the reaction medium to catch the acid released during the generation of the aldoxime, thus minimizing the generation of waste. However, the extremely long reaction



Scheme 19 $Cu(OAc)_2$-catalyzed synthesis of amides from aldehydes in water.



Scheme 20 Oxidative hydration of primary amines to amides *via* nitrile intermediates.

times required (2 days) may be a drawback for further applications of this catalytic system.

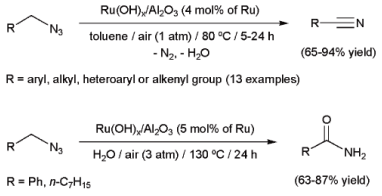
From amines

Aerobic oxidation of amines is an emerging research field that offers great opportunities for the sustainable production of a large variety of key nitrogen-containing compounds.[85] With regard to the synthesis of primary amides, the direct oxygenation of α-methylene groups in primary RCH_2NH_2 amines is a highly desirable reaction since the latter are readily available and inexpensive starting materials. However, it is very difficult to oxygenate primary amines, and highly reactive stoichiometric reagents are usually required.[86] In addition, the significantly higher reactivity of the amine functionality over the methylene α-carbon necessitates in some cases of functional-group protection, with the consequent decrease in atom efficiency.[86c] Recent research in this direction has brought to light a promising alternative route for the direct catalytic conversion of primary amines to primary amides through the oxidative dehydrogenation/hydration sequence depicted in Scheme 20, in which hydration of an *in situ* formed nitrile takes place.[62,87]

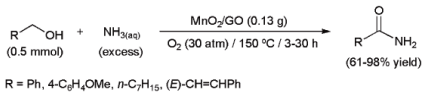
The number of catalytic systems capable of carrying out this reaction is still very limited and organic co-solvents or solvent-free conditions are required in most cases.[87] However, given the unique ability of $Ru(OH)_x/Al_2O_3$ to selectively oxidize amines to nitriles,[88] various kinds of primary amines could be effectively converted into the corresponding amides performing the catalytic reactions in pure water at 140 °C, and using air (5 atm) as the sole oxidant (77–92% yield after 10–24 h using a ruthenium loading of 5 mol%).[87a]

From azides

Although they are generally considered hazardous, azides are attractive functional groups in synthesis because of their enhanced reactivity (dipolar character) and easy introduction into organic molecules by many convenient methods, such as the simple S_N2 displacement of alkyl halides with NaN_3. The Staudinger and Schmidt reactions, the Curtius rearrangement and the "click" synthesis of triazoles are the most popular



Scheme 21 Aerobic oxidative transformations of primary azides.

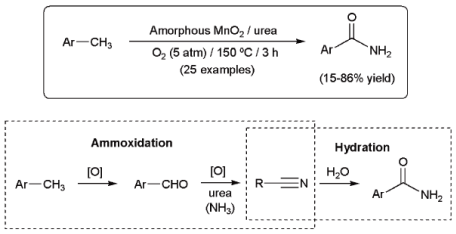


Scheme 22 MnO_2-catalyzed synthesis of primary amides from primary alcohols and aqueous ammonia.

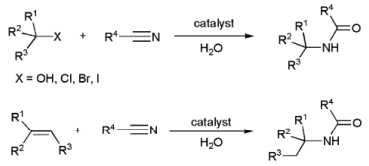
applications of these relevant molecules.[89] More contemporary developments revealed that azides that contain α-hydrogens are useful precursors for oxidation to the corresponding nitriles.[90] In this context, Mizuno and co-workers have described the aerobic oxidation of a wide range of azides by means of the supported ruthenium hydroxide catalyst Ru-$(OH)_x/Al_2O_3$ (Scheme 21).[91] In addition, they also demonstrated that primary amides can be generated in high yields by performing the catalytic transformations in water, *via* Ru-promoted hydration of the initially formed nitriles (Scheme 21). Although only a couple of examples were shown, this unprecedented sequential transformation represents a new synthetic tool for amide-bond formation which makes use of readily available starting materials.

From alcohols

Since the sound work of Milstein and co-workers in 2007 using PNN pincer-type ruthenium complexes,[92] transition-metal catalyzed direct amide synthesis from primary alcohols and amines has become a major field within current research.[93] Although most examples described to date are focused on the preparation of secondary amides (see below), some catalytic systems have also proven effective for primary amide formation using ammonia.[94] In this context, employing MnO_2 nanorods supported on graphene oxide (GO), Hou and co-workers were able to convert several primary alcohols to the corresponding primary amides employing aqueous ammonia (Scheme 22).[94f] Contrary to other catalytic systems, the reactions proceeded cleanly in the absence of any organic co-solvent. In addition, the heterogeneous catalyst showed good recyclability (up to five cycles). A reaction pathway involving the initial oxidation of the alcohol to the corresponding aldehyde, *via* Mn(IV)/Mn(II) reduction (O_2 is needed to regenerate the active Mn(IV)), followed by its reaction with NH_3 to form a hemiaminal that is subsequently dehydrogenated to the amide, was proposed. In complete accord with this, MnO_2/GO proved to be also effective for primary amide formation starting from aldehydes and aqueous ammonia.[94f]



Scheme 23 Aerobic oxidative amidation of methylarenes promoted by amorphous MnO_2.



Scheme 24 Formation of secondary amides through Ritter-type reactions.

Organic solvent-free amidation of benzyl alcohol with aqueous ammonia by virtue of water-soluble DNA-stabilized gold nanoparticles has also been described.[94c]

From methylarenes

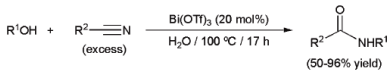
Quite recently, an unprecedented aerobic oxidative amidation reaction of methylarenes to primary amides in the presence of amorphous MnO_2 has been described (Scheme 23).[95] Although the best results were obtained using urea as the nitrogen source, aqueous ammonia proved to be also effective for the present MnO_2-catalyzed amidation. The process is believed to proceed through the initial ammoxidation of the methylarenes to generate the corresponding nitriles (*via* aldehydes), followed by hydration of the C≡N bond.

Catalytic synthesis of secondary and tertiary amides in water

Catalytic reactions leading to the formation of N-substituted amides in water have been comparatively much less studied. However, some synthetic approaches starting from nitriles, aryl halides, aldehydes, alcohols or alkynes are currently known, and they will be presented in this section.

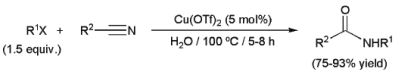
From nitriles

In addition to the well-known hydration reactions, which provide an easy access to primary amides (see above), different methodologies leading to secondary and tertiary amides have also been developed,[6] although they still remain little exploited. In this context, the Ritter reaction, based on the coupling of a nitrile with a carbocation (generated *in situ* from alcohols, halides or olefins) and further hydrolysis, offers an attractive entry to secondary amides (Scheme 24).[96] Since the



R^1 = alkyl group; R^2 = alkyl, aryl or heteroaromatic group (17 examples)

Scheme 25 $Bi(OTf)_3$-promoted Ritter reactions in water.



X = Cl, Br, I; R^1 = alkyl, allyl or benzyl group; R^2 = aryl or alkenyl group (18 examples)

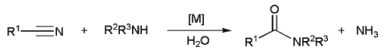
Scheme 26 Copper-catalyzed Ritter reaction between halides and nitriles.

stability of carbocations increases with the number of substituents, this procedure is especially useful for the preparation of bulky amides.

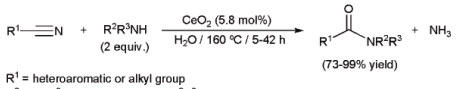
Traditionally promoted by stoichiometric amounts of a strong Brønsted acid (typically H_2SO_4), the process can also be catalyzed by Lewis acids under more environmentally friendly conditions.[96,97] In particular, some metallic salts showed to be suitable for performing the reaction in water. The first example reported was based on the coupling of alcohols with nitriles using 20 mol% of $Bi(OTf)_3$ (Scheme 25).[98] A wide range of aliphatic, aromatic and heteroaromatic nitriles with different substitution patterns was tolerated, giving rise in general to high yields of the corresponding amides. However, the process seems to be restricted to tertiary alcohols, such as *tert*-butanol, 2-methylbutan-2-ol, adamantol, 2-methyl-1-phenylpropan-2-ol and 1-methylcyclopentanol, in line with their propensity to generate carbocations. Interestingly, *tert*-butyl methyl ether could also be used as a carbocation precursor in this reaction, *via* ether bond cleavage. Although most of the reactions were carried out in pure water, in the case of poorly soluble solid nitriles, the addition of nitrobenzene as a co-solvent was required to achieve high conversions. It is also worth noting that the use of 20 mol% TfOH instead of $Bi(OTf)_3$ resulted in similar yields of the amides. This fact suggests that $Bi(OTf)_3$ generates TfOH under the reaction conditions employed, and that this is probably the effective catalyst involved in these transformations.

Related Ritter reactions between different benzonitriles and alcohols were successfully performed in water by Firouzabadi and Iranpoor using 5 mol% of the tungsten-oxoacid $H_3PW_{12}O_{40}$.[99] As in the precedent case, the transformation could be extended to protected alcohols (methyl-, trimethylsilyl- or tetrahydropyranyl-ethers) containing a tertiary alkyl or benzyl substituent subject to easy generation of a carbocation. This tungsten compound, and its molybdenum analogue, were also applied in the synthesis of *N*-bornyl amides through Ritter-type reactions of camphene with nitriles. However, in these cases, high catalyst loadings (50 mol%) were necessary to achieve only modest conversions.[100]

A more general copper-catalyzed procedure has been recently developed by Qu and co-workers employing halides and nitriles (Scheme 26).[101] In this case, not only tertiary alkyl substituents, but also primary and secondary ones, as well as allyl and benzyl groups, could be introduced on the nitrogen atom of the resulting amides. Among the different copper precursors evaluated, $Cu(OTf)_2$ showed the best catalytic performances, leading to the desired amides in high yields using a metal loading of only 5 mol%.



Scheme 27 The hydrolytic amidation of nitriles with amides.



R^1 = heteroaromatic or alkyl group
R^2 = H, R^3 = alkyl, aryl, benzyl; R^2R^3NH = morpholine (14 examples)

Scheme 28 CeO_2-promoted hydrolytic amidation of nitriles with amines in water.

Efficient couplings between 1-bromoadamantane and various alkyl-, alkenyl- or aryl-nitriles in water have also been described using the acetylacetonate derivative $[Mn(acac)_3]$ (3 mol%).[102] High selectivities in the corresponding *N*-(adamantan-1-yl)amides were reached at 130 °C in short reaction times (75–100% yield after 1–5 h). In contrast, the formation of adamantan-1-ol, by hydrolysis of the initial 1-bromoadamantane, became predominant at a lower temperature (70 °C). This alcohol is not an intermediate in the coupling process, since it was recovered unchanged after heating, even under harsh conditions (175 °C for 45 h), in the presence of the manganese(III) precursor and nitriles. Only when $[Mn(acac)_3]$ was associated with one equivalent of HBr, Ritter reactions between adamantan-1-ol and nitriles took place.

Metal-catalyzed hydrolytic amidation with amines represents an alternative synthetic method to access N-substituted amides starting from nitriles (Scheme 27). The process, first developed by Murahashi and co-workers,[34c,103] consists of the reaction between a nitrile, an amine and one equivalent of water to generate the corresponding amide along with ammonia. Although still little studied, this methodology has already shown to be applicable to a wide range of aliphatic and aromatic substrates, including both primary and secondary amines, and was also used in the synthesis of different alkaloids,[103] biologically active molecules[104] and polyamides.[103]

Most of these catalytic processes, promoted by ruthenium-,[34c,103] platinum-[105] or iron-based[104] homogeneous systems, have been carried out in wet organic solvents. However a few examples, recently reported by Shimizu and co-workers, were performed in pure water using heterogeneous catalysts.[106] In particular, they explored the activity and selectivity of different metal oxides in the coupling of heteroaromatic or aliphatic nitriles with primary amines, CeO_2 showing the best performances (Scheme 28). The reaction also proceeded efficiently with a secondary amine, such

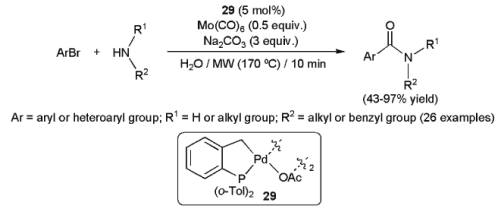
as morpholine. Interestingly, the insoluble catalyst could be separated by centrifugation and, after calcination at 300 °C, reused in at least three further runs.

Monitoring the course of the reactions, the authors evidenced that these hydrolytic amidations take place through the rapid hydration of the nitrile and further amination of the resulting primary amide, which furnishes the desired N-substituted amide with concomitant release of NH_3. In complete accord with these observations, Duchateau and co-workers also demonstrated that the hydrolytic amidation of pentanenitrile with *n*-hexylamine promoted by the ruthenium complex $[RuH_2(PPh_3)_4]$ or the heterogeneous catalyst ZrO_2 in water proceeds through the initial formation of the primary amide which either directly, or after hydrolysis to the corresponding carboxylic acid, reacts with the amine to give the *N*-hexylpentamide product.[107,108] These reaction pathways contrast with those generally proposed for processes realized in wet organic solvents where an amidine intermediate, which evolves to the final product by hydrolysis, is initially formed.[104,105]

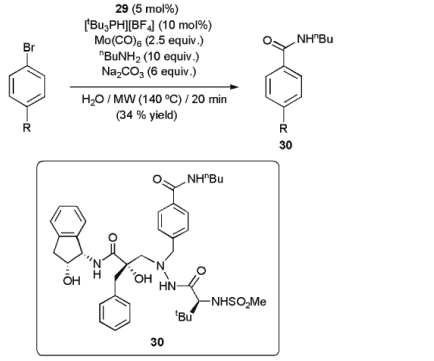
On the other hand, zirconia oxide was found to be a promising catalyst for the selective formation of the polyamide nylon-6 from 6-aminocapronitrile (H_2N–$(CH_2)_5$–C≡N), *via* intermolecular hydrolytic amidation.[108] However, although important advances have been realized in the field, the results obtained are still unsatisfactory since the presence of water required for the process prevented the build-up of the molecular weight. Formation of ε-caprolactam using Au NPs supported on TiO_2, through the intramolecular hydrolytic amidation of 6-aminocapronitrile (Scheme 10), has also been described.[55]

From aryl halides

Palladium-catalyzed aminocarbonylation of aryl halides has emerged in recent years as a powerful synthetic tool to generate secondary and tertiary amides. This three-component process, which involves the coupling between an aryl halide, a primary or secondary amine and CO, has been extensively studied in organic media with excellent results in terms of catalyst efficiency, selectivity and substrate scope.[109] In contrast, the development of such reactions in aqueous media has received much less attention. This is most likely due to the occurrence of competing hydroxycarbonylation of the aryl halides, in which water instead of the amine acts as a nucleophile, giving rise to the formation of undesirable carboxylic acids instead of the amides.[110] The first report on the amidation of aryl halides in water appeared in 2005.[111] Under optimal conditions (*i.e.* 5 mol% of the palladacycle complex **29**, microwave irradiation (170 °C), 1 equiv. of amine, 2 equiv. of aryl bromide, 3 equiv. of Na_2CO_3 and 0.5 equiv. of $Mo(CO)_6$ as the CO source), the hydroxycarbonylation could be minimized and the expected amides were generated in moderate to good yields, with only small amounts of the carboxylic acid by-products (Scheme 29). This protocol proved to be effective with a wide range of aryl bromides, bearing both electron-donating or -withdrawing functionalities, and primary or secondary aliphatic amines. However, we must note that highly sterically



Scheme 29 The first examples of aminocarbonylations of aryl halides in water.

