Universidad de Oviedo

Departamento de Química Orgánica e Inorgánica
Programa de Doctorado Síntesis y Reactividad Química

Gold-Catalyzed Synthesis and Functionalization of Heteroarenes

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Memoria para optar al grado
de Doctor presentada por
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Justificación

Oviedo, 28 de enero de 2014

Presidente de la Comisión Académica del Programa de Doctorado

Fdo.: Miguel Ángel Ruiz Álvarez

Contra la presente resolución podrá interponer recurso de alzada ente el Excmo. Sr. Rector Magfco. de esta Universidad en el plazo de un mes a contar desde el siguiente a la recepción de la presente resolución, de acuerdo con lo previsto en el artículo 114 de la Ley 30/92, de 26 de noviembre, del Régimen Jurídico de las Administraciones Públicas y Procedimiento Administrativo Común (B.O.E. de 27 de noviembre), modificada por la Ley 4/1999, de 13 de enero (B.OE. de 14 de enero)

SR/A. VALENTINA PIROVANO

The second chapter is focused on the cycloaddition reaction of 2-vinylindoles with enones towards the preparation of tetrahydrocarbazole derivatives. This process has been studies using classic Lewis acids and gold complexes as catalysts. According to the results, gold catalysts proved more efficient to accomplish the transformation.

In the third chapter, a study on gold-catalyzed cycloaddition reactions of 2-vinylindoles with allene derivatives is presented. This work has allowed to identify two different reaction pathways, a formal 4+2 cycloaddition and a multicomponent reaction, both leading to different tetrahydrocarbazole derivatives. The reaction outcome can be controlled with the judicious choice of the reaction conditions.

The forth chapter is devoted to the study of gold- and to less extend silver-catalyzed reactions of indoles with dehydroaminoacis. This study has enabled the discovery of a new reactivity of this substrates. The reaction involves the formation of α-indolylacrilate derivatives.

RESUMEN (en Italiano)

Questo lavoro descrive i risultati ottenuti dallo studio di reazioni di sintesi e funzionalizzazione di eterocicli in processi catalizzati da complessi di oro. La tesi è suddivisa in quattro capitoli che trattano argomenti distinti.

Il primo capitolo presenta un'introduzione generale sulla catalisi con complessi di oro, con particolare attenzione nella descrizione dei processi più rappresentativi.

Il secondo capitolo si concentra sull'analisi delle reazioni di cicloaddizione di 2-vinilindoli con enoni per la di derivati dei tetraidrocarbazolici. E' stato eseguito uno studio del processo, utilizzando come catalizzatori acidi di Lewis classici uniti a complessi di oro, i quali hanno dimostrato di conferire i migliori risultati.

Nel terzo capitolo si descrive lo studio delle reazioni di cicloaddizione di 2-vinilindoli con derivati di alleni, catalizzate da complessi di oro. Durante la messa a punto delle migliori condizioni di reazione, sono stati sviluppati due possibili percorsi di reattività: una reazione formale di cicloaddizione 4+2 e un processo multicomponente, che conduce alla formazione di differenti derivati tetraidrocarbazolici. Il risultato della reazione può essere controllato in forma totalmente selettiva tramite l'accurata selezione delle condizioni di reazione.

Il quarto capitolo si concentra nell'analisi della reattività degli indoli e dei deidroaminoacidi, utilizzando come catalizzatori complessi di oro e in minor parte di argento. Grazie a questo studio, si è potuto descrivere una nuova forma di reattività di questi substrati, la cui reazione porta alla formazione di derivati α-indolilacrilati.

SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN SÍNTESIS Y REACTIVIDAD QUÍMICA

Abbreviations

Ac	Acetyl
Acac	Acetylacetonate
Alk	Alkyl
Ar	Aryl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*t*-Butyloxycarbonyl
Bs	Broad signal
Bu	Butyl
°C	Celsius degree
COSY	Correlation spectrometry
CSA	Camphorsulfuric acid
cat.	Catalytic
cm	Centimetre
Cy	Cyclohexyl
δ	Chemical shift
d	Doublet
DA	Diels-Alder
dd	Double doublet
d.e.	Diastereomeric excess
DEPT	Distortionless Enhancement by Polarization Transfer
ddd	Double double doublet
DME	1,2-Dimethoxyethan
DCM	Dichloromethane
DMF	Dimethylformamide
dt	Double triplet
ED	Electron-donating
EI	Electron collision ionization
Equiv.	Equivalents
ESI	Electronspray ionization
Et	Ethyl
eV	Electronvolt
EW	Electron-withdrawing
g	Gram

h	hours
Hex	Hexyl
HRMS	High resolution Mass spectrometry
Hz	Hertz
IR	Infrared spectrometry
i-Pr	*iso*-Propyl
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	Coupling constant
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
L	Ligand
LA	Lewis Acid
m	Multiplet
m-	meta
M	Molar
$[M^+]$	Molecular ion peak
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minutes
mL	Millilitre
mmol	Millimol
MOM	Methoxymethyl ether
m.p.	Melting point
MS	Mass spectrometry
m/z	Mass / Load
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
NOE(SY)	Nuclear Overhauser Effect
o-	ortho
ORTEP	Oak Ridge Thermal Ellipse Program
p-	para
Pent	Pentyl
Ph	Phenyl
PMB	*p*-methoxybenzyl

ppm	parts per million
PPTS	Pyridinium *p*-toluensulphonate
Pr	Propyl
Py	Pyridine
p-Tol	*p*-Tolyl
q	Quartet
rt	room temperature
s	Singlet
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SEM	2-(Trimethylsilyl)ethoxymethyl Ether
T	Temperature
t	Triplet
t	Time
td	Triple doublet
tert	tertiary
t-Bu	*tert*-Butyl
Tf	Trifluorometansulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBS	*t*-Butyldimethylsilyl
Ts	*p*-Toluensulfonyl

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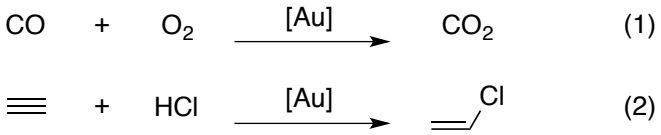
Chapter 1. Homogeneous gold catalysis and applications in organic synthesis

1.1 Introduction

For centuries gold was used mainly for coinage and artworks becoming the precious metal *par* excellence. Gold has a rich coordination and organometallic chemistry[1] but in the field of catalysis, particularly in homogeneous processes, it was considered to be catalytically inactive. Probably a low catalytic activity was mistakenly deduced from the inertness of elemental gold, due to the highest electrode potential among the neighbor elements in the periodic table. Moreover, the high economical value of this metal contributed to the scarce interest in its use as catalyst. However, gold complexes are, in general, less expensive than other commonly used catalysts derived from platinum or rhodium salts.[2] Early applications of gold catalysis appeared in 1973 when Bond and coworkers[3] reported the hydrogenation of olefins over supported gold catalysts. Later, Haruta[4] investigated the low-temperature oxidation of CO (Scheme 1.1, Eq. 1) and Hutchings[5] the hydrochlorination of ethyne to vinyl chloride (Scheme 1.1, Eq. 2).



Scheme 1.1

All these processes, involving heterogeneous reactions,[6] showed that gold could be the metal of choice to promote these transformations, in sharp contrast to the previous reports on the poor reactivity of gold.[7]

However, the use of gold as homogeneous catalyst remained less explored and it was only from the beginning of this century that this field comes into attention. Thus, an impressive number of papers have appeared on this topic in the last few years, generating a true "gold rush".[8,9]

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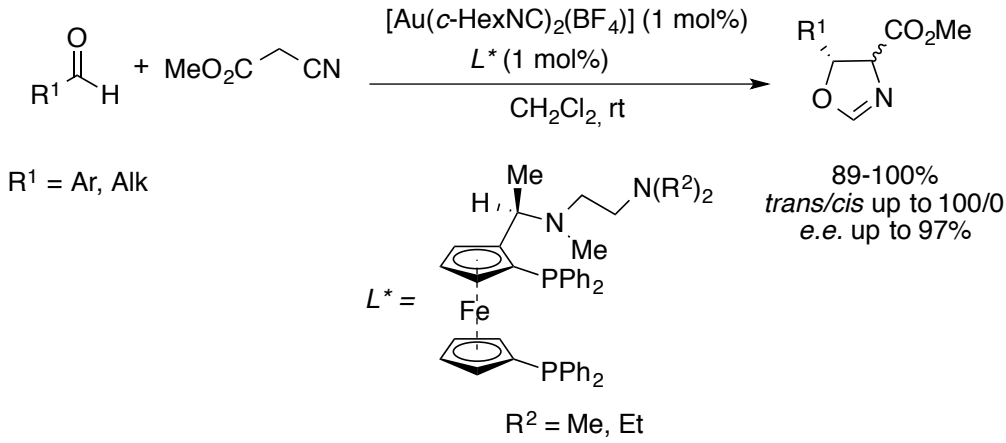
[1] C. Helschenbroich, *Organometallics*, Wiley-VCH, Weinheim, **2011**, p. 262-271.
[2] Prices of metals on 10.01.14: gold, 29.15 €/g; rhodium, 25.42 €/g; platinum, 33.59 €/gr. Source: http://heraeus-trading.com/en/marktinformationen/edelmetallpreise/edelmetallpreise.aspx
[3] G. C. Bond, P. A. Sermon, G. Webb, D. A. Buchanan, P. B. Wells, *J. Chem. Soc. Chem. Commun*. **1973**, 444-445.
[4] M. Haruta, T. Kobayashi, H. Sano, N. Yamada, *Chem. Lett*. **1987**, *16*, 405-408.
[5] G. J. Hutchings, *J. Catal*. **1985**, *96*, 292-295.
[6] For some reviews on heterogeneous gold catalysis see: a) G. C. Bond, *Gold Bull*. **1972**, *5*, 11-13; b) J. Schwank, *Gold Bull*. **1985**, *18*, 2-10; c) D. Thompson, *Gold Bull*. **1998**, *31*, 111-118; d) D. Thompson, D. *Gold Bull*. **1999**, *32*, 12-19; e) G. C. Bond, *Catal. Today* **2002**, *72*, 5-9; f) G. J. Hutchings, *Chem. Commun*. **2008**, 1148-1164; g) T. Takei, T. Akita, I. Nakamura, T. Fujitani, M. Okumura, K. Okazaki, J. Huang, T. Ishida, M. Haruta, *Adv. Catal.* **2012**, *55*, 1-26; h) M. Peixoto de Almeida, S. A. C. Carabineiro, *ChemCatChem* **2012**, *4*, 18-29.
[7] For an inclusion of these early examples see: a) ref. 6a; b) A. S. K. Hashmi, *Gold Bull*. **2004**, *37*, 51-65.
[8] For some reviews on general gold catalysis see: a)A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed*. **2006**, *45*, 7896-7936; b) A. S. K. Hashmi, *Chem. Rev*. **2007**, *107*, 3180-3211; c) G. J. Hutchings, M. Brust, H. Schmidbaur, *Chem. Soc. Rev*. **2008**, *37*, 1759-1765; d) A. S. K. Hashmi, *Top. Organomet. Chem*. **2013**, *44*, 143-164.

Previously, early and scattered reports on the use of gold in homogenous catalysis already existed.[10] In particular two reactions were explored with regards to their potential for synthesis.

The first reaction is the Ito-Sawamura-Hayashi asymmetric aldol condensation developed by Ito and coworkers in 1986.[11] This work represents a milestone in homogeneous gold catalysis field. A gold(I) catalyst was employed together with an enantiomerically pure ferrocene diphosphane ligand to promote the addition of a carbon nucleophile to a carbonyl group yielding oxazole derivatives with excellent yields and enantioselectivities (Scheme 1.2).



Scheme 1.2

The second transformation involved the addition of nucleophiles to alkynes and was reported by Fukuda and Utimoto in 1991.[12] This reaction made use of alcohols, water and amines as nucleophiles and gold(III) salts as catalysts. Interestingly, Teles and coworkers,[13] almost ten years later, demonstrated that cationic gold(I) species were also competent for the addition of alcohols or

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[9] For some recent reviews on homogeneous gold catalysis see: a) S. Ma, S. Yu, Z. Gu, *Angew. Chem. Int. Ed.* **2006**, *45*, 200-203; b) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271-2296; c) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555-4563; d) C. Nieto-Oberhuber, S. López, E. Jiménez-Núñez, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 5916-5923; e) N. Marion, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2750-2757; f) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350; g) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885-3903; h) H. C. Shen, *Tetrahedron* **2008**, *64*, 7847-7870; i) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766-1775; j) N. Marion, S. P. Nolan, *Chem. Soc. Rev.* **2008**, *37*, 1776-1782; k) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378; l) N. Bongers, N. Krause, *Angew. Chem. Int. Ed.* **2008**, *47*, 2178-2181; m) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232-5241; n) M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2011**, *47*, 6536-6544; o) E. W. Brenzovich, *Angew. Chem. Int. Ed.* **2012**, *51*, 8933-8935; p) C. Obradors, A. M. Echavarren, *Chem. Commun.* **2014**, *50*, 16-28.

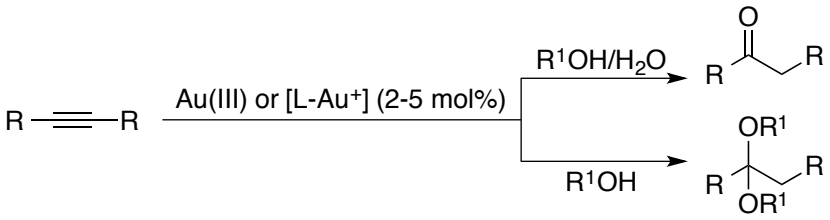
[10] a)W. Schwemberger, W. Gordon, *Chem. Zentralbl* **1935**, *106*, 514-518; b) P. G. Gassman, G. R. Meyer, F. J. Williams, *J. Am. Chem. Soc.* **1972**, *94*, 7741-7748; c) L. U. Meyer, A. de Meijere, *Tetrahedron Lett.* **1976**, 497-500; d) F. Gasparrini, M. Giovannoli, D. Misiti, G. Natile, G. Palmieri, *Tetrahedron* **1983**, *39*, 3181-3184.

[11] Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406.

[12] a) Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729-3731; b) Y. Fukuda, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013-2015; c) Y. Fukuda, K. Utimoto, *Synthesis* **1991**, 975-978.

[13] J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

water to alkynes. The reaction took place under mild conditions and with TOF up to 5400 h^{-1} (Scheme 1.3).



Scheme 1.3

The formation of new C–C and/or C–X (X = O, N, S) bonds, as well as the activation of multiple bonds described in these reactions served as promoters for the development of homogeneous gold catalysis. Subsequently, impressive research efforts have evolved into the development of other reactivity patterns, highlighting the possibilities that gold catalyzed reactions could offer to synthetic organic chemistry.

Due to the extensive number of reports, the aim of this introduction will be to give an overview on the most representative homogeneous reactions catalyzed by gold, especially in those involving the activation of multiple bonds. The reactivity of allenes in the presence of gold catalysts will be discussed in Chapter 3.