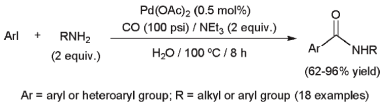


Scheme 30 Synthesis of the HIV-1 protease inhibitor **30** by aminocarbonylation.

demanding amines, such as di-*n*-butylamine, dramatically affected the conversion.

Remarkably, the palladacycle **29** was also operative in the aminocarbonylation of aryl chlorides,[112] usually poorly reactive.[109,113] Nevertheless, longer reaction times (30 min of MW irradiation at 170 °C) and the addition of $[^tBu_3PH][BF_4]$ to the medium were in these cases mandatory to reach acceptable conversions. Under the basic conditions employed, the phosphonium salt liberates tributylphosphine which presumably coordinates onto the metallic center, leading to a more catalytically active Pd-species.[114] Remarkably, this methodology was applied to the synthesis of compound **30**, a HIV-1 protease inhibitor, albeit only a modest yield could be achieved (Scheme 30).[112]

In line with the relative C–X bond energies, amidation of aryl iodides results by far easier than that of bromide or chloride derivatives. Thus, even phosphine-free catalytic systems, known to be less effective,[109] are suitable for promoting the transformation of ArI substrates. Accordingly, aromatic or heteroaromatic iodides were smoothly converted into the corresponding secondary amides, in water under a CO atmosphere (100 psi), using the commercially available palladium catalyst $Pd(OAc)_2$ (Scheme 31).[115] A low metal loading (0.5 mol%) and relatively smooth conditions (100 °C) were enough to attain high conversions. In addition, not only aliphatic amines, but also less nucleophilic anilines, with different



Scheme 31 $Pd(OAc)_2$-promoted aminocarbonylation of aryl iodides in water.

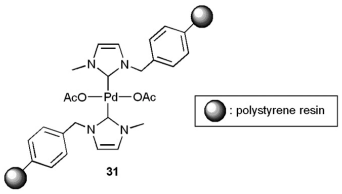


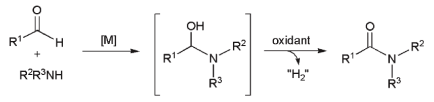
Fig. 6 Structure of the polymer-supported palladium catalyst **31**.

electron-donating or -withdrawing substituents, including the highly hindered *ortho*-substituted ones, were tolerated. Worthy of note, the catalytic performances attained in an aqueous medium exceeded those observed in polar or apolar organic solvents, as well as those under solvent-free conditions. Similar transformations of aryl iodides into the corresponding secondary or tertiary amides promoted by $Pd(OAc)_2$ have also been described using $[Mo(CO)_6]$ as the CO source under MW heating.[112]

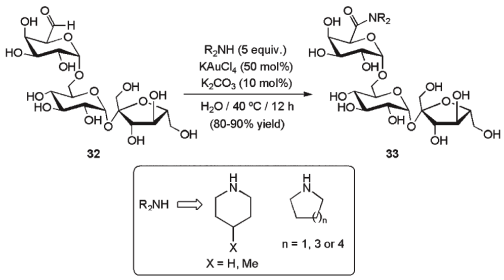
Very recently, Bhanage and co-workers have reported that the heterogeneous system **31**, based on a polystyrene-supported NHC–palladium complex (Fig. 6), associated with Na_2CO_3 features a similar reactivity to homogeneous $Pd(OAc)_2$, leading also to efficient couplings between aryl iodides, primary and secondary aliphatic or aromatic amines and gaseous CO.[116] High selectivities in the desired amides were attained, albeit small amounts of dehalogenation products of the aryl iodides were in all cases detected. This heterogeneous catalyst could be easily recycled by simple filtration without loss of activity and selectivity (up to four consecutive runs).

From aldehydes

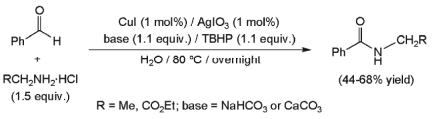
In 1966, Nagakawa and co-workers discovered that aromatic aldehydes can be directly converted into primary amides in the presence of ammonia and stoichiometric amounts of nickel peroxide.[117] Since this pioneering work, this oxidative amidation of aldehydes has been successfully extended to primary and secondary amines to furnish the corresponding N-substituted amides,[79] and the process could be performed under catalytic conditions in the presence of only small amounts of ruthenium,[118] palladium,[119] rhodium[120] or lanthanide[121] derivatives. In most of the cases, the transformation was assumed to take place through a sequential two-step mechanism involving the initial coupling between the aldehyde and the amine, followed by the subsequent oxidation of the resulting hemiaminal *via* formal H_2 release (Scheme 32). Accordingly, stoichiometric or excess amounts of an oxidant, such as aryl bromides, hydrogen peroxide, amine *N*-oxides,



Scheme 32 One-pot oxidative amidation of aldehydes with amines.



Scheme 33 Gold-catalyzed oxidative amidation of D-raffinose aldehyde **32**.

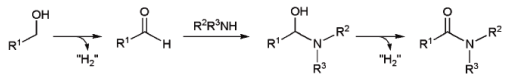


Scheme 34 Copper-promoted oxidative amidation of benzaldehyde.

hypervalent iodine compounds, *etc.*, are necessary to achieve good conversions. In some cases, the own aldehyde can act as the hydrogen acceptor and, therefore, three-fold excess with respect to the amine must be employed.[121] Formation of the desired amides is in these cases accompanied by the generation of alcohol and ester byproducts.

Although amidation reactions of aldehydes often require strict moisture-free conditions,[120a,121] with some catalytic systems the addition of a small quantity of water resulted crucial to reach high selectivities towards the amides.[118a,122,123] Despite this, examples of this reaction in a pure aqueous medium are extremely limited. In this context, Wong and co-workers reported recently the coupling of several cyclic diamines with the oligosaccharide derivative D-raffinose aldehyde **32** in water (Scheme 33).[122] The process, promoted by $KAuCl_4$ (50 mol%), delivered the corresponding tertiary amides **33** in good to excellent yields under smooth conditions (40 °C), demonstrating a high functional group tolerance. Using a 1 : 1 mixture of acetonitrile and water as the reaction medium, this catalytic system was also operative with only 1–10 mol% of $KAuCl_4$ for a wide range of aromatic and aliphatic aldehydes, including formaldehyde.[122]

Copper(I) iodide, combined with the additive $AgIO_3$ and a stoichiometric amount of the oxidant *tert*-butyl hydroperoxide (TBHP), was also found to be suitable to promote the amidation of benzaldehyde in water (Scheme 34).[123] The primary amines involved in the process were in this case generated



Scheme 35 One-pot transformation of alcohols to amides.

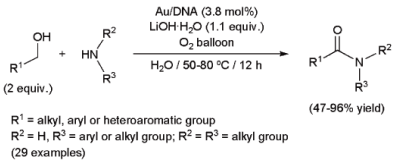
in situ from the appropriate hydrochloride salt in the presence of a base. Under these conditions, low to moderate yields of the desired secondary amides were reached. However, we must note that better results, in terms of both conversion and substrate scope, were attained performing the catalytic transformations in an organic solvent (MeCN) with only a small quantity of water (T-HYDRO®, *i.e.* aqueous TBHP, was in this case used as an oxidant).

From alcohols

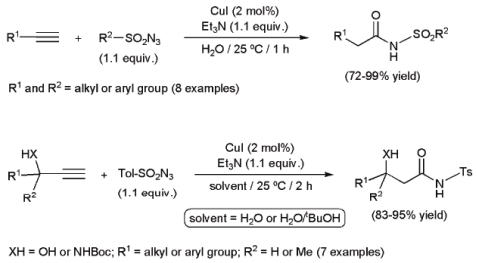
Closely related oxidative-amidation protocols have been developed starting from primary alcohols, *via in situ* generation of the corresponding aldehydes (Scheme 35). These chemical transformations, known for a long, were first applied to the synthesis of five-, six- and seven-membered ring lactams, through intramolecular couplings in aminoalcohols, with the aid of ruthenium or rhodium catalysts.[118a,124] At least, two-fold excess of a hydrogen acceptor, such as benzalacetone or acetone, was needed to observe full conversions.

Remarkably, this methodology regained popularity after Milstein's report on a highly atom-economical protocol that does not need a hydrogen acceptor.[92,93a] In this case, the two oxidation steps take place with formation of molecular hydrogen as the only by-product. Another important advantage of the Milstein's catalytic system, based on a PNN-pincer ruthenium complex, is the possibility to extend the reaction to intermolecular couplings of alcohols and amines. From then on, several ruthenium[93c,118c,125] and rhodium[93c,94a] complexes, associated or not with a hydrogen acceptor, as well as silver and gold nanoparticles,[126] proved to be effective for this reaction in organic media. The advances achieved in the field have rendered the process feasible at room temperature,[94a] allowing high functionality tolerance and the use of a wide range of aldehydes. Both primary and secondary amines, as well as NH_3, could be employed, although highly hindered non-cyclic *N*,*N*-disubstituted amines usually led to unsatisfactory conversions. Worthy of note, polyamines with both primary and secondary groups could react with complete chemoselectivity at the $-NH_2$ positions keeping untouched the NH functions, without the need of a protection/deprotection strategy.[125i]

Very recently, the first examples of this transformation in an aqueous medium have been reported by Wang and co-workers.[94c] They developed a new water-soluble catalytic system immobilizing gold nanoparticles on inexpensive natural fish sperm DNA (Au/DNA) (Scheme 36). In contrast with other systems which required cumbersome hydrogen acceptors, this nanohybrid catalyst cleanly proceeded under an oxygen atmosphere, water being then the sole by-product of the oxidation steps. Moreover, the Au–DNA system smoothly promoted the reaction of challenging anilines with different



Scheme 36 Synthesis of amides from alcohols by means of a gold nanohybrid catalyst.



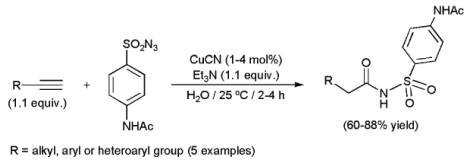
Scheme 37 Synthesis of amides from alkynes, sulfonyl azides and water.

aliphatic or aromatic aldehydes, in spite of their low nucleophilicity. Both primary and secondary amines were also tolerated, although steric hindrance strongly affected the efficiency. For example, high yields were observed for dimethylamine or piperidine, while the reaction completely failed starting from *N*-methylaniline. Although water-soluble, this nanocatalyst could only be recycled (up to five consecutive runs) by precipitation with EtOH and EtOAc and centrifugation, without significant loss in activity.

Polymer-supported gold nanoparticles were also successfully employed to convert alcohols into amides, albeit water–organic solvent mixtures were used in these cases as the reaction media.[94b,127]

From alkynes[128]

Several metal-catalyzed synthetic routes to N-substituted amides have been established starting from alkynes, such as aminocarbonylation reactions,[129] oxidative couplings with amines[130] or hydrative amidations with azides.[131] However, as far as we know, only the latter have found application in aqueous media. In fact, a great rate acceleration has been evidenced when performing the reactions in pure water, the catalytic activity and selectivity being significantly lower in 1 : 2 mixtures of water with ^{t}BuOH, DMF, MeCN or $CHCl_3$, or using $CHCl_3$ with only the stoichiometric quantity of water.[132] This three-component coupling, which involves a terminal alkyne, a sulfonyl azide and one equivalent of water, could be efficiently promoted by different copper(I) catalytic systems (Scheme 37). In particular, CuI combined with Et_3N delivered the corresponding secondary amides in good to excellent yields under smooth conditions (25 °C) and short reaction times (1 h). Aromatic and aliphatic substrates were readily



Scheme 38 CuCN-promoted gram-scale synthesis of sulfonyl amides.

transformed, with conversions being not significantly affected by electronic and/or steric variations. Not only 1-alkynes but also acetylene gas was allowed to react with the azides and water. However, a mixture of ^{t}BuOH and water was required in this case to enhance the solubility of HC≡CH in the medium. The synthetic protocol was also applicable to the preparation of synthetically useful β-hydroxy- or β-amino-amides starting from propargylic alcohols or *N*-Boc protected propargylamines, respectively (Scheme 37). But, once again, these reactions needed the use of ^{t}BuOH–water mixtures, transformations in pure water being so exothermic that thermal degradations took place lowering significantly the selectivity. Interestingly, enantiomerically enriched propargyl alcohols and amines were converted without racemization. Taking advantage of this property, a synthetic approach of chiral polyhydroxy amides, hardly accessible by other methods, was designed.

Copper(I) cyanide also proved to be active in the hydrative coupling of alkynes with the 4-acetamidobenzenesulfonyl azide, and was employed in the gram-scale production of sulfonyl amides in an aqueous medium (Scheme 38).[133] Aromatic, heteroaromatic and aliphatic 1-alkynes, as well as 1,7-octadiyne, were tolerated in the process.