1.2 Homogeneous gold catalysis: Theoretical aspects and π-activation of unsaturated substrates

The unique properties of gold catalysts arise from the special nature of the metal center and could be rationalized considering both the theories of frontiers orbitals and of relativity.[14] Gold has the electronic configuration [Xe] $4f^{14}$ $5d^{10}$ $6s^1$ and its oxidation states range from −1 to +5, although the most common are by far +1 and +3. Furthermore, is characterized by a strong contraction of the 6s and 6p orbitals. Thus, the electrons located in these orbitals, if present, are closer to the nucleus and have greater ionization energies. On the other hand, 5d and 4f orbitals, which experiment a weaker nuclear attraction, being shielded by the 6s and 6p orbitals, are expanded and have a fine splitting as consequence of the spin-orbit interaction. Pyykkö and coworkers estimated that these relativistic effects are more significant for gold than for any other transition metal.[15]

An important and direct consequence of these peculiarities is that gold atoms are less electropositive and form stronger gold–ligand bonds compared to other group 11 metals. They can also interact with each other, and Au–Au interactions are of the same intensity as the hydrogen bonds ("aurophilicity"). Another even more important consequence is that gold complexes are excellent Lewis acids. However, because of their large diffuse orbitals, orbital interactions are preferred than charge interactions. They can be considered "soft" Lewis acids, reacting preferentially with "soft" species, such as π-systems, being less oxophilic. Gold complexes present sometimes a very particular reactivity allowing transformations that are not possible to achieve with other transition metals, or giving faster and/or more selective transformations. This superior activity is also due to relativistic effects and cannot be explained merely by a faster ligand-exchange rate.[16]

Gold(I) and gold(III) complexes have high oxidation potentials and, since they are also less oxophilic, they tolerate very well the presence of oxygen, air, water or alcohols, showing high stability in various reaction conditions. The reactions catalyzed by these complexes are therefore very easy to set up, being usually air and moisture tolerant, and can be performed in an open flask. In addition, the insensitivity of gold complexes to various oxygenated solvents has been exploited sometimes to develop ecoMfriendly reactions using water or alcohols.

Reactions performed with homogeneous gold catalysts usually require mild reaction conditions: room temperature or very gentle heating, relatively low catalyst loadings and often short reaction times. Moreover, the experiments can be followed by NMR since both gold(I) and gold(III) atoms

[14] For some reviews on the theoretical chemistry of gold, see: a) P. Pyykkö, *Angew. Chem. Int. Ed.* **2004**, *43*, 4412-4456; b) P. Pyykkö, *Inorg. Chim. Acta* **2005**, *358*, 4113-4130, c) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395-403.
[15] P. Pyykko, J. P. Desclaux, *Acc. Chem. Res.* **1979**, *12*, 276-281.
[16] Au(I) and Au(III) ligand exchange reactions follow an associative pathway and are very fast.

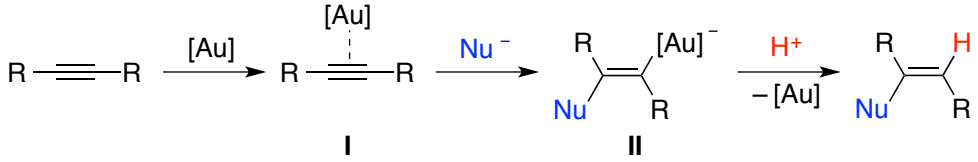
are diamagnetic. Another remarkable advantage is the reduced toxicity of gold complexes compared to other transition metals.

The L-Au^+ fragment, often involved in homogeneous gold catalysis, is isolobal to H^+ and presents sometimes the behavior of a "big soft proton". Therefore gold catalysis can be applied, at least in theory, to a large number of transformations usually catalyzed by Brønsted or Lewis acids.[17]

These catalysts are also characterized by a particular affinity for alkynes and allenes, even in the presence of other functional groups showing an exceptional tolerance that allows the use of complex substrates. Thus, gold has the ability to selectively activate alkynes and allenes towards the attack of various nucleophiles, but its reactivity goes beyond that of a simple soft Lewis acid, since can also stabilize the cationic reaction intermediates by backdonation processes. The non-classical nature of these intermediates, together with a low propensity to give β-hydride eliminations frequently results in excellent reactivities and selectivities.

It is well known that the addition reactions to alkynes or alkenes catalyzed by Brønsted acid usually require harsh conditions and are affected by numerous side reactions of the carbocation intermediates. Replacement of the proton by Hg^{2+} cations constitutes a classical solution to this problem and enables to operate in milder conditions with higher yields of the desired addition products.[18] However, the use of mercury has various drawbacks including the toxicity of the relative salts, difficult handling and disposal and fast reduction to inactive metallic form. Due to these reasons, the replacement of mercury for less toxic and more active catalysts has become a central field in synthetic research. In particular the use of gold species for alkyne activation looks as a particular interesting alternative.[19]

Coordination of C–C multiple bonds of alkynes, allenes or olefins to gold complexes is by far the most common reactivity pattern in gold catalyzed organic reactions with the consequent activation of these systems to nucleophilic attack as exemplified in Scheme 1.4.

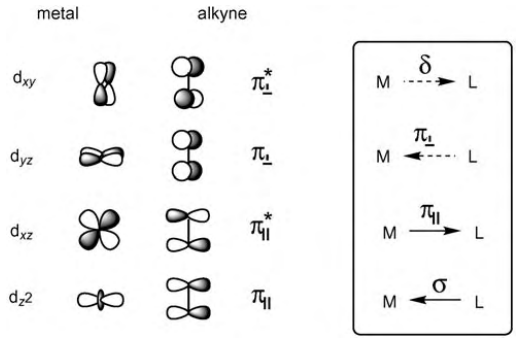


Scheme 1.4

[17] A. S. K. Hashmi, *Catal. Today* **2007**, *122*, 211-214.
[18] a) R. C. Larock in *Solvomercuration/Demercuration Reactions in Organic Synthesis*, Springer, Berlin, **1986**; b) F. Freeman, *Chem. Rev.* **1975**, *75*, 439-490.
[19] L. Hintermann, A. Labonne, *Synthesis* **2007**, 1121-1150.

The mechanism of this transformation involves a first interaction of the gold catalyst with the π-system of the substrate to form intermediate **I**, which undergoes to nucleophilic attack to form **II** usually in an *anti* manner. Final protodemetallation of organogold species **II** led to the addition product and regenerates the active catalyst.

Considering the orbitals involved in gold–alkyne interaction there are four principal components that can contribute to the bonding of these molecules as ligands. The in-plane $\pi_{\parallel}$ orbitals are responsible for a σ-symmetric ligand→metal donation as well as for the π-symmetric metal→ligand back-donation. The orthogonal, out-of-plane $\pi_{\perp}$-orbitals can engage in ligand→metal π donation (an interaction of importance in alkyne complexes in which the ligand serves as a four-electron donor), while mixing of an occupied d orbital of the metal and the empty $\pi_{\perp}^*$ orbital of the alkyne can result in an additional component of metal→ligand back-donation. This latter interaction, however, has σ symmetry, which results in only a weak overlap, and therefore leads to a residual contribution to the bonding (Scheme 1.5).[20]



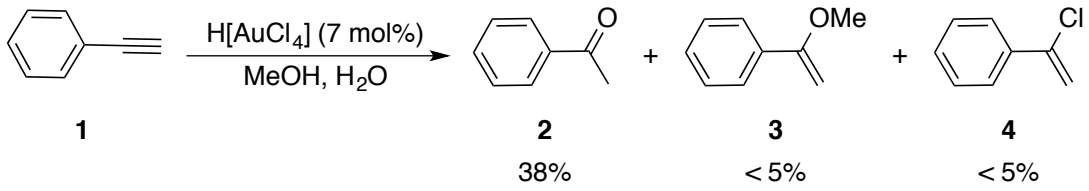
Scheme 1.5

[20] A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.

1.3 Gold-catalyzed transformations of alkynes

1.3.1 Nucleophilic Addition of Heteroatoms

The first experiments of nucleophilic additions onto alkynes were reported in 1976 by Thomas and coworkers.[21] The authors investigated the reactivity of different alkynes, such as **1**, with tetrachloroauric acid in aqueous methanol, observing the formation of ketone **2** as major reaction product, which corresponded to the Markovnikov addition of the nucleophile. Small amounts of the corresponding methyl vinyl ether **3** and vinyl chloride **4** were also formed (Scheme 1.6). This result disclosed the potential of gold catalysis in alkyne chemistry. However, the importance of these last products was not recognized at the time and the reaction catalyzed by $H[AuCl_4]$ was considered to be a gold(III) oxidation.

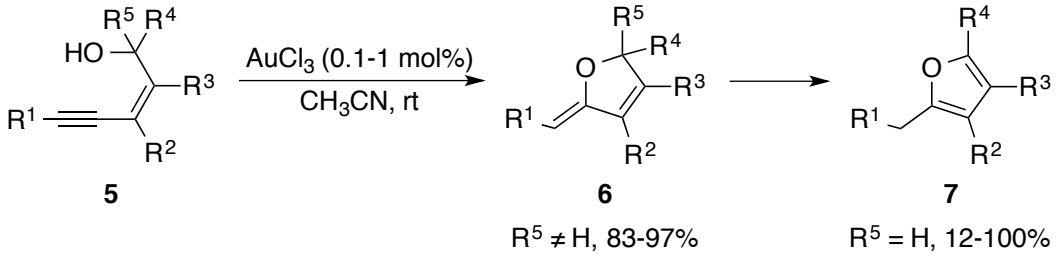


Scheme 1.6

Synthetically useful protocols for alkyne hydration were later reported by Fukuda, Utimoto[12] and Teles,[13] as well as by Arcadi[22] in 2000 using both gold(III) and gold(I) catalysts, operating under mild conditions. Apart from hydration reaction, the use of alcohols has been applied in the preparation of acetal or enol ether derivatives. A recent report by Nolan and coworkers on the hydroalkoxylation of alkynes with phenols shows the continuous interests in these processes.[23]

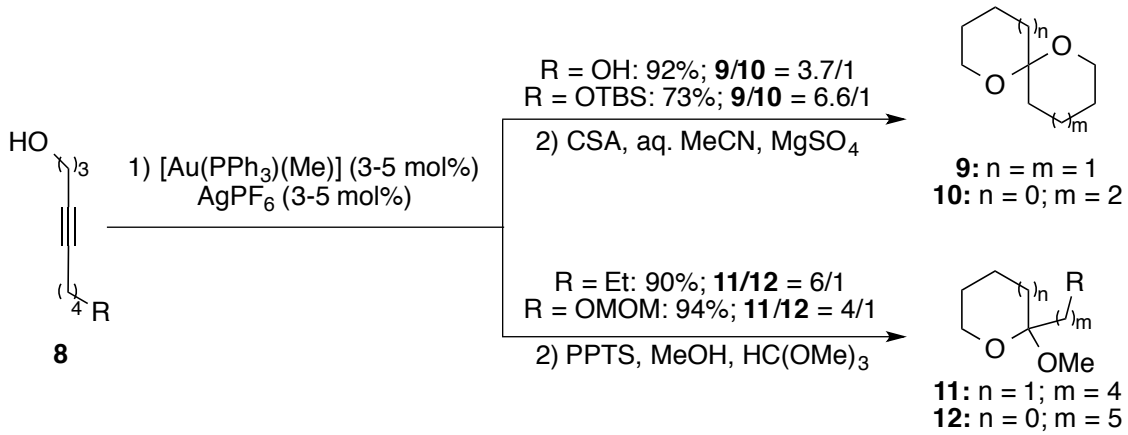
The intramolecular version of alcohol addition to alkynes has also been reported. This process constitutes a valuable tool for the preparation of oxygen heterocycles. As a representative example, Hashmi and coworkers demonstrated that (*Z*)-3-ethynylallylacohols **5** could efficiently cyclize to furan derivatives **7**.[24] The intramolecular addition of the alcohol leads to intermediate **6**, which tautomerize to the more stable arene when R^5 is an hydrogen atom (Scheme 1.7).

[21] R. O. C. Norman, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc. Perkin Trans. 1*, **1976**, 1983-1987.
[22] A. Arcadi, G. Cerichelli, M. Chiarini, S. Di Giuseppe, F. Marinelli, *Tetrahedron Lett.* **2000**, *41*, 9195-9198.
[23] Y. Oonishi, A. Gómez-Suárez, A. R. Martin, S. P. Nolan, *Angew. Chem. Int. Ed.* **2013**, *52*, 9767-9771.
[24] A. S. K Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285-2288.



Scheme 1.7

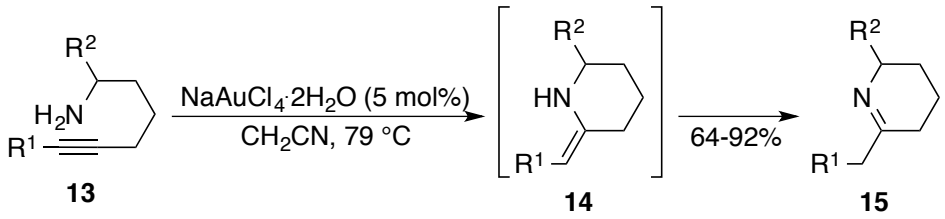
In 2006, De Branbander reported that gold can act as active catalyst for the *5-exo* selective cycloisomerization of diol derivatives **8** to spiroketals **9**/**10** or acetals **11**/**12**.[25] This reaction demonstrated that gold(I) cationic species could promote the transformation of unactivated internal alkynes that usually suffers for low regioselectivity (Scheme 1.8).



Scheme 1.8

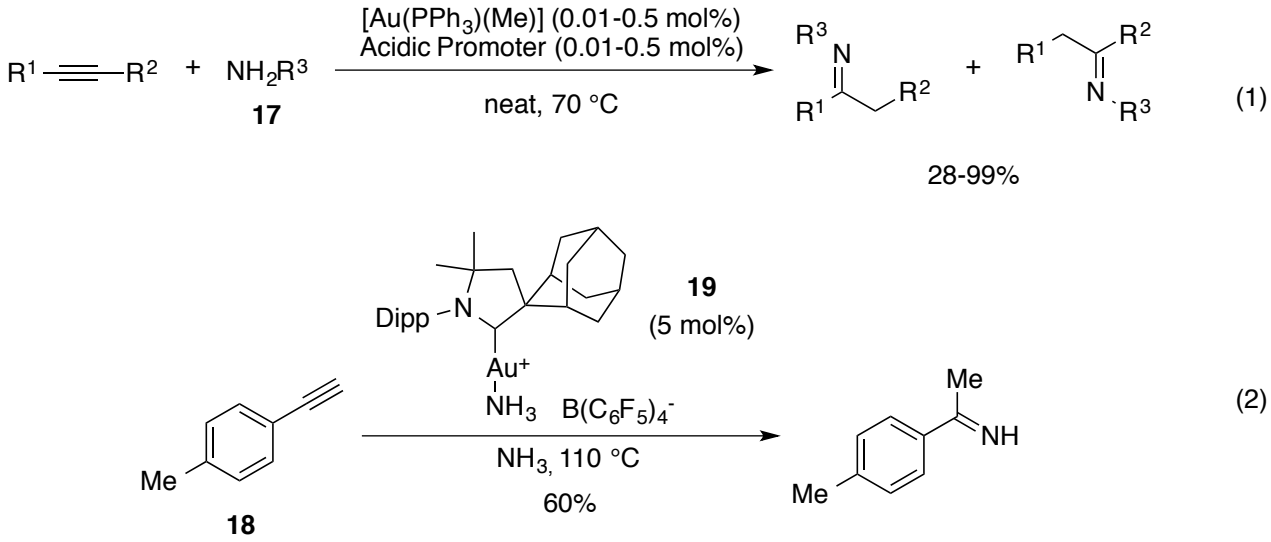
Not only alcohols or water but also amines can act as nucleophiles. Utimoto and coworkers investigated the intramolecular hydroamination reaction of alkynes **13** under mild and neutral conditions.[12,26] In this transformation gold(III) catalyst proved to be superior to palladium(II) species in the formation of the *N*-heterocycles **15**. The hydroamination takes place through a *6-exo-dig* cyclization affording enamine **14**, which tautomerized to the more stable imine **15** (Scheme 1.9).