Conclusions

Catalytic methods are nowadays the most powerful tools for the atom-economical and cost effective synthesis of amides. A large number of previously unavailable routes, starting from substrates other than the classical carboxylic acid derivatives, have been disclosed in recent years with the aid of transition metals.[6] In line with the increasing environmental concerns, remarkable efforts have also been devoted to the development of these catalytic processes in the aqueous medium, since water is the most reliable alternative to the harmful petroleum-based solvents.[8] Advances reached in the field have been comprehensively outlined in this review article, from which the following conclusions can be drawn. Formation of primary amides has been comparatively much more studied than that of N-substituted amides, with most of the published work being devoted to the catalytic hydration of nitriles. For this particular transformation, a large number of homogeneous and heterogeneous catalysts, as well as nanocatalysts, able to operate efficiently in water and showing a wide substrate scope are now available. Examples of recyclable systems, and of catalysts active under mild temperature regimes, are also increasingly common for this reaction. Several synthetic methods of primary amides in water that make use of alternative starting materials (aldoximes, aldehydes, amines, azides, alcohols or even methylarenes) have also appeared in recent years. However, in most of the cases, the processes have been comparatively much less studied than in organic media, and the number of catalysts currently active in water is very limited. The same can be said for the synthesis of secondary and tertiary amides, where the methods described in an aqueous medium, regardless of the starting materials employed, present a low generality. Chemists should take note of the opportunities existing in the field, and devise new catalytic systems for these poorly studied transformations. The authors hope that this comprehensive account will stimulate further work in this direction.

Acknowledgements

Financial support by the Ministerio de Economía y Competitividad of Spain (Projects CTQ2010-14796/BQU and CSD2007-00006) is gratefully acknowledged.

Notes and references

1 See, for example: (*a*) *The Chemistry of Amides*, ed. J. Zabicky, Wiley-Interscience, New York, 1970; (*b*) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*, ed. A. Greenberg, C. M. Breneman and J. F. Liebman, John Wiley & Sons, New York, 2000; (*c*) *Polyesters and Polyamides*, ed. B. L. Deopura, B. Gupta, M. Joshi and R. Alagirusami, CRC Press, Boca Raton, 2008; (*d*) I. Johansson, in *Kirk-Othmer Encyclopedia of Chemical Technology*, JohnWiley & Sons, New York, 2004, vol. 2, pp. 442–463.

2 (*a*) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337; (*b*) See also: R. W. Dugger, J. A. Ragan and D. H. B. Ripin, *Org. Process Res. Dev.*, 2005, **9**, 253.

3 See, for example: (*a*) *Methoden Org. Chem. (Houben Weyl)*, ed. D. Dopp and H. Dopp, Thieme Verlag, Stuttgart, 1985, vol. E5 { (2)}, pp. 1024–1031; (*b*) P. D. Bailey, T. J. Mills, R. Pettecrew and R. A. Price, in *Comprehensive Organic Functional Group Transformations II*, ed. A. R. Katritzky and R. J. K. Taylor, Elsevier, Oxford, 2005, vol. 5, pp. 201–294; (*c*) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606.

4 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411.

5 A drastic waste reduction in classical amide syntheses from carboxylic acids and amines has been recently achieved by using a continuous method based on the recycling of the reaction mixture: K. Thalluri,

K. C. Nadimpally, A. Paul and B. Mandal, *RSC Adv.*, 2012, **2**, 6838.

6 (*a*) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405; (*b*) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471.

7 D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133.

8 See, for example: (*a*) W. M. Nelson, in *Green Solvents for Chemistry: Perspectives and Practice*, Oxford University Press, New York, 2003; (*b*) J. H. Clark and S. J. Taverner, *Org. Process Res. Dev.*, 2007, **11**, 149; (*c*) F. M. Kerton, in *Alternative Solvents for Green Chemistry*, RSC Publishing, Cambridge, 2009.

9 (*a*) P. T. Anastas and J. C. Warner, in *Green Chemistry Theory and Practice*, Oxford University Press, Oxford, 1998; (*b*) A. S. Matlack, in *Introduction to Green Chemistry*, Marcel Dekker, New York, 2001; (*c*) *Handbook of Green Chemistry and Technology*, ed. J. H. Clark and D. J. Macquarrie, Blackwell Publishing, Abingdon, 2002; (*d*) M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**, 807; (*e*) M. Lancaster, in *Green Chemistry: An Introductory Text*, RSC Publishing, Cambridge, 2010.

10 See, for example: (*a*) C.-J. Li, *Chem. Rev.*, 1993, **93**, 2023; (*b*) A. Lubineau, J. Auge and Y. Queneau, *Synthesis*, 1994, 741; (*c*) *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie Academic & Professional, London, 1998; (*d*) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751; (*e*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095; (*f*) C. K. Z. Andrade and L. M. Alves, *Curr. Org. Chem.*, 2005, **9**, 195; (*g*) C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68; (*h*) L. Chen and C.-J. Li, *Adv. Synth. Catal.*, 2006, **348**, 1459; (*i*) C. I. Herrerías, X. Yao, Z. Li and C.-J. Li, *Chem. Rev.*, 2007, **107**, 2546; (*j*) C.-J. Li and T. H. Chan, in *Comprehensive Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 2007; (*k*) *Organic Reactions in Water: Principles, Strategies and Applications*, ed. U. M. Lindström, Blackwell Publishing, Oxford, 2007; (*l*) *Handbook of Green Chemistry (vol. 5)*, ed. P. T. Anastas and C.-J. Li, Wiley-VCH, Weinheim, 2010; (*m*) M.-O. Simon and C.-J. Li, *Chem. Soc. Rev.*, 2012, **41**, 1415; (*n*) *Water in Organic Synthesis*, ed. S. Kobayashi, Thieme, Stuttgart, 2012.

11 See, for example: (*a*) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 1998; (*b*) *Aqueous Organometallic Catalysis*, ed. I. T. Horváth and F. Joó, Kluwer, Dordrecht, 2001; (*c*) *Recoverable and Recyclable Catalysts*, ed. M. Benaglia, John Wiley & Sons, Chichester, 2009; (*d*) *Metal-Catalyzed Reactions in Water*, ed. P. Dixneuf and V. Cadierno, Wiley-VCH, Weinheim, 2013.

12 See, for example: (*a*) J. Yeo, S. Y. Kim, S. Kim, D. Y. Ryu, T.-H. Kim and M. J. Park, *Nanotechnology*, 2012, **23**, 245703/1; (*b*) B. Al-Rashdi, C. Somerfield and N. Hilal, *Sep. Purif. Rev.*, 2011, **40**, 209; (*c*) A. K. Goyal, E. S. Johal and G. Rath, *Curr. Nanosci.*, 2011, 7, 460; (*d*) *Nanotechnology in Water Treatment Applications*, ed. T. E. Cloete, M. de Kwaadsteniet, M. Botes and J. M. López-Romero, Caister Academic Press, Norfolk, 2010.

13 See, for example: (*a*) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 1957, 2000; (*b*) P. J. Steynberg, Z. Denga, R. Steyn, B. C. Bezuidenhout and N. L. Stark, *PCT Int. Appl.*, WO 0026178, 2000.

14 For selected reviews covering the use of enzymes in catalytic nitrile hydrations, see: (*a*) M. Kobayashi and S. Shimizu, *Curr. Opin. Chem. Biol.*, 2000, **4**, 95; (*b*) I. Endo, M. Nojori, M. Tsujimura, M. Nakasako, S. Nagashima, M. Yohda and M. J. Odaka, *J. Inorg. Biochem.*, 2001, **83**, 247; (*c*) J. A. Kovacs, *Chem. Rev.*, 2004, **104**, 825; (*d*) G. De Santis and R. Di Cosimo, in *Biocatalysis for the Pharmaceutical Industry: Discovery, Development and Manufacturing*, ed. J. Tao, G.-Q. Lin and A. Liese, Wiley-VCH, Weinheim, 2009, pp. 153–181; (*e*) S. Prasad and T. C. Bhalla, *Biotechnol. Adv.*, 2010, **28**, 725.

15 See, for example: (*a*) H. Yamada and M. Kobayashi, *Biosci., Biotechnol., Biochem.*, 1996, **60**, 1391; (*b*) S. van Pelt, F. van Rantwijk and R. A. Sheldon, in *Focus in Catalysis Applications* {supplement to *Chimica Oggi/Chemistry Today*}, Teknoscienze Srl, Milano, 2008, vol. 26, pp. 2–4; (*c*) S. Sanchez and A. L. Demain, *Org. Process Res. Dev.*, 2011, **15**, 224; (*d*) B. Li, J. Su and J. Tao, *Org. Process Res. Dev.*, 2011, **15**, 291.

16 For reviews on metal-catalyzed nitrile hydration reactions, see: (*a*) A. W. Parkins, *Platinum Metals Rev.*, 1996, **40**, 169; (*b*) V. Y. Kukushkin and A. J. L. Pombeiro, *Chem. Rev.*, 2002, **102**, 1771; (*c*) N. A. Bokach and V. Y. Kukushkin, *Russ. Chem. Rev.*, 2005, **74**, 153; (*d*) V. Y. Kukushkin and A. J. L. Pombeiro, *Inorg. Chim. Acta*, 2005, **358**, 1; (*e*) T. J. Ahmed, S. M. M. Knapp and D. R. Tyler, *Coord. Chem. Rev.*, 2011, **255**, 949.

17 (*a*) T. Ghaffar and A. W. Parkins, *Tetrahedron Lett.*, 1995, **36**, 8657; (*b*) A. W. Parkins and T. Ghaffar, *PCT Int. Appl.*, WO 9630379, 1996; (*c*) T. Ghaffar and A. W. Parkins, *J. Mol. Catal. A: Chem.*, 2000, **160**, 249.

18 Examples of the synthetic applications of this catalyst can be found in: (*a*) J. Akisanya, A. W. Parkins and J. W. Steed, *Org. Process Res. Dev.*, 1998, **2**, 274; (*b*) A. Papakyprianou, A. W. Parkins, P. D. Prince and J. W. Steed, *Org. Prep. Proced. Int.*, 2002, **34**, 436; (*c*) M. North, A. W. Parkins and A. N. Shariff, *Tetrahedron Lett.*, 2004, **45**, 7625; (*d*) X.-B. Jiang, A. J. Minnaard, B. L. Feringa and J. G. de Vries, *J. Org. Chem.*, 2004, **69**, 2327; (*e*) R. G. Gieling and M. B. Groen, *PCT Int. Appl.*, WO 2006097342, 2006; (*f*) T. J. Greshock and R. L. Funk, *Org. Lett.*, 2006, **8**, 2643; (*g*) A. Myers, S. B. Herzon, J. E. Wulff, R. Siegrist, J. Svenda and M. A. Zajac, *PCT Int. Appl.*, WO 2006102097, 2006; (*h*) X. Jiang, N. Williams and J. K. De Brabander, *Org. Lett.*, 2007, **9**, 227; (*i*) B. Wang, F. Wu, Y. Wang, X. Liu and L. Deng, *J. Am. Chem. Soc.*, 2007, **129**, 768; (*j*) T. Kan, Y. Kawamoto, T. Asakawa, T. Furuta and T. Fukuyama, *Org. Lett.*, 2008, **10**, 169; (*k*) L. Tafesse, *PCT Int. Appl.*,

WO 2008133973, 2008; (*l*) R. A. Jones and M. J. Krische, *Org. Lett.*, 2009, **11**, 1849; (*m*) D. R. Saito, D. D. Long, P. van Dyke, T. J. Church, L. Jiang and B. Frieman, *PCT Int. Appl.*, WO 2009029256, 2009; (*n*) L. E. Brown, Y. R. Landaverry, J. R. Davies, K. A. Milinkevich, S. Ast, J. S. Carlson, A. G. Oliver and J. P. Konopelski, *J. Org. Chem.*, 2009, 74, 5405; (*o*) F. D. J. Cortez and R. Sarpong, *Org. Lett.*, 2010, **12**, 1428; (*p*) C.-K. Mai, M. F. Sammons and T. Sammakia, *Angew. Chem., Int. Ed.*, 2010, **49**, 2397; (*q*) T. A. Brugel, R. W. Smith, M. Balestra, C. Becker, T. Daniels, G. M. Koether, S. R. Throner, L. M. Panko, D. G. Brown, R. Liu, J. Gordon and M. F. Peters, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5405; (*r*) M. K. M. Tun, D.-J. Wüstmann and S. B. Herzon, *Chem. Sci.*, 2011, **2**, 2251; (*s*) L. Yao, B. Pitta, P. C. Ravikumar, M. Purzycki and F. F. Fleming, *J. Org. Chem.*, 2012, 77, 3651; (*t*) R. S. Andrews, J. L. Becker and M. R. Gagné, *Angew. Chem., Int. Ed.*, 2012, **51**, 4140.

19 T. J. Ahmed, B. R. Fox, S. M. M. Knapp, R. B. Yelle, J. J. Juliette and D. R. Tyler, *Inorg. Chem.*, 2009, **48**, 7828.

20 (*a*) K. L. Breno, M. D. Pluth and D. R. Tyler, *Organometallics*, 2003, **22**, 1203; (*b*) K. L. Breno, M. D. Pluth, C. W. Landorf and D. R. Tyler, *Organometallics*, 2004, **23**, 1738; (*c*) K. L. Breno, T. J. Ahmed, M. D. Pluth, C. Balzarek and D. R. Tyler, *Coord. Chem. Rev.*, 2006, **250**, 1141; (*d*) T. J. Ahmed, L. V. Zakharov and D. R. Tyler, *Organometallics*, 2007, **26**, 5179; (*e*) T. J. Ahmed and D. R. Tyler, *Organometallics*, 2008, **27**, 2608.

21 E. Tílvez, M. I. Menéndez and R. López, *Organometallics*, 2012, **31**, 1618.

22 (*a*) M. G. Crestani, A. Arévalo and J. J. García, *Adv. Synth. Catal.*, 2006, **348**, 732; (*b*) A. Arévalo and J. J. García, *Eur. J. Inorg. Chem.*, 2010, 4063.

23 C. Crisóstomo, M. G. Crestani and J. J. García, *J. Mol. Catal. A: Chem.*, 2007, **266**, 139.

24 (*a*) C. Crisóstomo, M. G. Crestani and J. J. García, *Chim. Oggi*, 2009, **27**, 36; (*b*) C. Crisóstomo, M. G. Crestani and J. J. García, *Inorg. Chim. Acta*, 2010, **363**, 1092.

25 M. G. Crestani and J. J. García, *J. Mol. Catal. A: Chem.*, 2009, **299**, 26.

26 M. N. Kopylovich, V. Y. Kukushkin, M. Haukka, J. J. R. Fraústo da Silva and A. J. L. Pombeiro, *Inorg. Chem.*, 2002, **41**, 4798.

27 See, for example: (*a*) T. Oshiki, H. Yamashita, K. Sawada, M. Utsunomiya, K. Takahashi and K. Takai, *Organometallics*, 2005, **24**, 6287; (*b*) T. Šmejkal and B. Breit, *Organometallics*, 2007, **26**, 2461; (*c*) T. Oshiki, I. Hyodo and A. Ishizuka, *J. Synth. Org. Chem. Jpn.*, 2010, **68**, 41; (*d*) M. Muranaka, I. Hyodo, W. Okumura and T. Oshiki, *Catal. Today*, 2011, **164**, 552; (*e*) P. Daw, A. Sinha, S. M. W. Rahaman, S. Dinda and J. K. Bera, *Organometallics*, 2012, **31**, 3790.

28 For leading accounts and reviews on bifunctional catalysts, see: (*a*) D. B. Grotjahn, *Chem.–Eur. J.*, 2005, **11**, 7146; (*b*) A. S. Borovik, *Acc. Chem. Res.*, 2005, **38**, 54; (*c*) T. Ikariya, K. Murata and R. Noyori, *Org. Biomol. Chem.*, 2006, **4**, 393; (*d*) T. Ikariya and A. J. Blacker, *Acc. Chem. Res.*, 2007, **40**, 1300; (*e*) D. B. Grotjahn, *Dalton Trans.*, 2008, 6497; (*f*) D. B. Grotjahn, *Chem. Lett.*, 2010, **39**, 908; (*g*) D. B. Grotjahn, *Pure Appl. Chem.*, 2010, **82**, 635; (*h*) T. Ikariya and I. D. Gridnev, *Top. Catal.*, 2010, **53**, 894; (*i*) D. B. Grotjahn, *Top. Catal.*, 2010, **53**, 1009.

29 V. Cadierno, J. Francos and J. Gimeno, *Chem.–Eur. J.*, 2008, **14**, 6601.

30 V. Cadierno, J. Díez, J. Francos and J. Gimeno, *Chem.–Eur. J.*, 2010, **16**, 9808.

31 Performing the catalytic reactions in a water–glycerol mixture (1 : 1 v/v), this catalyst could also be recycled by selective extraction of the reaction products with ethyl acetate. A. E. Díaz-Álvarez, R. García-Álvarez, P. Crochet and V. Cadierno, in *Glycerol: Production, Structure and Applications*, ed. M. D. S. Silva and P. C. Ferreira, Nova Science Publishers, New York, 2012, pp. 249–262.

32 W.-C. Lee and B. J. Frost, *Green Chem.*, 2012, **14**, 62.

33 (*a*) R. García-Álvarez, J. Francos, P. Crochet and V. Cadierno, *Tetrahedron Lett.*, 2011, **52**, 4218; (*b*) R. García-Álvarez, J. Díez, P. Crochet and V. Cadierno, *Organometallics*, 2011, **30**, 5442.

34 Such a tandem process promoted by $[RuH_2(PPh_3)_4]$ in an organic medium was earlier described by Murahashi and co-workers: (*a*) S.-I. Murahashi, S. Sasao, E. Saito and T. Naota, *J. Org. Chem.*, 1992, **57**, 2521; (*b*) S.-I. Murahashi, S. Sasao, E. Saito and T. Naota, *Tetrahedron*, 1993, **49**, 8805; (*c*) S.-I. Murahashi and H. Takaya, *Acc. Chem. Res.*, 2000, **33**, 225.

35 S. M. M. Knapp, T. J. Sherbow, J. J. Juliette and D. R. Tyler, *Organometallics*, 2012, **31**, 2941.

36 R. García-Álvarez, J. Díez, P. Crochet and V. Cadierno, *Organometallics*, 2010, **29**, 3955.

37 R. García-Álvarez, S. E. García-Garrido, J. Díez, P. Crochet and V. Cadierno, *Eur. J. Inorg. Chem.*, 2012, 4218.

38 Modest catalytic activities were also achieved with the related complexes $[RuCl_2(\eta^6\text{-arene})(PR_3)]$ (arene = C_6H_6, *p*-cymene; PR_3 = PPh_3, P^iPr_3, $P(OEt)_3$, $PPh(OEt)_2$, $PPh_2(OEt)$). In addition, surfactants were needed to ensure the solubilization of these catalysts in water: A. Cavarzan, A. Scarso and G. Strukul, *Green Chem.*, 2010, **12**, 790.

39 Z. Li, L. Wang and X. Zhou, *Adv. Synth. Catal.*, 2012, **354**, 584.

40 (*a*) G. Villain, P. Kalck and A. Gaset, *Tetrahedron Lett.*, 1980, **21**, 2901; (*b*) G. Villain, G. Constant, A. Gaset and P. Kalck, *J. Mol. Catal.*, 1980, 7, 355; (*c*) G. Villain, A. Gaset and P. Kalck, *J. Mol. Catal.*, 1981, **12**, 103.

41 M. A. Bennett and T. Yoshida, *J. Am. Chem. Soc.*, 1973, **95**, 3030.

42 C. S. Chin, S. Y. Kim, K.-S. Joo, G. Won and D. Chong, *Bull. Korean Chem. Soc.*, 1999, **20**, 535.

43 W. K. Fung, X. Huang, M. L. Man, S. M. Ng, M. Y. Hung, Z. Lin and C. P. Lau, *J. Am. Chem. Soc.*, 2003, **125**, 11539.

44 M. C. K.-B. Djoman and A. N. Ajjou, *Tetrahedron Lett.*, 2000, 4845.

45 M. G. Crestani, A. Steffen, A. M. Kenwright, A. S. Batsanov, J. A. K. Howard and T. B. Marder, *Organometallics*, 2009, **28**, 2904.

46 E. Cariati, C. Dragonetti, L. Manassero, D. Roberto, F. Tessore and E. Lucenti, *J. Mol. Catal. A: Chem.*, 2003, **204–205**, 279.

47 M. Martín, H. Horváth, E. Sola, Á. Kathó and F. Joó, *Organometallics*, 2009, **28**, 561.

48 (*a*) I. N. Stepanenko, B. Cebrián-Losantos, V. B. Arion, A. A. Krokhin, A. A. Nazarov and B. K. Keppler, *Eur. J. Inorg. Chem.*, 2007, 400; (*b*) S. M. Ashraf, I. Berger, A. A. Nazarov, C. G. Hartinger, M. P. Koroteev, E. E. Nifant'ev and B. K. Keppler, *Chem. Biodiversity*, 2008, **5**, 1640; (*c*) S. M. Ashraf, W. Kandioller, M. G. Mendoza-Ferri, A. A. Nazarov, C. G. Hartinger and B. K. Keppler, *Chem. Biodiversity*, 2008, **5**, 2060.

49 See, for example: (*a*) *Nanoparticles and Catalysis*, ed. D. Astruc, Wiley-VCH, Weinheim, 2007; (*b*) V. Polshettiwar and R. S. Varma, *Green Chem.*, 2010, **12**, 743; (*c*) G. A. Somorjai and Y. Li, *Top. Catal.*, 2010, **53**, 832; (*d*) H. Cong and J. A. Porco, *ACS Catal.*, 2012, **2**, 65; (*e*) S. B. Kalidindi and B. R. Jagirdar, *ChemSusChem*, 2012, **5**, 65.

50 (*a*) N. Toshima and Y. Wang, *Chem. Lett.*, 1993, **22**, 1611; (*b*) N. Toshima and Y. Wang, *Langmuir*, 1994, **10**, 4574; (*c*) Y. Wang, H. Liu and N. Toshima, *J. Phys. Chem.*, 1996, **100**, 19533; (*d*) N. Toshima, P. Lu and Y. Wang, *Stud. Surf. Sci. Catal.*, 2011, **132**, 243.

51 For related works using Cu/Ni alloys, Cu NPs, and copper suspended on PVP or silica-magnesia see: (*a*) H. Hayashi, H. Nishi, Y. Watanabe and T. Okazaki, *J. Catal.*, 1981, **69**, 44; (*b*) N. Ravindranathan, N. Kalyanam and S. Sivaram, *J. Org. Chem.*, 1982, **47**, 4812; (*c*) K. Sugiyama, H. Miura, Y. Watanabe, Y. Ukai and T. Matsuda, *Chem. Lett.*, 1986, **15**, 47; (*d*) K. Sugiyama, H. Miura, Y. Watanabe, Y. Ukai and T. Matsuda, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 1579.

52 (*a*) A. Ishizuka, Y. Nakazaki and T. Oshiki, *Chem. Lett.*, 2009, **38**, 360; (*b*) T. Oshiki and A. Ishizuka, *Jpn. Kokai Tokkyo Koho*, JP 2009214099, 2009.

53 (*a*) T. Mitsudome, Y. Mikami, H. Mori, S. Arita, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Chem. Commun.*, 2009, 3258; (*b*) A. Y. Kim, H. S. Bae, S. Park, S. Park and K. H. Park, *Catal. Lett.*, 2011, **141**, 685.

54 K. Shimizu, N. Imaiida, K. Sawabe and A. Satsuma, *Appl. Catal., A*, 2012, **421–422**, 114.

55 Y.-M. Liu, L. He, M.-M. Wang, Y. Cao, H.-Y. He and K.-N. Fan, *ChemSusChem*, 2012, **5**, 1392.

56 (*a*) The use of gold NPs supported on different metal-oxides has been covered by a recent patent: Y. Cao, Y. Liu and L. He, *Faming Zhuanli Shenqing*, CN 102285850, 2011; (*b*) A catalytic system consisting of hydrotalcite-clay supported nickel nanoparticles, active in an aqueous medium, has also very recently appeared: T. Subramanian and K. Pitchumani, *Catal. Commun.*, 2012, **29**, 109.

57 V. Polshettiwar and R. S. Varma, *Chem.–Eur. J.*, 2009, **15**, 1582.

58 S. E. García-Garrido, J. Francos, V. Cadierno, J. M. Basset and V. Polshettiwar, *ChemSusChem*, 2011, **4**, 104.

59 R. B. N. Baig and R. S. Varma, *Chem. Commun.*, 2012, **48**, 6220.

60 (*a*) E. J. Gasson and D. J. Hadley, *US Pat.*, US2904552, 1959; (*b*) S. K. Roy, S. C. Ray and P. K. Ray, *J. Indian Chem. Soc.*, 1980, **57**, 195; (*c*) H. Miura, K. Sugiyama, S. Kawakami, T. Aoyama and T. Matsuda, *Chem. Lett.*, 1982, **11**, 183; (*d*) E. N. Zil'berman, *Russ. Chem. Rev.*, 1984, **53**, 900; (*e*) S. C. Roy, P. Dutta, L. N. nandy, S. K. Roy, P. Samuel, S. M. Pillai, V. K. Kaushik and M. Ravindranathan, *Appl. Catal., A*, 2005, **290**, 175; (*f*) Y. Gangarajula and B. Gopal, *Chem. Lett.*, 2012, **41**, 101; (*g*) M. Tamura, H. Wakasugi, K.-I. Shimizu and A. Satsuma, *Chem.–Eur. J.*, 2011, **17**, 11428; (*h*) K. Yamaguchi, Y. Wang, H. Kobayashi and N. Mizuno, *Chem. Lett.*, 2012, **41**, 574.

61 (*a*) K. Yamaguchi, M. Matsushita and N. Mizuno, *Angew. Chem., Int. Ed.*, 2004, **43**, 1576; (*b*) K. Yamaguchi and N. Mizuno, *Synlett*, 2010, 2365.

62 K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani and K. Kaneda, *Chem. Commun.*, 2001, 461.

63 G. K. S. Prakash, S. B. Munoz, A. Papp, K. Masood, I. Bychinskaya, T. Mathew and G. A. Olah, *Asian J. Org. Chem.*, 2012, **1**, 146.

64 For reviews on the Beckmann rearrangement, see: (*a*) R. R. Kumar, K. A. Vanithan and M. Balasubramanian, in *Name Reactions for Homologations – Part 2*, ed. J. J. Li, John Wiley & Sons, Hoboken, 2009, pp. 274–292; (*b*) R. E. Gawley, *Org. React.*, 1988, **35**, 1.

65 (*a*) E. C. Horning and V. L. Stromberg, *J. Am. Chem. Soc.*, 1952, **74**, 5151; (*b*) D. S. Hoffenberg and C. R. Hauser, *J. Org. Chem.*, 1955, **20**, 1496; (*c*) L. Field, P. B. Hughmark, S. H. Shumaker and W. S. Marshall, *J. Am. Chem. Soc.*, 1961, **83**, 1983.

66 (*a*) A. J. Leusink, T. G. Meerbeek and J. G. Noltes, *Recl. Trav. Chim. Pays-Bas*, 1976, **95**, 123; (*b*) A. J. Leusink, T. G. Meerbeek and J. G. Noltes, *Recl. Trav. Chim. Pays-Bas*, 1977, **96**, 142; (*c*) C. L. Allen, S. Davulcu and J. M. J. Williams, *Org. Lett.*, 2010, **12**, 5096.

67 (*a*) T. Setsuda, *Jpn. Kokai Tokkyo Koho*, JP 52128302, 1977; (*b*) S. Komiya, H. Shimazu and T. Tamashima, *Jpn. Kokai Tokkyo Koho*, JP 2003342245, 2003.

68 (*a*) S. K. Sharma, S. D. Bishopp, C. L. Allen, R. Lawrence, M. J. Bamford, A. A. Lapkin, P. Plucinski, R. J. Watson and J. M. J. Williams, *Tetrahedron Lett.*, 2011, **52**, 4252; (*b*) G. Saidulu, N. Anand, K. S. R. Rao, A. Burri, S.-E. Park and D. R. Burri, *Catal. Lett.*, 2011, **141**, 1865; (*c*) A. Martínez-Asensio, M. Yus and D. J. Ramón, *Tetrahedron*, 2012, **68**, 3948.

69 R. S. Ramón, J. Bosson, S. Díez-González, N. Marion and S. P. Nolan, *J. Org. Chem.*, 2010, **75**, 1197.

70 (*a*) N. A. Owston, A. J. Parker and J. M. J. Williams, *Org. Lett.*, 2007, **9**, 3599; (*b*) D. Gnanamgari and R. H. Crabtree,

Organometallics, 2009, **28**, 922; (*c*) J. F. Hull, S. T. Hilton and R. H. Crabtree, *Inorg. Chim. Acta*, 2010, **363**, 1243; (*d*) P. Kumar, A. K. Singh, R. Pandey and D. S. Pandey, *J. Organomet. Chem.*, 2011, **696**, 3454.

71 (*a*) S. Park, Y. Choi, H. Han, S. H. Yang and S. Chang, *Chem. Commun.*, 2003, 1936; (*b*) M. Kim, J. Lee, H.-Y. Lee and S. Chang, *Adv. Synth. Catal.*, 2009, **351**, 1807.