[25] B. Liu, K. De Brabander, *Org. Lett.* **2006**, *8*, 4907-4910.
[26] Y. Fukuda, K. Utimoto, *Heterocycles* **1987**, *25*, 297-300.



Scheme 1.9

The first intermolecular hydroamination was reported by Tanaka and coworkers in 2003 using anilines **17** as nucleophiles (Scheme 1.10, Eq. 1).[27] These reactions lack of selectivity when using internal alkynes, affording a mixture of regioisomers. A remarkable achievement, later reported by Bertrand and coworkers is shown in Scheme 1.10, Eq. 2.[28] Making use of NHC-gold complex **19** they were able to accomplish the hydroamination of alkyne **18** with simple ammonia.

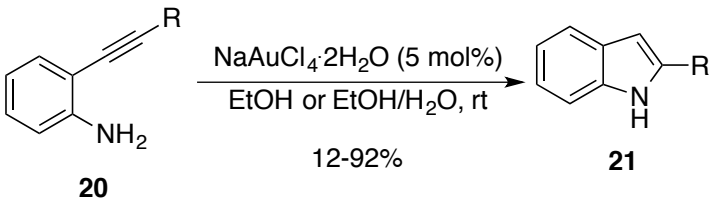


Dipp: 2,6-diisopropylphenyl

Scheme 1.10

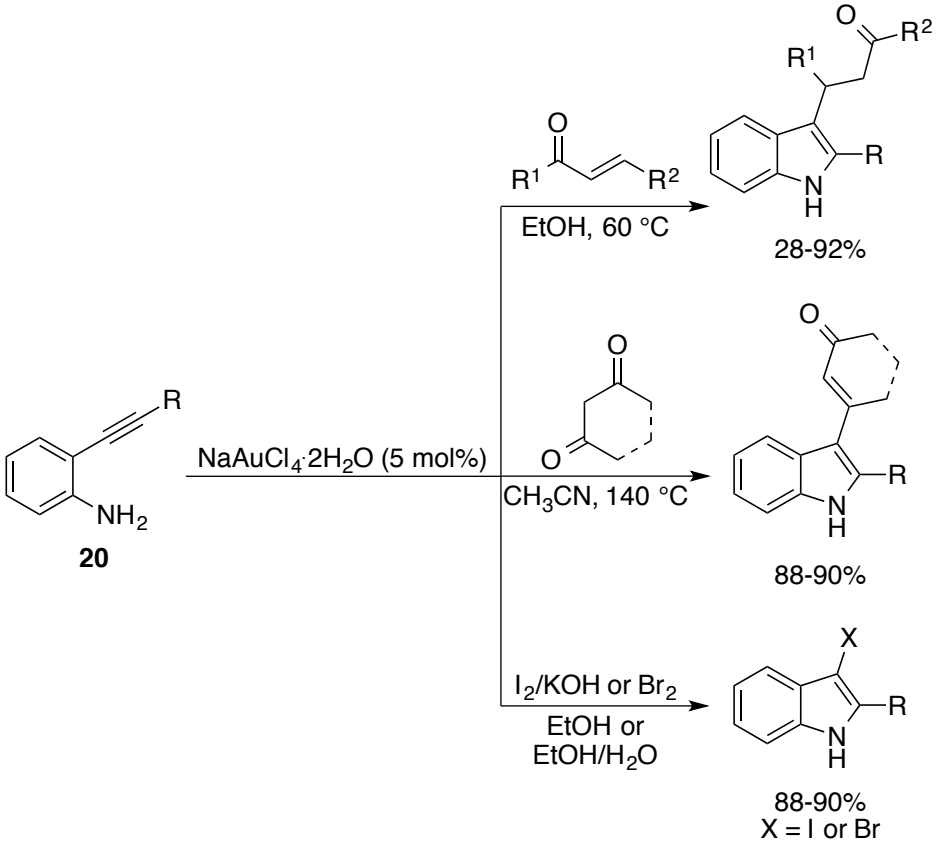
The ability of gold catalysts to promote hydroamination reactions has been exploited in the synthesis of a prevalent heterocyclic compound as indole.[9n] Starting from 2-alkynylanilines **20** in 2004, Arcadi and Marinelli reported the synthesis of functionalized indoles **21** through a gold catalyzed cyclization (Scheme 1.11).[29]

[27] E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett.* **2003**, *5*, 3349-3352.
[28] V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2008**, *47*, 5224-5228.
[29] A. Arcadi, G. Bianchi, F. Marinelli, *Synthesis* **2004**, 610-618.



Scheme 1.11

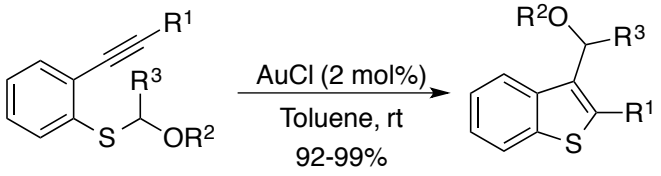
Furthermore, starting from compound **20** the same strategy was applied in domino processes completed with indole C–3 functionalization as indicated in Scheme 1.12.[29,30,31]



Scheme 1.12

The fact that sulfur is generally poisonous towards transition metals seems to indicate a general incompatibly in its use in catalysis.[32] Despite that, some gold-catalyzed additions of a different range of functionalized sulfur derivatives to alkynes have been reported. For example, Nakamura and coworkers[33] described in 2006 the efficient synthesis of 2,3-disubstituted benzotiophenes **23** under mild conditions starting from the corresponding sulfides **22** (Scheme 1.13).

[30] M. Alfonsi, A. Arcadi, M. Aschi, G. Bianchi, F. Marinelli, *J. Org. Chem* **2005**, *70*, 2265-2273.
[31] A. Arcadi, M. Alfonsi, G. Bianchi, G. D'Anniballe, F. Marinelli, *Adv. Synth. Catal.* **2006**, *348*, 331-338.
[32] L. L. Hegedus, R. W. McCabe, *Catalyst poisoning*, Marel Dekker, New York, **1984**.
[33] I. Nakamura, T. Sato, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 4473-4475.

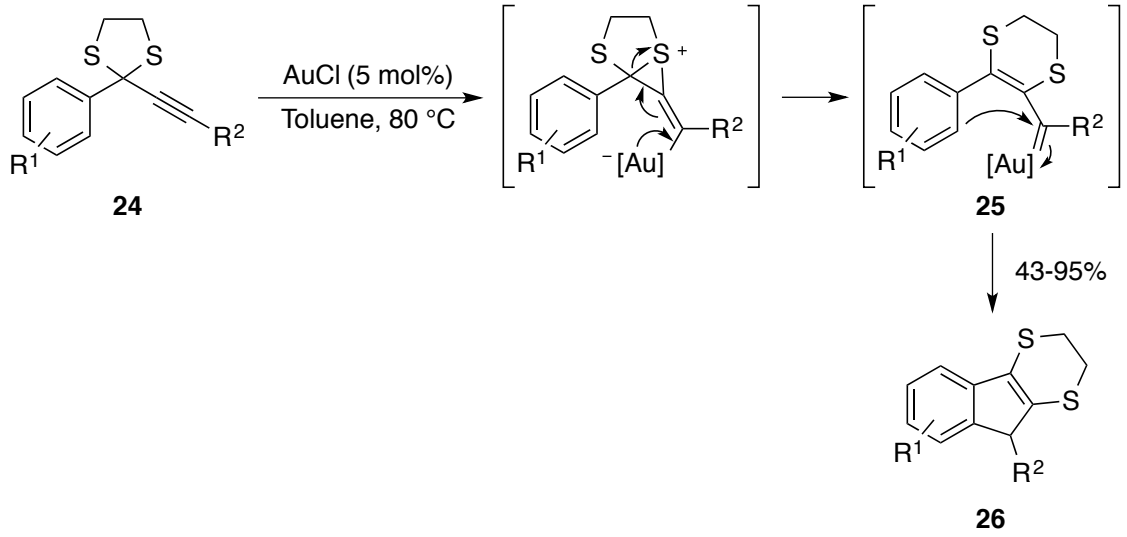


22 **23**

Scheme 1.13

Interestingly this transformation afforded C–3 functionalized benzotiophenes, a structural framework often present in biologically active molecules,[34] otherwise difficult to prepare through by electrophilic aromatic substitution reactions.