72 N. A. Owston, A. J. Parker and J. M. J. Williams, *Org. Lett.*, 2007, **9**, 73.

73 (*a*) A. Mishra, A. Ali, S. Upreti and R. Gupta, *Inorg. Chem.*, 2008, **47**, 154; (*b*) C. L. Allen, C. Burel and J. M. J. Williams, *Tetrahedron Lett.*, 2010, **51**, 2724.

74 Selective dehydration of aldoximes to nitriles with the aid of transition metals is a well-known process. Recent examples can be found in: (*a*) H. S. Kim, S. Kim and J. N. Kim, *Tetrahedron Lett.*, 2009, **50**, 1717; (*b*) N. Jiang and A. J. Ragauskas, *Tetrahedron Lett.*, 2010, **51**, 4479; (*c*) Y.-T. Li, B. S. Liao, H.-P. Chen and S.-T. Liu, *Synthesis*, 2011, 2639.

75 Catalytic hydration of nitriles to amides using aldoximes as the water source has been described in: (*a*) E. S. Kim, H. S. Kim and J. N. Kim, *Tetrahedron Lett.*, 2009, **50**, 2973; (*b*) J. Lee, M. Kim, S. Chang and H.-Y. Lee, *Org. Lett.*, 2009, **11**, 5598; (*c*) E. S. Kim, H. S. Lee, S. H. Kim and J. N. Kim, *Tetrahedron Lett.*, 2010, **51**, 1598; (*d*) E. S. Kim, Y. M. Kim and J. N. Kim, *Bull. Korean Chem. Soc.*, 2010, **31**, 700; (*e*) Á. Kiss and Z. Hell, *Tetrahedron Lett.*, 2011, **52**, 6021; (*f*) X.-Y. Ma, Y. He, Y.-L. Hu and M. Lu, *Tetrahedron Lett.*, 2012, **53**, 449; (*g*) X. Ma, Y. He, P. Wang and M. Lu, *Appl. Organomet. Chem.*, 2012, **26**, 377.

76 C. L. Allen, R. Lawrence, L. Emmett and J. M. J. Williams, *Adv. Synth. Catal.*, 2011, **353**, 3262.

77 (*a*) H. Fujiwara, Y. Ogasawara, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2007, **46**, 5202; (*b*) H. Fujiwara, Y. Ogasawara, M. Kotani, K. Yamaguchi and N. Mizuno, *Chem.–Asian J.*, 2008, **3**, 1715.

78 R. García-Álvarez, A. E. Díaz-Álvarez, J. Borge, P. Crochet and V. Cadierno, *Organometallics*, 2012, **31**, 6482.

79 For a recent review on oxidative esterification and amidation of aldehydes, see: K. Ekoue-Kovi and C. Wolf, *Chem.–Eur. J.*, 2008, **14**, 6302.

80 N. C. Ganguly, S. Roy and P. Mondal, *Tetrahedron Lett.*, 2012, **53**, 1413.

81 B. K. Allam and K. N. Singh, *Tetrahedron Lett.*, 2011, **52**, 5851.

82 R. R. Gowda and D. Chakraborty, *Eur. J. Org. Chem.*, 2011, 2226.

83 (*a*) N. Raja, M. U. Raja and R. Ramesh, *Inorg. Chem. Commun.*, 2012, **19**, 51; (*b*) R. N. Prabhu and R. Ramesh, *RSC Adv.*, 2012, **2**, 4515.

84 M. A. Ali and T. Punniyamurthy, *Adv. Synth. Catal.*, 2010, **352**, 288.

85 For a recent review, see: M. T. Schümperli, C. Hammond and I. Hermans, *ACS Catal.*, 2012, **2**, 1108.

86 (*a*) R. Tang, S. E. Diamond, N. Neary and F. Mares, *J. Chem. Soc., Chem. Commun.*, 1978, 562; (*b*) A. Nishinaga, T. Shimizu and T. Matsuura, *J. Chem. Soc., Chem. Commun.*, 1979, 970; (*c*) K.-I. Tanaka, S. Yoshifuji and Y. Nitta, *Chem. Pharm. Bull.*, 1988, **36**, 3125.

87 (*a*) J. W. Kim, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2008, **47**, 9249; (*b*) Y. Wang, H. Kobayashi, K. Yamaguchi and N. Mizuno, *Chem. Commun.*, 2012, **48**, 2642; (*c*) K. Yamaguchi, Y. Wang and N. Mizuno, *Chem. Lett.*, 2012, **41**, 633; (*d*) W. Xu, Y. Jiang and H. Fu, *Synlett*, 2012, 801.

88 (*a*) K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2003, **42**, 1480; (*b*) N. Mizuno and K. Yamaguchi, *Catal. Today*, 2008, **132**, 18.

89 (*a*) M. E. C. Biffin, J. Miller and D. B. Paul, in *The Chemistry of the Azide Group*, ed. S. Patai, Interscience Publishers, New York, 1971, pp. 57–190; (*b*) S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188; (*c*) *Organic Azides: Syntheses and Applications*, ed. S. Bräse and K. Banert, John Wiley & Sons, Chichester, 2010.

90 See, for example: M. Lamani, P. Devadig and K. R. Prabhu, *Org. Biomol. Chem.*, 2012, **10**, 2753 and references cited therein.

91 J. He, K. Yamaguchi and N. Mizuno, *J. Org. Chem.*, 2011, **76**, 4606.

92 (*a*) C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790; (*b*) D. Milstein, E. Balaraman, C. Gunanathan, B. Gnanaprakasam and J. Zhang, *PCT Int. Appl.*, WO 2012052996, 2012.

93 For review articles, see: (*a*) D. Milstein, *Top. Catal.*, 2010, **53**, 915; (*b*) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (*c*) C. Chen and S. H. Hong, *Org. Biomol. Chem.*, 2011, **9**, 20.

94 (*a*) T. Zweifel, J.-V. Naubron and H. Grützmacher, *Angew. Chem., Int. Ed.*, 2009, **48**, 559; (*b*) J.-F. Soulé, H. Miyamura and S. Kobayashi, *J. Am. Chem. Soc.*, 2011, **133**, 18550; (*c*) Y. Wang, D. Zhu, L. Tang, S. Wang and Z. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8917; (*d*) K. Yamaguchi, H. Kobayashi, T. Oishi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2012, **51**, 544; (*e*) T. Ishida, H. Watanabe, T. Takei, A. Hamasaki, M. Tokunaga and M. Haruta, *Appl. Catal., A*, 2012, **85**, 425–426; (*f*) R. Nie, J. Shi, S. Xia, L. Shen, P. Chen, Z. Hou and F.-S. Xiao, *J. Mater. Chem.*, 2012, **22**, 18115.

95 Y. Wang, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2012, **51**, 7250.

96 For a very recent review on the Ritter reaction, see: A. Guérinot, S. Reymond and J. Cossy, *Eur. J. Org. Chem.*, 2012, 19.

97 See, for example: (*a*) M. Mukhopadhyay and J. Iqbal, *J. Org. Chem.*, 1997, **62**, 1843; (*b*) B. Anxionnat, A. Guérinot, S. Reymond and J. Cossy, *Tetrahedron Lett.*, 2009, **50**, 3470.

98 E. Callens, A. J. Burton and A. G. M. Barrett, *Tetrahedron Lett.*, 2006, **47**, 8699.

99 H. Firouzabadi, N. Iranpoor and A. Khoshnood, *Catal. Commun.*, 2008, **9**, 529.

100 (*a*) V. R. Kartashov, K. V. Malkova, A. V. Arkhipova and T. N. Sokolova, *Russ. J. Org. Chem.*, 2006, **42**, 966; (*b*) V. R. Kartashov, A. V. Arkhipova, K. V. Malkova and T. N. Sokolova, *Russ. Chem. Bull.*, 2006, **55**, 387.

101 G.-R. Qu, Y.-W. Song, H.-Y. Niu, H.-M. Guo and J. S. Fossey, *RSC Adv.*, 2012, **2**, 6161.

102 R. I. Khusnutdinov, N. A. Shchadneva, Y. Y. Mayakova, L. F. Khisamova and U. M. Dzhemilev, *Russ. J. Org. Chem.*, 2011, **47**, 1682.

103 S.-I. Murahashi, T. Naota and E. Saito, *J. Am. Chem. Soc.*, 1986, **108**, 7846.

104 C. L. Allen, A. A. Lapkin and J. M. J. Williams, *Tetrahedron Lett.*, 2009, **50**, 4262.

105 C. J. Cobley, M. van den Heuvel, A. Abbadi and J. G. de Vries, *Tetrahedron Lett.*, 2000, **41**, 2467.

106 M. Tamura, T. Tonomura, K.-I. Shimizu and A. Satsuma, *Appl. Catal., A*, 2012, **417–418**, 6.

107 A. J. M. van Dijk, T. Heyligen, R. Duchateau, J. Meuldijk and C. E. Koning, *Chem.–Eur. J.*, 2007, **13**, 7664.

108 A. J. M. van Dijk, R. Duchateau, E. J. M. Hensen, J. Meuldijk and C. E. Koning, *Chem.–Eur. J.*, 2007, **13**, 7673.

109 For reviews on this topic, see: (*a*) R. Skoda-Foldes and L. Kollar, *Curr. Org. Chem.*, 2002, **6**, 1097; (*b*) A. Brennführer, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114; (*c*) R. Skoda-Foldes and L. Kollar, *Lett. Org. Chem.*, 2010, 7, 621; (*d*) S. Roy, S. Roy and G. W. Gribble, *Tetrahedron*, 2012, **68**, 9867.

110 See, for example: Y. Uozumi and T. Watanabe, *J. Org. Chem.*, 1999, **64**, 6921.

111 X. Wu and M. Larhed, *Org. Lett.*, 2005, 7, 3327.

112 X. Wu, J. K. Ekegren and M. Larhed, *Organometallics*, 2006, **25**, 1434.

113 O. Lagerlund and M. Larhed, *J. Comb. Chem.*, 2006, **8**, 4.

114 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295.

115 P. J. Tambade, Y. P. Patil, M. J. Bhaushali and B. M. Bhanage, *Synthesis*, 2008, 2347.

116 Z. S. Qureshi, S. A. Revankar, M. V. Khedkar and B. M. Bhanage, *Catal. Today*, 2012, DOI: 10.1016/j.cattod.2012.03.039, in press.

117 K. Nakagawa, H. Onoue and K. Minami, *Chem. Commun.*, 1966, 17.

118 (*a*) T. Naota and S.-I. Murahashi, *Synlett*, 1991, 693; (*b*) J. W. W. Chang and P. W. H. Chan, *Angew. Chem., Int. Ed.*, 2008, **47**, 1138; (*c*) S. Muthaiah, S. C. Ghosh, J.-E. Jee, C. Cheng, J. Zhang and S. H. Hong, *J. Org. Chem.*, 2010, **75**, 3002.

119 (*a*) Y. Tamaru, Y. Yamada and Z.-I. Yoshida, *Synthesis*, 1983, 474; (*b*) K. Ekoue-Kovi and C. Wolf, *Org. Lett.*, 2007, **9**, 3429; (*c*) Y. Suto, N. Yamagiwa and Y. Torisawa, *Tetrahedron Lett.*, 2008, **49**, 5732.

120 (*a*) A. Tillack, I. Rudloff and M. Beller, *Eur. J. Org. Chem.*, 2001, 523; (*b*) J. Chan, K. D. Baucom and J. A. Murry, *J. Am. Chem. Soc.*, 2007, **129**, 14106.

121 (*a*) S. Y. Seo and T. J. Marks, *Org. Lett.*, 2008, **10**, 317; (*b*) C. Qian, X. Zhang, J. Li, F. Xu, Y. Zhang and Q. Shen, *Organometallics*, 2009, **28**, 3856; (*c*) Q. Qian, X. Zhang, Y. Zhang and Q. Shen, *J. Organomet. Chem.*, 2010, **695**, 747.

122 G.-L. Li, K. K.-Y. Kung and M.-K. Wong, *Chem. Commun.*, 2012, **48**, 4112.

123 W.-J. Yoo and C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 13064.

124 K.-I. Fujita, Y. Takahashi, M. Owaki, K. Yamamoto and R. Yamaguchi, *Org. Lett.*, 2004, **6**, 2785.

125 (*a*) L. U. Nordstrøm, H. Vogt and R. Madesen, *J. Am. Chem. Soc.*, 2008, **130**, 17672; (*b*) S. C. Ghosh, S. Muthaiah, Y. Zhang, X. Xu and S. H. Hong, *Adv. Synth. Catal.*, 2009, **351**, 2643; (*c*) A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *Org. Lett.*, 2009, **11**, 2667; (*d*) S. C. Ghosh and S. H. Hong, *Eur. J. Org. Chem.*, 2010, 4266; (*e*) Y. Zhang, C. Chen, S. C. Ghosh, Y. Li and S. H. Hong, *Organometallics*, 2010, **29**, 1374; (*f*) J. H. Dam, G. Ostrovszky, L. U. Nordstrøm and R. Madsen, *Chem.–Eur. J.*, 2010, **16**, 6820; (*g*) J. Zhang, M. Senthilkumar, S. C. Ghosh and S. H. Hong, *Angew. Chem., Int. Ed.*, 2010, **49**, 6391; (*h*) A. Prades, E. Peris and M. Albrecht, *Organometallics*, 2011, **30**, 1162; (*i*) H. Zeng and Z. Guan, *J. Am. Chem. Soc.*, 2011, **133**, 1159.

126 (*a*) K.-I. Shimizu, K. Ohshima and A. Satsuma, *Chem.–Eur. J.*, 2009, **15**, 9977; (*b*) J. Zhu, Y. Zhang, F. Shi and Y. Deng, *Tetrahedron Lett.*, 2012, **53**, 3178.

127 P. Preedasuriyachai, H. Kitahara, W. Chavasiri and H. Sakurai, *Chem. Lett.*, 2010, **39**, 1174.

128 Isolated examples of amide formation in an aqueous medium from azides and thioacids, promoted by $RuCl_3$, and from silylketene pyridylthioacetal and imines, promoted by $Sc(OTf)_3$, have also been described: (*a*) F. Fazio and C.-H. Wong, *Tetrahedron Lett.*, 2003, **44**, 9083; (*b*) C. Biaggi, M. Benaglia and A. Puglisi, *J. Organomet. Chem.*, 2007, **692**, 5795.

129 See, for example: (*a*) B. Gabriele, G. Salerno, L. Veltri and M. Costa, *J. Organomet. Chem.*, 2001, **622**, 84; (*b*) B. E. Ali and J. Tijani, *Appl. Organomet. Chem.*, 2003, **17**, 921; (*c*) D. J. Knapton and T. Y. Meyer, *Org. Lett.*, 2004, **6**, 687; (*d*) K. M. Driller, S. Prateeptongkum, R. Jackstell and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 537.

130 W.-K. Chan, C.-M. Ho, M.-K. Wong and C.-M. Che, *J. Am. Chem. Soc.*, 2006, **128**, 14796.

131 (*a*) S. H. Cho, E. J. Yoo, I. Bae and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 16046; (*b*) M. P. Cassidy, J. Raushel and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 3154.

132 S. H. Cho and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1897.

133 S. H. Cho, S. J. Hwang and S. Chang, *Org. Synth.*, 2008, **85**, 131.

In: Glycerol: Production, Structure and Applications
Editors: M. De Santos Silva and P. Costa Ferreira
ISBN: 978-1-62081-120-7

Chapter 11

RUTHENIUM-CATALYZED NITRILE HYDRATION REACTIONS USING GLYCEROL AS SOLVENT

Alba E. Díaz-Álvarez, Rocío García-Álvarez, Pascale Crochet* and Victorio Cadierno*
Departamento de Química Orgánica e Inorgánica,
Instituto Universitario de Química Organometálica "Enrique Moles"
(Unidad Asociada al CSIC), Facultad de Química, Universidad de Oviedo,
Principado de Asturias, Spain

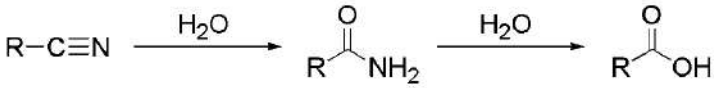
ABSTRACT

The rapid growth of the biodiesel industry has led to a large surplus of its major byproduct, *i.e.* glycerol, for which new applications need to be found. In line with the increasing interest by the chemical community in the use of "green" solvents, an innovative way to revalorize glycerol has seen the light in recent years, *i.e.* its use as environmentally friendly reaction medium for synthetic organic chemistry. In this context, herein we would like to communicate that glycerol is an adequate solvent to perform nitrile hydration reactions. Thus, using the arene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (PTA-Bn = 1-benzyl-3,5-diaza-1-azonia-7-phosphatricyclo $[3.3.1.1^{3,7}]$decane chloride) as catalyst (5 mol%), we have found that a large variety of aromatic, heteroaromatic, aliphatic and α,β-unsaturated organonitriles can be selectively converted into the corresponding amides, in short times (0.5-3 h) and high yields (≥ 95% by GC), performing the catalytic reactions in a 1:1 v/v glycerol/water mixture at 160 ºC. Remarkably, the use of this inexpensive and green reaction medium also enables easy product separation by simple extraction with ethyl acetate, as well as the recycling of the catalytically active ruthenium species.

* crochetpascale@uniovi.es.
* vcm@uniovi.es.

INTRODUCTION

Amides are versatile and important synthetic intermediates used in the manufacture of a variety of pharmacological products, polymers, detergents, lubricants, and drug stabilizers, as well as key structural motifs present in numerous natural products [1]. Consequently, the development of atom-efficient catalytic methods for amide formation is currently an extremely active area of research [2]. In this context, one of the simplest methods of synthesizing primary amides is the catalytic hydration of nitriles (Scheme 1).

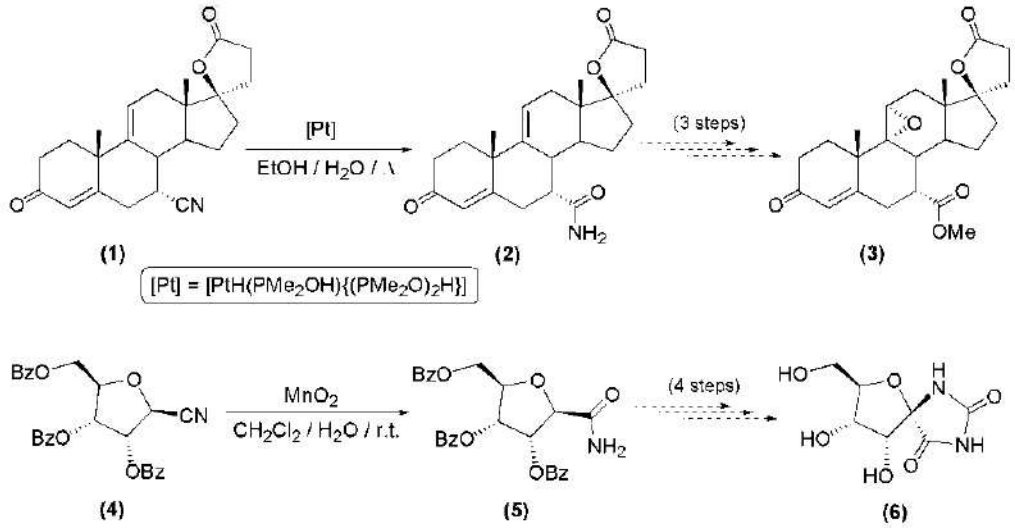


Scheme 1. Nitrile hydration and amide hydrolysis reactions.

Traditional protocols for hydrating nitriles involve the use of strong bases or acids under harsh conditions, often inducing undesired hydrolysis to carboxylic acids (Scheme 1) [3]. During neutralization, salts formation can lead to contamination, separation and pollution problems. Moreover, poor tolerance for sensitive functional groups is often observed under such conditions. All these drawbacks can be overcome using metallic catalysts able to activate the C≡N bond by coordination to the metal atom, thus favouring the selective nucleophilic addition of the water molecule. In this sense, a variety of transition-metal complexes (mainly of Groups 8-12) have been largely investigated during the last years [4], with the Murahashi´s ruthenium dihydride [$RuI_2(PPh_3)_4$] [5], the Parkins´s platinum hydride [$PtH(PMe_2OH)\{(PMe_2O)_2H\}$] [6], the acetylacetonate complex *cis*-[$Ru(acac)_2(PPh_2py)_2$] [7], and the Rh(I)-based system [$\{Rh(\mu\text{-OMe})(cod)\}_2$]/$PCy_3$ (cod = 1,5-cyclooctadiene) [8], showing remarkable activities and selectivities under mild and neutral conditions. The interest of chemical companies in the development of selective catalysts for this relevant transformation is clearly exemplified in (see Scheme 2): (*i*) the preparation of the steroidal compound 7α-carbamoyl-9(11)$^{\Delta}$-canrenone *2*, an advanced intermediate in the production of the orally-active aldosterone antagonist eplerenone *3* used for the treatment of hypertension and congestive heart failure, by catalytic hydration of 7α-cyano-9(11)$^{\Delta}$-canrenone *1* [9], and (*ii*) the conversion of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide *4* into the corresponding primary amide *5* as a key step in the large-scale synthesis of the herbicide (+)-hydantocidin *6* [10]. Hydration of acrylonitrile, 3-cyanopyridine and adiponitrile into acrylamide, nicotinamide and 5-cyanovaleramide, respectively, by the aid of metalloenzymes are other relevant examples of the industrial applications of this process [11].

During the last years, in order to meet with the sustainability criteria imposed by the Green Chemistry principles [12], our group has focused on the search of homogeneous catalysts able to perform the selective hydration of nitriles into amides in pure aqueous medium, without the assistance of harmful organic co-solvents. Note that water is one of the most convenient solvents that one can imagine in terms of cost, availability, safety, and environmental impact [13]. In addition, its use is particularly adequate when water itself participates as one of the reactants of the process. In this context, our studies have brought to light the arene-ruthenium(II) complexes *7-8* and the bis(allyl)-ruthenium(IV) derivatives *9-10* (Figure 1) as effective catalysts for the selective hydration of nitriles into amides in pure aqueous medium [14]. Remarkably, all of them operate at neutral pH without the assistance of

any acidic or basic additive, showing also a wide scope with respect to nature of the substrates and high tolerance toward common functional groups. Impressive TOF values of up to 11400 h^{-1} could be reached with them, representing the highest activity reported to date for this catalytic transformation under these challenging reaction conditions and close to the benchmarks set in organic media (up to 20900 h^{-1}) [7].



Scheme 2. Examples of nitrile hydration reactions with industrial interest.

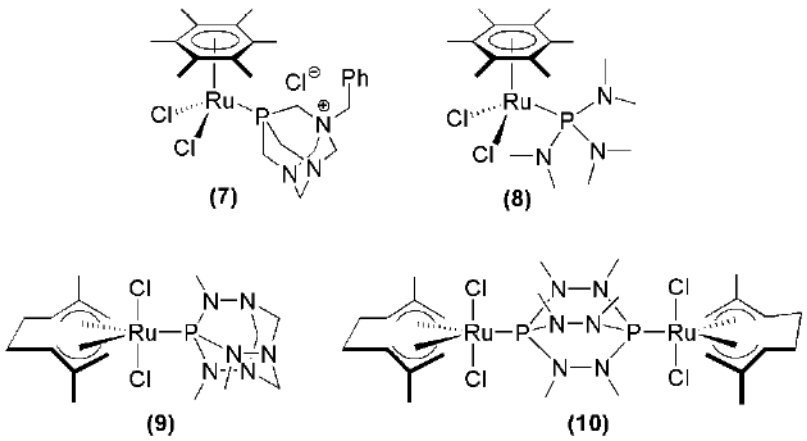
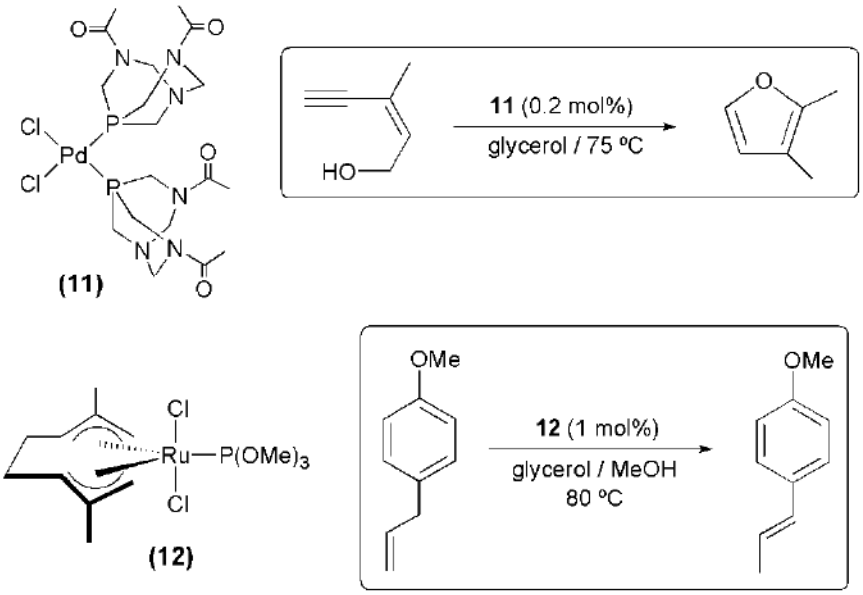


Figure 1. Structure of the ruthenium catalysts *7-10*.

On the other hand, other crucial factors in realizing a "green" catalytic process concern the effective separation of the final reaction products and the recycling of the catalyst [15]. In this sense, despite that the use of water as solvent is usually associated to an easy catalyst/product separation due to the hydrophobic character of most organic compounds (selective extraction methods) [16], the recycling of complexes *7-10* was not possible since isolation of the amides required of a column chromatographic purification which destroys the catalysts. Only the anchoring of this type of complexes on the surface of silica-coated

magnetic Fe_3O_4-nanoparticles allowed their recycling [17]. In search of a simpler method for product separation and catalyst recycling, our attention was turned to glycerol. This by-product (*ca.* 10% by weight) of the biodiesel production process [18] has recently emerged as an economically appealing and safe solvent for organic synthesis [19]. Thus, as suggested by Gu and Jérôme [19a], glycerol can be considered as "organic water" since, like water, it is abundant, biodegradable, inexpensive, non-toxic, highly polar, immiscible with hydrocarbons and ethers (adequate therefore for biphasic catalysis and for product isolation by liquid-liquid extraction), and able to form strong hydrogen bonds. In addition, compared to water, it has the advantage to dissolve transition-metal complexes in a remarkably greater extent. This latter property has already been successfully exploited in our group for improving the products isolation and recycling of complexes *11* and *12* during the catalytic isomerization of (Z)-3-methyl-2-penten-4-yn-1-ol and estragole into 2,3-dimethylfuran [20] and *trans*-anethole [21], respectively (Scheme 3) [22].



Scheme 3. Examples of catalytic processes performed in glycerol.

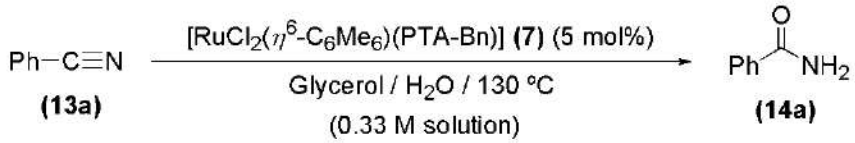
Herein we would like to communicate that glycerol is also an adequate solvent to perform nitrile hydration reactions. In particular, using the arene-ruthenium(II) complex [$RuCl_2(\eta^6$-C_6Me_6)(PTA-Bn)] (*7* in Figure 1), a new protocol for the catalytic hydration of nitriles into amides allowing their easy isolation and the recycling of the catalytically active species is presented.

Results and Discussion

The feasibility of the nitrile hydration reactions in glycerol was evaluated employing the hydration of benzonitrile (*13a*) into benzamide (*14a*) as model. Our initial efforts focused on the search of optimal glycerol/water ratios to perform the process. To this end, a series of

experiments were conducted at 130 °C with 1 mmol of benzonitrile (*13a*) and 5 mol% of the ruthenium(II) catalyst [$RuCl_2(\eta^6\text{-}C_6Me_6)$(PTA-Bn)] (*7*) in 3 mL of different glycerol/water mixtures (0.33 M solutions of the nitrile). The results obtained are collected in Table 1.

Table 1. Hydration of Benzonitrile (13a) into Benzamide (14a) Catalyzed by Complex [$RuCl_2(\eta^6\text{-}C_6Me_6)$(PTA-Bn)] (7) in Glycerol/Water: Influence of the Glycerol/Water Ratio[a]



Entry	Glycerol/Water	Time	Yield[b]
1	100:0	24 h	7%
2[c]	100:0	24 h	45%
3	90:10	24 h	33%
4	80:20	24 h	77%
5	70:30	24 h	98%
6	60:40	24 h	> 99%
7	50:50	24 h	> 99%

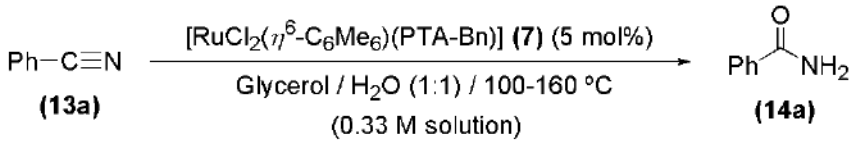
[a] Reactions performed under N_2 atmosphere at 130 °C using 1 mmol of benzonitrile (0.33 M solution). Substrate/Ru ratio: 100/5.