In 2007 Wang reported that dithioacetals **24** produced indenes derivatives **26** through pentannulation of aromatic rings.[35] In fact, sulfur group can participate in gold-catalyzed addition reactions to alkynes, through 1,2-sulfur migration to generate a vinylcarbenoid **25** which evolved into the final indene **26** (Scheme 1.14).



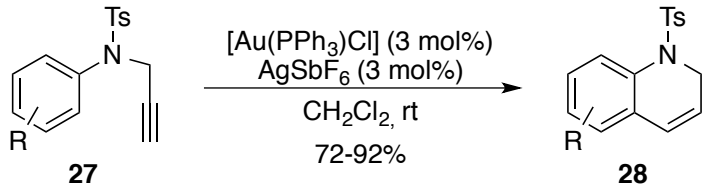
24 **25** **26**

Scheme 1.14

[34] K. C. Lee, B. S. Moon, J. H. Lee, K. -H Chung, J. A. Katzenellenbogen, D. Y. Chi, *Bioorg. Med. Chem.* **2003**, *11*, 3649-3658.
[35] L. Peng, X. Zhang, S. Zhang, J. Wang, *J. Org. Chem.* **2007**, *72*, 1192-1197.

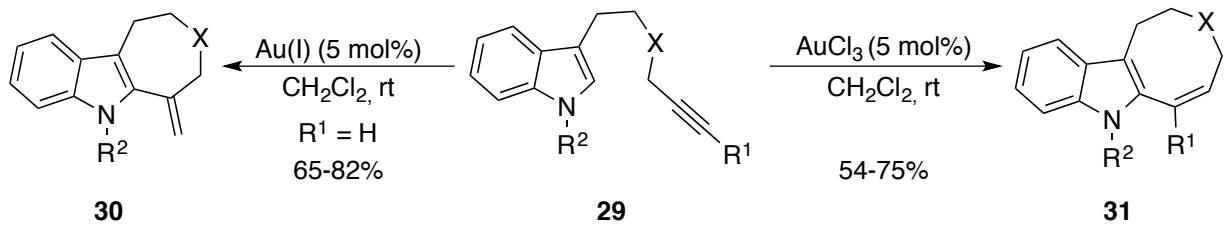
1.3.2 Nucleophilic Addition of Carbon Nucleophiles

Gold catalysts are also able to promote the addition of nucleophilic carbons to alkynes. Thus, electron-rich arenes or heteroarenes serve as nucleophiles to form the corresponding hydroarylation products.[36] For example the synthesis of *N*-tosyl-1,2-dihydroquinolines **28** was reported by Echavarren starting from *N*-propargyl-*N*-tosyl anilines **27** in the presence of a cationic gold(I) catalyst formed *in situ* by chloride abstraction from [$Au(PPh_3)Cl$] with a silver salt (Scheme 1.15).[37]



Scheme 1.15

In an interesting contribution, the same group reported a gold-catalyzed intramolecular cyclization of functionalized indoles **29**.[38] The choice of the catalyst proved crucial as two different hydroarylation processes can occur. The use of cationic Au(I) gave rise to compounds **30** *via* 7-*exo-dig* cyclization, whereas when Au(III) was employed, a rare *8-endo-dig* cyclization took place giving rise to **31** (Scheme 1.16).



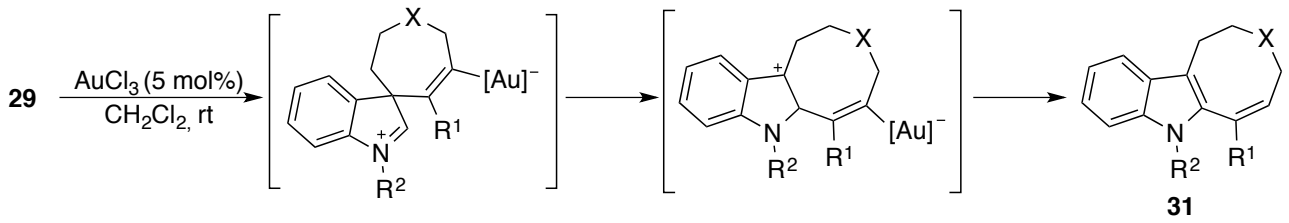
Au(I) = [$Au(PPh_3)Cl$] (5mol%), $AgSbF_6$ (5 mol%)

Scheme 1.16

The process leading to cyclooctane derivatives **31** were explained by the authors to occur through the initial formation of a C–C bond at C–3, followed by a ring expansion (1,2-migration) to afford, after protodemetallation, the final annulated indoles (Scheme 1.17).

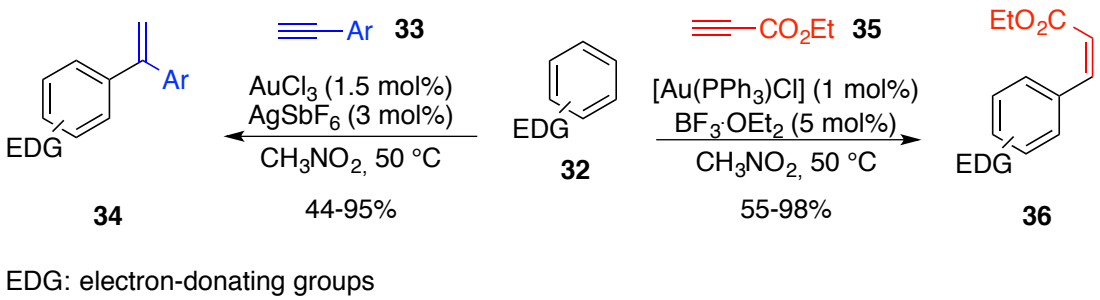
---

[36] P. de Mendoza, A. M. Echavarren, *Pure Appl. Chem.* **2010**, *82*, 801-820.
[37] C. Nevado, A. M. Echavarren, *Chem. Eur. J.* **2005**, *11*, 3155-3164.
[38] a) C. Ferrer, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 1105-1109; b) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358-1373.



Scheme 1.17

Intermolecular hydroarylation reactions with electron-rich arenes **32** were also reported and resulted in the formation of different kind of products according to the nature of the alkyne. Thus, the use of simple arylacetylenes **33** led to 1,1-disubstituted alkenes such as **34** as a result of an addition proceeding with Markovnikov regiochemistry.[39,40] On the contrary, alkynes **35** bearing electron-withdrawing groups afforded the corresponding 1,2-disubstituted derivatives **36** (Scheme 1.18).[41]

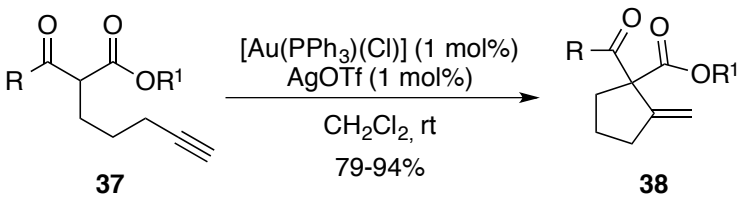


Scheme 1.18

In the case of gold(I) catalyzed reactions of electron-deficient alkynes **35**, the authors explained the formation of the *Z*-alkene as result of nucleophilic attack of the arene on the opposite side of the gold-activated alkyne. This would lead to the formation of a vinyl gold intermediate and, after protodemetallation, to the corresponding *Z*-olefin.