[b] Yields determined by GC (uncorrected GC areas).

[c] Technical grade glycerol was employed.

As expected, performing the catalytic reaction in the absence of water, that is, using exclusively pharmaceutical grade glycerol (99.5% purity), only a very minor amount (7%; determined by Gas Chromatography (GC)) of benzamide (*14a*) was formed after heating the reaction mixture for 24 hours (entry 1). Formation of *14a* was obviously due to the traces of water present in the solvent. The same reaction performed in technical grade glycerol (87% purity), which is assumed to contain about 12-13% of water, allowed to increase the yield of *14a* to 45% (entry 2), thus confirming the need for an appreciable amount of water for the hydration process to proceed. In accord with this, further experiments carried out using pharmaceutical grade glycerol/water mixtures, with v/v ratios ranging from 90:10 to 50:50 (entries 3-7), indicated that an improvement of the effectiveness of the process takes place with increasing the proportion of water present in the reaction medium. In particular, the highest conversions toward the desired benzamide (*14a*) were reached employing 60:40 and 50:50 v/v glycerol/water mixtures (entries 6-7). Under these conditions, complete disappearance of the starting material was observed after 24 h with quantitative and selective formation of *14a* (benzoic acid was not detected by GC in the crude reaction mixtures). Based on these results, a 50:50 v/v glycerol/water mixture was chosen as the solvent for the rest of our studies.

Table 2. Hydration of Benzonitrile (13a) into Benzamide (14a) Catalyzed by Complex [$RuCl_2(\eta^6\text{-}C_6Me_6)$(PTA-Bn)] (7) in Glycerol/Water: Influence of the Temperature[a]



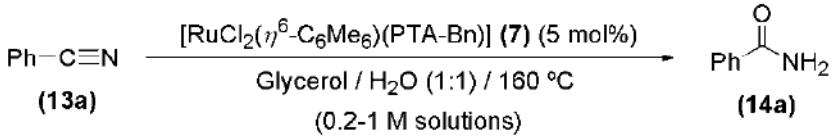
Entry	Temperature	Time	Yield[b]
1	100 °C	24 h	41%
2	110 °C	24 h	81%
3	120 °C	24 h	90%
4	130 °C	24 h	> 99%
5	140 °C	5 h	> 99%
6	150 °C	5 h	> 99%
7	160 °C	2 h	> 99%

[a] Reactions performed under N_2 atmosphere using 1 mmol of benzonitrile (0.33 M solution). Substrate/Ru ratio: 100/5.

[b] Yields determined by GC (uncorrected GC areas).

Using this optimal mixture of solvents, the catalytic hydration of benzonitrile (*13a*) by complex *7* (5 mol%; 0.33 M solution of the substrate) was studied at different temperatures, ranging from 100 to 160 °C. As shown in Table 2, increasing the temperature from 130 °C to 140-160 °C resulted in a remarkable acceleration of the process (entry 4 *vs* entries 5-7). In particular, performing the catalytic reaction at 160 °C, quantitative formation of benzamide (*14a*) was observed by GC after only 2 h (entry 7). Conversely, although complex [$RuCl_2(\eta^6\text{-}C_6Me_6)$(PTA-Bn)] (*7*) remained active, remarkably poorer results were obtained below 130 °C (entries 1-3).

Table 3. Hydration of Benzonitrile (13a) into Benzamide (14a) Catalyzed by Complex [$RuCl_2(\eta^6\text{-}C_6Me_6)$(PTA-Bn)] (7) in Glycerol/Water: Influence of the Concentration[a]



Entry	Concentration	Time	Yield[b]
1	0.20 M	1 h (2 h)	89% (99%)
2	0.25 M	1 h (2 h)	91% (> 99%)
3	0.33 M	1 h (2 h)	91% (> 99%)
4	0.50 M	1 h (2 h)	91% (> 99%)
5	1.00 M	1 h	> 99%

[a] Reactions performed under N_2 atmosphere at 160 °C using 1 mmol of benzonitrile (0.2-1 M solutions). Substrate/Ru ratio: 100/5.

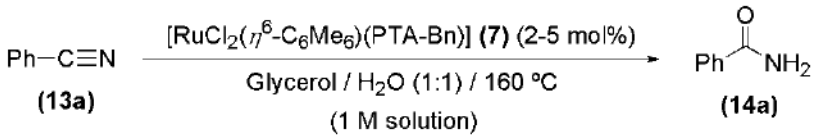
[b] Yields determined by GC (uncorrected GC areas).

In order to improve the efficiency of the process, some experiments were also performed at different concentrations of the substrate (from 0.20 M to 1.00 M solutions), using 5 mol% of complex *7* and a constant temperature regime of 160 ºC (see Table 3). Thus, while no marked differences in activity were observed working in the concentration range 0.20-0.50 M (entries 1-3), the rate of the reaction slightly increased when a more concentrated 1 M solution of benzonitrile (*13a*) was employed. Under these new conditions, quantitative and selective formation of the desired benzamide (*14a*) was achieved in only 1 hour, leading to a turnover frequency (TOF) of 20 h^{-1} (entry 5). Such a TOF value could be further increased to 120 h^{-1} employing microwave irradiation, a non-classical low-energy-consuming heating source of prime interest within the Green Chemistry context [23]. Thus, using an MW-irradiation power of 300 W, formation of *14a* was quantitative after only 10 minutes at 160 ºC. However, we must note that partial degradation of the catalyst upon irradiation takes place. This fact is appreciable with the naked eye as the solution, initially orange, darkens and a black precipitate appears in suspension. Such a phenomenon was not observed employing conventional thermal heating in oil-bath.

Remarkably, the TOF values reached in glycerol/water are comparable to those previously described for complex $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (*7*) in the hydration of benzonitrile in pure aqueous medium (TOF = 9.9 and 126.7 h^{-1} under classical thermal or MW heating, respectively) [14a]. Consequently, we can conclude that the use of a 1 M solution of the substrate, in a 50:50 v/v glycerol/water mixture of solvents, and a reaction temperature of 160 ºC (oil-bath) are also optimal conditions for the maximum efficiency of this ruthenium catalyst.

We must also note that the use of these unprecedented reaction conditions allows the reduction of the catalyst loading. In this sense, we have observed that, even with only 2 mol% of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (*7*), the hydration of benzonitrile proceeded to completion. However, as shown in Table 4, this reduction of the catalyst loading is associated with an increase in the reaction time (from 1 to 7 h) and a decrease of the turnover frequency (from 20 to 7.1 h^{-1}).

Table 4. Hydration of Benzonitrile (13a) into Benzamide (14a) Catalyzed by Complex $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (7) in Glycerol/Water: Influence of the Ruthenium Loading[a]



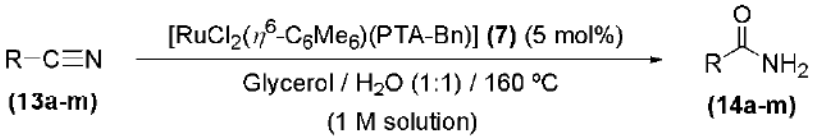
Entry	mol% of Ru	Time	Yield[b]	TOF[c]
1	5 mol%	1 h	> 99%	20.0 h^{-1}
2	4 mol%	2 h	> 99%	12.5 h^{-1}
3	3 mol%	3 h	> 99%	11.1 h^{-1}
4	2 mol%	7 h	> 99%	7.1 h^{-1}

[a] Reactions performed under N_2 atmosphere at 160 ºC using 1 mmol of benzonitrile (1 M solution). Substrate/Ru ratio: from 100/5 to 100/2.

[b] Yields determined by GC (uncorrected GC areas).

[c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case.

Table 5. Hydration of Nitriles into Amides Catalyzed by Complex [$RuCl_2(\eta^6\text{-}C_6Me_6)$(PTA-Bn)] (7) in Glycerol/Water: Scope of the Reaction[a]



Entry	Substrate	Time	Yield[b]	TOF[c]
1	R = Ph (**13a**)	1 h	**14a**; > 99% (82%)	20.0 h^{-1}
2	R = 2-C_6H_4F (**13b**)	1 h	**14b**; > 99% (86%)	20.0 h^{-1}
3	R = 4-C_6H_4Cl (**13c**)	30 min	**14c**; > 99% (88%)	40.0 h^{-1}
4	R = 3-C_6H_4Br (**13d**)	30 min	**14d**; > 99% (85%)	40.0 h^{-1}
5	R = C_6F_5 (**13e**)	30 min	**14e**; > 99% (87%)	40.0 h^{-1}
6	R = 4-C_6H_4Me (**13f**)	1 h	**14f**; > 99% (90%)	20.0 h^{-1}
7	R = 3-C_6H_4OMe (**13g**)	1 h	**14g**; > 99% (84%)	20.0 h^{-1}
8	R = 3-C_5H_4N (**13h**)	30 min	**14h**; > 99% (89%)	40.0 h^{-1}
9	R = 2-Thienyl (**13i**)	1 h	**14i**; 95% (80%)	19.0 h^{-1}
10	R = *n*-C_5H_{11} (**13j**)	1 h	**14j**; > 99% (87%)	20.0 h^{-1}
11	R = $(CH_2)_3Ph$ (**13k**)	3 h	**14k**; 98% (83%)	6.5 h^{-1}
12	R = CH_2-4-C_6H_4Cl (**13l**)	1 h	**14l**; > 99% (89%)	20.0 h^{-1}
13	R = (*E*)-CH=CHPh (**13m**)	1 h	**14m**; > 99% (91%)	20.0 h^{-1}

[a] Reactions performed under N_2 atmosphere at 160 °C using 1 mmol of of the corresponding nitrile *13a-m* (1 M solution). Substrate/Ru ratio: 100/5. [b] Yields of *14a-m* determined by GC (uncorrected GC areas). Isolated yields after appropriate work-up are given in brackets. [c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case.

In order to assess the scope of this new protocol, the hydration of other nitriles was explored employing the best reaction conditions found, *i.e.* using a ruthenium loading of 5 mol% in a 50:50 v/v glycerol/water mixture at 160 °C (oil-bath). The results obtained are collected in Table 5. Gratifyingly, we have found that, as observed for benzonitrile (entry 1), other aromatic (*13b-g*; entries 2-7) and heteroaromatic (*13h-i*; entries 8-9) substrates could also be selectively converted into the corresponding amides *14b-i* (≥ 95% GC yields) in short times (30 min or 1 h). Influence of the electronic properties of the aryl rings on the reaction rates was observed. Thus, aromatic nitriles with electron-withdrawing groups showed in general a higher reactivity as compared to those with electron-donating substituents (entries 2-5 *vs* 6-7). In the case of 2-fluorobenzonitrile (*13b*), the steric effects associated with its *ortho*-substitution may be behind its anomalous behaviour (entry 2).

As shown in entries 10-13, the effectiveness of the process is not restricted to aromatic organonitriles, the hydration of substrates *13j-m* containing alkyl- or alkenyl-CN bonds being also conveniently achieved under the standard reaction conditions. Remarkably, upon completion of the reaction, the final amides could be in all cases easily separated from the water-glycerol phase by selective extraction with ethyl acetate (3 x 1 mL), thus avoiding the use of "destructive" chromatographic methods. Further purification by recrystallization from hot water (or hot methanol) afforded analytically pure samples of the amides *14a-m* in 80-91% isolated yields. Finally, the possible recycling of complex [$RuCl_2(\eta^6\text{-}C_6Me_6)$(PTA-Bn)]

(*7*) was also investigated. In this sense, we have found that, after extraction of 4-chlorobenzamide (*14c*) and pentafluorobenzamide (*14e*) with EtOAc, the respective water-glycerol phases containing *7* remained active in the hydration process when a new charge of 4-chlorobenzonitrile (*13c*) and pentafluorobenzonitrile (*13e*), respectively, was added. Almost complete (≥ 95% GC yield) and selective conversions into *14c,e* were reached in 1-3 h in these second runs.

CONCLUSIONS

In summary, we have demonstrated that selective hydration of nitriles into amides by means of the arene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (*7*) can be conveniently performed in glycerol/water. Remarkably, the use of this inexpensive and green reaction medium enables easy product separation and catalyst recycling, thus providing a simpler method for the recycling of this type of catalysts as compared with the immobilization on the surface of silica-coated magnetic Fe_3O_4-nanoparticles previously described by us [17]. Overall, the results reported herein represents a new example of the utility of glycerol as solvent for synthetic organic chemistry [19-22], an emerging research field that has as main objective the revalorization of a waste generated by the biodiesel industry [18]. Although there is already a body of work in this area, we are still at the beginning to learn what the real potential of this green solvent in organic synthesis is. Obviously, the area remains open with many opportunities for new discoveries and further advances in this field can be expected in the near future.

EXPERIMENTAL SECTION

General Comments

All catalytic reactions were performed under an atmosphere of dry nitrogen using vacuum-line and standard sealed-tube techniques. All reagents were obtained from commercial suppliers and used without further purification, with the exception of compound $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (*7*) which was prepared by following the method reported in the literature [14a]. Pharmaceutical (99.5%) and technical (87%) grade glycerol were purchased from VWR International and used as received. GC measurements were made on a Hewlett-Packard HP6890 equipment using a Supelco Beta-Dex™ 120 column (30 m length; 250 µm diameter). NMR spectra were recorded on Bruker DPX300 or AV400 instruments. Chemical shifts are given in ppm, relative to internal tetramethylsilane (^1H and ^{13}C) or $CFCl_3$ (^{19}F) standards.

General Procedure for the Catalytic Hydration Reactions

Under nitrogen atmosphere, the corresponding nitrile *13a-m* (1 mmol), pharmaceutical grade glycerol (0.5 mL), water (0.5 mL), and the ruthenium catalyst $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}$

Bn)] (*7*) (31 mg; 5 mol% of Ru) were introduced into a Teflon-capped sealed tube, and the resulting solution stirred at 160 °C (oil-bath) for the indicated time (see Table 5). The course of the reaction was monitored by taking regularly samples of *ca.* 20 µL which after extraction with ethyl acetate (3 mL) were analyzed by GC. After that, the reaction mixture was washed with ethyl acetate (3 x 1 mL), the upper organic phase separated from the aqueous glycerol phase, and evaporated under reduced pressure. The resulting solid residue was then recrystallized from hot water (or hot methanol) to yield amides *14a-m* in pure form. The identity of *14a-m* was assessed by comparison of their ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopic data with those reported in the literature:

Benzamide (14a) [24]: White solid. 0.099 g (82%). ^{1}H NMR ($CDCl_3$): δ = 6.31 (br, 2H), 7.41-7.55 (m, 3H), 7.82 (m, 2H) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ = 127.3, 128.5, 131.9, 133.3, 169.7 ppm.

2-Fluorobenzamide (14b) [24]: White solid. 0.119 g (86%). ^{1}H NMR ($CDCl_3$): δ = 6.73 (br, 2H), 7.01-7.50 (m, 3H), 8.07 (m, 1H) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ = 116.0 (d, $^{2}J_{FC}$ = 24.4 Hz), 120.2 (d, $^{2}J_{FC}$ = 11.6 Hz), 124.7 (d, $^{4}J_{FC}$ = 2.9 Hz), 132.1, 133.7 (d, $^{3}J_{FC}$ = 9.3 Hz), 160.8 (d, $^{1}J_{FC}$ = 248.6 Hz), 165.3 ppm. $^{19}F\{^{1}H\}$ NMR ($CDCl_3$): δ = -112.8 (s) ppm.

4-Chlorobenzamide (14c) [24]: White solid. 0.137 g (88%). ^{1}H NMR ($CDCl_3$): δ = 5.97 (br, 2H), 7.42-7.75 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ = 128.7, 128.8, 131.6, 168.0 ppm.

3-Bromobenzamide (14d) [25]: White solid. 0.170 g (85%). ^{1}H NMR (CD_3OD): δ = 7.38-7.83 (m, 3H), 8.03 (br, 1H) ppm; NH_2 protons not observed. $^{13}C\{^{1}H\}$ NMR (CD_3OD): δ = 125.4, 129.3, 133.3, 133.7, 137.7, 139.1, 172.5 ppm.

Pentafluorobenzamide (14e) [26]: White solid. 0.183 g (87%). $^{13}C\{^{1}H\}$ NMR (CD_3OD): δ = 113.5 (m), 135.6-146.6 (m), 160.3 (br) ppm. $^{19}F\{^{1}H\}$ NMR (CD_3OD): δ = -164.0 (m), -143.8 (m), -155.7 (m) ppm.

4-Methylbenzamide (14f) [25]: White solid. 0.105 g (90%). ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3H), 6.06 (br, 2H), 7.24 and 7.70 (d, 2H each, $^{3}J_{HH}$ = 6.9 Hz) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ = 21.4, 127.3, 129.2, 130.4, 142.5, 169.4 ppm.

3-Methoxybenzamide (14g) [24]: White solid. 0.127 g (84%). ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 3H), 6.08 (br, 2H), 7.07 (m, 1H), 7.31-7.40 (m, 3H) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ = 55.4, 112.5, 118.3, 119.1, 129.5, 134.4, 159.8, 169.3 ppm.

Nicotinamide (14h) [24]: White solid. 0.109 g (89%). ^{1}H NMR (CD_3OD): δ = 7.54 (dd, 1H, $^{3}J_{HH}$ = 7.9 and 5.0 Hz), 8.28 (dt, 1H, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 2.5 Hz), 8.67 (dd, 1H, $^{3}J_{HH}$ = 5.0 Hz, $^{4}J_{HH}$ = 2.5 Hz), 9.02 (s, 1H) ppm; NH_2 protons not observed. $^{13}C\{^{1}H\}$ NMR (CD_3OD): δ = 123.1, 129.4, 135.4, 147.4, 150.8, 167.8 ppm.

2-Thienylamide (14i) [27]: White solid. 0.102 g (80%). ^{1}H NMR (CD_3OD): δ = 7.11 (dd, 1H, $^{3}J_{HH}$ = 5.0 and 3.8 Hz), 7.65 (dd, 1H, $^{3}J_{HH}$ = 5.0 Hz, $^{4}J_{HH}$ = 1.0 Hz), 7.70 (dd, 1H, $^{3}J_{HH}$ = 3.8 Hz, $^{4}J_{HH}$ = 1.0 Hz) ppm; NH_2 protons not observed. $^{13}C\{^{1}H\}$ NMR (CD_3OD): δ = 127.3, 129.0, 130.7, 148.3, 169.4 ppm.

Hexanamide (14j) [24]: White solid. 0.100 g (87%). ^{1}H NMR (CD_3OD): δ = 0.91 (t, 3H, $^{3}J_{HH}$ = 6.9 Hz), 1.32 (m, 4H), 1.60 (m, 2H), 2.18 (m, 2H) ppm; NH_2 protons not observed. $^{13}C\{^{1}H\}$ NMR (CD_3OD): δ = 11.8, 21.0, 24.2, 30.1, 34.1, 176.9 ppm.

4-Phenylbutyramide (14k) [24]: White solid. 0.135 g (83%). ^{1}H NMR (CD_3OD): δ = 1.94 (m, 2H), 2.25 (m, 2H), 2.65 (m, 2H), 7.19-7.31 (m, 5H) ppm; NH_2 protons not observed. $^{13}C\{^1H\}$ NMR (CD_3OD): δ = 25.7, 32.9, 33.3, 123.9, 126.4, 126.5, 140.0, 175.9 ppm.

(4-Chlorophenyl)acetamide (14l) [28]: White solid. 0.151 g (89%). ^{1}H NMR (CD_3OD): δ = 3.50 (s, 2H), 7.30 (br, 4H) ppm; NH_2 protons not observed. $^{13}C\{^1H\}$ NMR (CD_3OD): δ = 40.6, 127.7, 129.9, 131.9, 133.9, 174.5 ppm.

(E)-3-Phenylacrylamide (14m) [29]: White solid. 0.134 g (91%). ^{1}H NMR (CD_3OD): δ = 6.63 and 7.54 (d, 1H each, $^3J_{HH}$ = 15.8 Hz), 7.37 (m, 3H), 7.59 (m, 2H) ppm; NH_2 protons not observed. $^{13}C\{^1H\}$ NMR (CD_3OD): δ = 119.5, 127.0, 128.1, 129.1, 134.3, 140.8, 169.1 ppm.

Catalyst Recycling

After completion of the reaction the mixture was allowed to reach the room temperature. Ethyl acetate (1 mL) was then added and two phases appeared. The upper organic phase containing the desired amide was separated with the aid of a Pasteur pipette, and the extraction process was repeated twice more. After that, to the aqueous glycerol phase a new load of the nitrile was added, and the mixture heated at 160 °C in an oil-bath for the indicated time (see the discussion section).

ACKNOWLEDGMENTS

Financial support by the Ministerio de Ciencia e Innovación (MICINN) of Spain (Projects CTQ2010-14796/BQU and CSD2007-00006) and the Gobierno del Principado de Asturias (FICYT Project FC-11-COF11-13) is gratefully acknowledged.

REFERENCES

[1] See, for example: (a) *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970; (b) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Greenberg, A.; Breneman, C. M.; Liebman, J. F., Eds.; Wiley: New York, 2000; (c) *Polyesters and Polyamides*; Deopura, B. L.; Gupta, B.; Joshi, M.; Alagirusami, R., Eds.; CRC Press: Boca Raton, 2008; (d) Johansson, I. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley: New York, 2004; Vol. 2, pp 442-463.

[2] For a recent review, see: Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* 2011, *40*, 3405-3415.

[3] See, for example: (a) Bailey, P. D.; Mills, T. J.; Pettecrew, R.; Price, R. A. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. 5, pp 201-294; (b) *Methoden Org. Chem. (Houben Weyl)*; Dopp, D.; Dopp, H., Eds.; Thieme Verlag: Stuttgart, 1985; Vol. E5(2), pp 1024-1031.

[4] For reviews covering this field, see: (a) Parkins, A. W. *Platinum Metals Rev.* 1996, *40*, 169-174; (b) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* 2002, *102*, 1771-1902; (c) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* 2005, *358*, 1-21; (d) Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* 2011, *255*, 949-974.

[5] (a) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* 1992, *57*, 2521-2523; (b) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* 1993, *49*, 8805-8826; (c) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* 2000, *33*, 225-233.

[6] (a) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* 1995, *36*, 8657-8660; (b) Akisanya, J.; Parkins, A. W.; Steed, J. W. *Org. Proc. Res. Dev.* 1998, *2*, 274-276; (c) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A: Chem.* 2000, *160*, 249-261; (d) Jiang, X.-B.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Org. Chem.* 2004, *69*, 2327-2331.

[7] Oshiki, T.; Yamashita, H.; Sawada, K.; Utsunomiya, M.; Takahashi, K.; Takai, K. *Organometallics* 2005, *24*, 6287-6290.

[8] Goto, A.; Endo, K.; Saito, S. *Angew. Chem. Int. Ed.* 2008, *47*, 3607-3609.

[9] Gieling, R. G.; Groen, M. B. *PCT Int. Appl.* WO2006/097342, 2006 (Synthon B. V.).

[10] Harrington, P. M.; Jung, M. E. *US Patent* US5354868, 1994 (American Cyanamid Co.).

[11] See, for example: (a) Yamada, H.; Kobayashi, M. *Biosci. Biotech. Biochem.* 1996, *60*, 1391-1400; (b) van Pelt, S.; van Rantwijk, F.; Sheldon, R. A. In *Focus in Catalysis Applications* (supplement to *Chimica Oggi/Chemistry Today*); Teknoscienze Srl: Milano, Italy, 2008; Vol. 26, pp 2-4; (c) Sanchez, S.; Demain, A. L. *Org. Process Res. Dev.* 2011, *15*, 224-230; (d) Li, B.; Su, J.; Tao, J. *Org. Process Res. Dev.* 2011, *15*, 291-293.

[12] (a) Anastas, P. T.; Warner, J. C. In *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998; (b) Matlack, A. S. In *Introduction to Green Chemistry*; Marcel Dekker: New York, 2001; (c) Lancaster, M. In *Handbook of Green Chemistry and Technology*; Clark, J. H., Macquarrie, D. J., Eds.; Blackwell Publishing: Abingdon, 2002; (d) Lancaster, M. In *Green Chemistry: An Introductory Text*; RSC Publishing: Cambridge, 2010.

[13] (a) Nelson, W. M. In *Green Solvents for Chemistry: Perspectives and Practice*; Oxford University Press: New York, 2003; (b) Clark, J. H.; Taverner, S. J. *Org. Process Res. Dev.* 2007, *11*, 149-155; (c) Kerton, F. M. In *Alternative Solvents for Green Chemistry*; RSC Publishing: Cambridge, 2009.

[14] (a) Cadierno, V.; Francos, J.; Gimeno, J. *Chem. Eur. J.* 2008, *14*, 6601-6605; (b) Cadierno, V.; Díez, J.; Francos, J.; Gimeno, J. *Chem. Eur. J.* 2010, *16*, 9808-9817; (c) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno, V. *Organometallics* 2010, *29*, 3955-3965; (d) García-Álvarez, R.; Francos, J.; Crochet, P.; Cadierno V. *Tetrahedron Lett.* 2011, *52*, 4218-4220; (e) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno V. *Organometallics* 2011, *30*, 5442-5451.

[15] See, for example: (a) Sheldon, R. A.; Arends, I.; Hanefeld, U. In *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, 2007; (b) *Recoverable and Recyclable Catalysts*; Benaglia, M., Ed.; John Wiley & Sons: Chichester, 2009.

[16] See, for example: (a) *Aqueous Organometallic Chemistry and Catalysis*; Horváth, I. T.; Joó, F., Eds.; Kluwer: Dodrecht, 1995; (b) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*; Cornils, B.; Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1998; (c) *Aqueous Organometallic Catalysis*; Horváth, I. T.; Joó, F., Eds.; Kluwer: Dodrecht, 2001.

[17] García-Garrido, S. E.; Francos, J.; Cadierno, V.; Basset, J. M.; Polshettiwar, V. *ChemSusChem* 2011, *4*, 104-111.
[18] Pagliaro, M.; Rossi, M. In The *Future of Glycerol: New Usages for a Versatile Raw Material*; RSC Publishing: Cambridge, 2008.
[19] For reviews on this topic, see: (a) Gu, Y.; Jérôme, F. *Green Chem.* 2010, *12*, 1127-1138; (b) Díaz-Álvarez, A. E.; Francos, J.; Lastra-Barreira, B.; Crochet, P.; Cadierno, V. *Chem. Commun.* 2011, *47*, 6208-6227; (c) Wolfson, A.; Dlugy, C.; Tavor, D. In *Homogeneous Catalysis: Types, Reactions and Applications*; Poehler, A. C., Ed.; Nova Science Publishers: New York, 2011, pp 185-203.
[20] Francos, J.; Cadierno, V. *Green Chem.* 2010, *12*, 1552-1555.
[21] Lastra-Barreira, B.; Francos, J.; Crochet, P.; Cadierno, V. *Green Chem.* 2011, *13*, 307-313.
[22] Catalyst recycling was also possible in the ruthenium-catalyzed reduction of allylic alcohols, using glycerol as solvent and hydrogen donor, recently developed by us: Díaz-Álvarez, A. E.; Crochet, P.; Cadierno, V. *Catal. Commun.* 2011, *13*, 91-96.
[23] For recent reviews and a book on microwave-assisted chemistry in aqueous media, see: (a) Dallinger, D.; Kappe, O. C. *Chem. Rev.* 2007, *107*, 2563-2591; (b) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* 2008, *37*, 1546-1557; (c) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* 2008, *41*, 629-639; (d) *Aqueous Microwave-Assisted Chemistry*; Polshettiwar, V.; Varma, R. S., Eds.; RSC Publishing: Cambridge, 2010.
[24] *AIST: RIO-DB Spectral Database for Organic Compounds*; National Institute of Advanced Industrial Science and Technology (AIST), Japan.
[25] Li, X.-Q.; Wang, W.-K.; Han, Y.-X.; Zhang, C. *Adv. Synth. Catal.* 2010, *352*, 2588-2598.
[26] Zibarev, A. V.; Furin, G. G.; Yakobson, G. G. *Izv. Sibir. Otd. Akad Nauk, Ser. Khim.* 1980, 107-112.
[27] Ali, M. A.; Punniyamurthy, T. *Adv. Synth. Catal.* 2010, *352*, 288-292.
[28] Van Baelen, G.; Maes, B. U. W. *Tetrahedron* 2008, *64*, 5604-5619.
[29] Yi, C. S.; Zeczycki, T. N.; Lindeman, S. V. *Organometallics* 2008, *27*, 2030-2035.