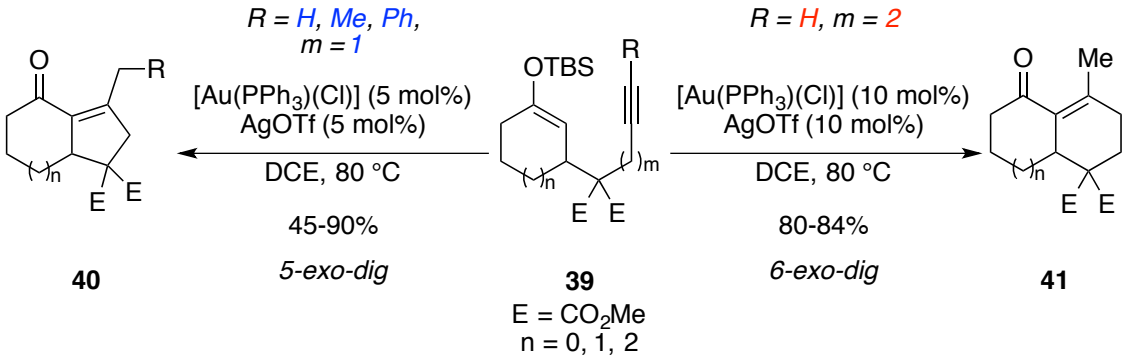
Formation of C–C bonds through reaction of alkynes with enolates has also been described. For example, Toste and coworkers reported in 2004 the intramolecular addition of a β-ketoester to an unactivated alkyne.[42] This transformation, named Conia-ene reaction, proceeded at room temperature affording functionalized cyclopentenes **38** in high yield starting from **37** (Scheme 1.19, Eq. 1). Furthermore, carbocyclization of alkynylenol ethers **39** was described by Lee for the synthesis of α,β-enones **40** and **41** through *5-* or *6-exo-dig* processes, respectively (Scheme 1.19, Eq. 2).[43]

[39] Z. Shi, C. He, *J. Org. Chem.* **2004**, *69*, 3669-3671.
[40] Z. Li, Z. Shi, C. He, *J. Organomet. Chem.* **2005**, *690*, 5049-5054.
[41] M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485-3496.
[42] J. J. Kennedy-Smith, S. T. Stauben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526-4527.
[43] K. Lee, P. H. Lee, *Adv. Synth. Catal.* **2007**, *349*, 2092-2096.



37 **38**

(1)



40 **39** **41**

E = CO_2Me
n = 0, 1, 2

(2)

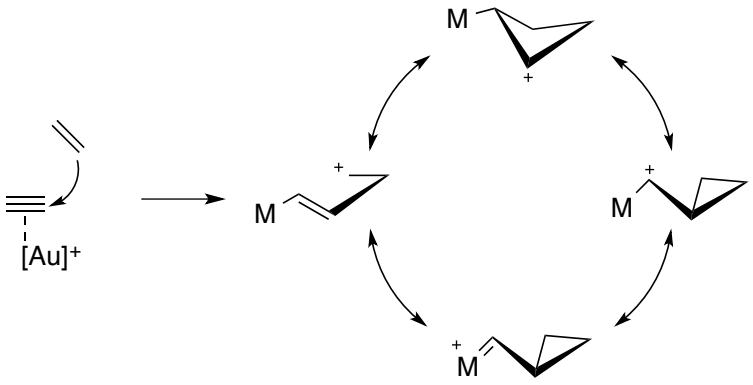
Scheme 1.19

1.3.3 Nucleophilic Additions of Alkenes: Enyne Cycloisomerization

Cycloisomerizations of enynes are probably the most representative C–C bond forming reactions catalyzed by electrophilic metal complexes like gold.[44] These transformations enable the creation of molecular complexity from relatively easily available starting materials in a straightforward manner.

Despite the structural simplicity of the 1,*n*-enynes, their reactivities in the presence of gold catalysts are very different due to the complex mechanistic scenario. However, all the transformations are initiated by the gold coordination to the alkyne followed by a nucleophilic attack of the olefin.

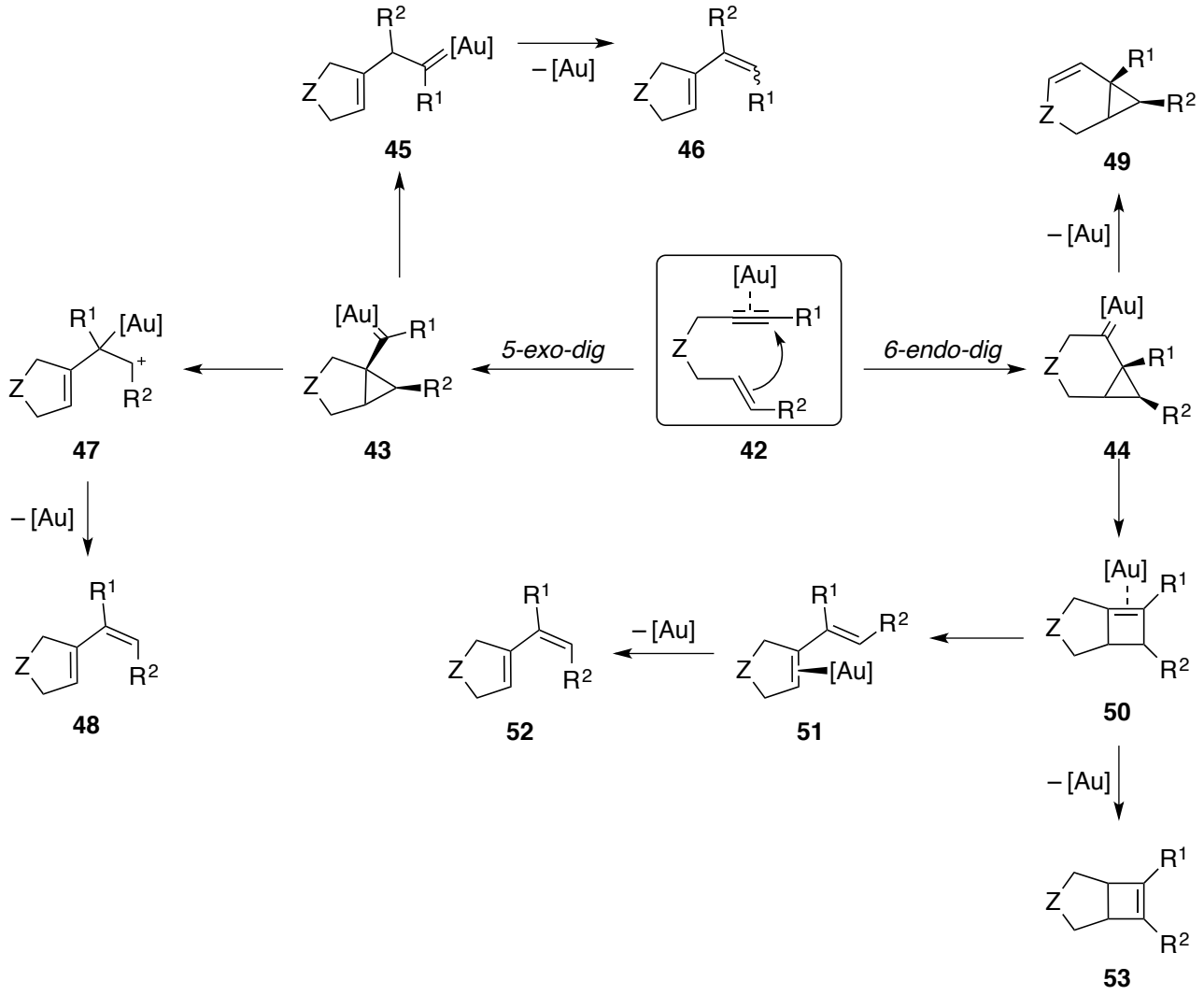
This process generates a new C–C bond resulting in a species, which can be represented in several resonance forms from carbene to carbocations (Scheme 1.20). The existence of this variety of resonance forms translates into a variety of possible reaction pathways. Thus, it is normally not easy to predict the result of these reactions.



Scheme 1.20

As an illustration of this complexity, a general overview of the molecular diversity accessible from 1,6-enynes of general structure **42** is shown in Scheme 1.21. Herein, two regiodivergent nucleophilic attacks can take place, a *5-exo-dig* cyclization leading to intermediate **43** or a *6-endo-dig* cyclization towards intermediate **44** (only the resonance structure corresponding to the carbene are shown). Depending on the substituents, the gold catalyst and the reaction conditions, these two intermediates can evolve in different manners into a variety of structures.

[44] For recent reviews on enyne cycloisomerization see: a) Ref. 9a; b) Ref. 9f; c) D.-H. Zhang, Z. Zhang, M. Shi, *Chem. Commun*. **2012**, *48*, 10271-10279.

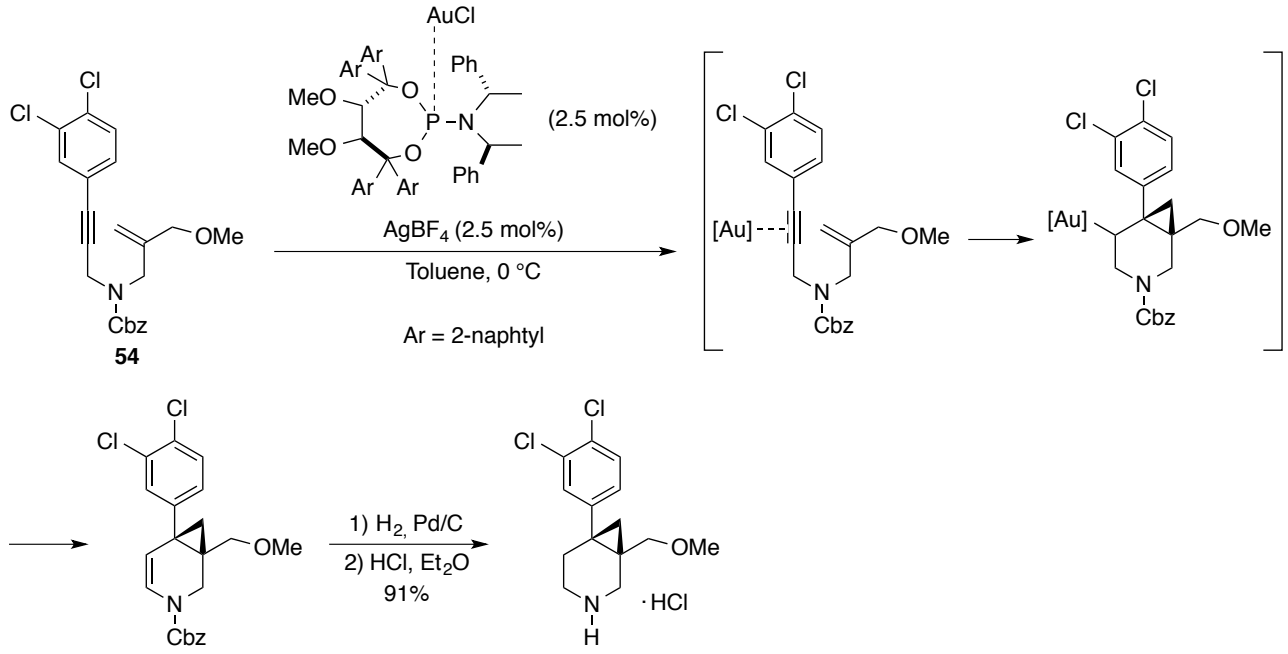


Scheme 1.21

Intermediate **43** can evolve to generate new rearranged carbene **45** by the formal insertion of the terminal alkene carbon into the alkyne carbons. This new carbene **45** undergoes 1,2-CH insertion to yield 1,3-diene **46**. Alternatively, carbene intermediate **43** can also give rise to products of single-cleavage rearrangement **48** through intermediate **47**. On the contrary, intermediate **44** derived from the *6-endo* cyclization can lead to bicyclo[4.1.0]hept-2-ene derivatives **49** by 1,2-CH insertion. Besides, isomerization of **44** by ring expansion of the cyclopropane gives (η^2-cyclobutene) gold(I) complex **50**. The opening of this gold(I) complex can form complex **51**, precursor of 1,3-dienes **52**. Highly strained bicyclo[3.2.0]hept-5-ene **53**, have been also isolated. The complexity of this picture can be increased as some of the intermediates can be further trapped with additional nucleophiles in both inter- and intramolecular manner. Moreover, the length and structure connecting the alkene and the alkyne can provide further reaction modes.

The utility of this rich reactivity has been exploited in the synthesis of natural products or compounds with relevant properties in medicinal or biological chemistry. As an example, in

Scheme 1.22 is illustrated the use of an enantioselective gold-catalyzed cycloisomerization of 1,6-enyne **54** as key step in the synthesis of antidepressive drug candidate GSK1073636, **55**.[45]

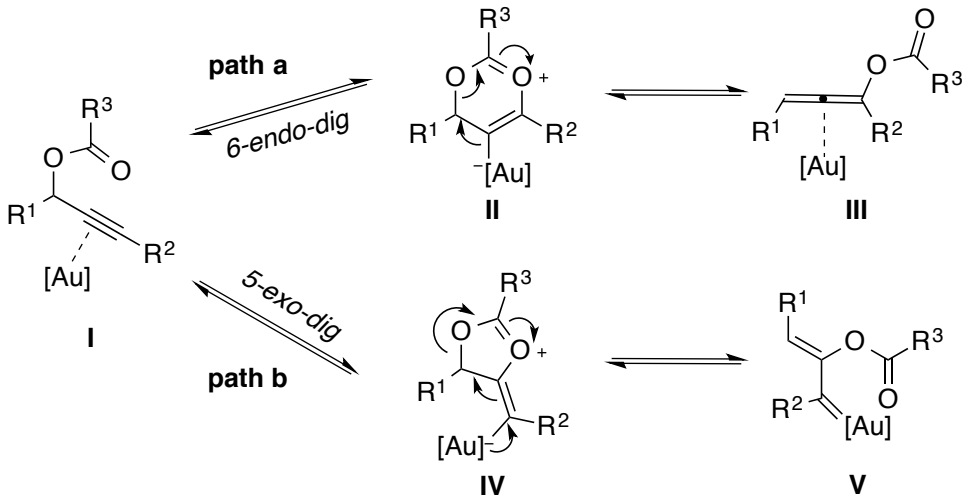


Scheme 1.22

[45] H. Teller, A. Fürstner, *Chem. Eur. J.* **2011**, *17*, 7764-7767.

1.3.4 Rearrangements of Propargylic Esters

An important group of gold-catalyzed transformations involves the participation of propargyl esters and derivatives.[46] As reported in scheme 1.23, after activation of the alkyne by gold, intermediate **I** can evolve according to two different paths. Thus, it can undergo a *6-endo-dig* cyclization to produce intermediate **II**, which further rearrange into allene **III** (path a). This transformation into allenyl esters is an example of [3,3] sigmatropic rearrangement and is generally described as a 1,3 acyloxy migration. Alternatively, activated substrate **I** can undergo a *5-exo-dig* cyclization to form intermediate **IV**, which through ring opening form the metal-stabilized carbene **V**. This process, which involve a 1,2-acyloxy migration, is often referred to as a Rautenstrauch rearrangement.[47]



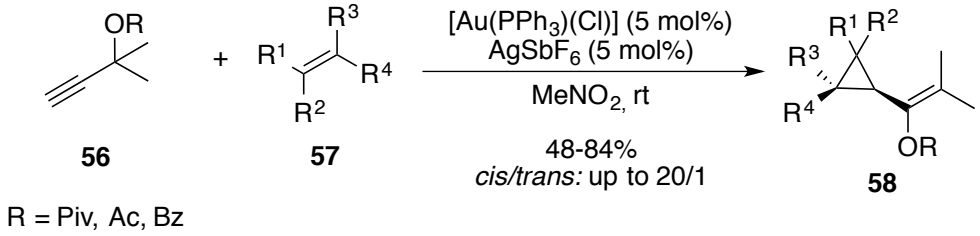
Scheme 1.23

As a general trend, when R^2 is H or an EWG, 1,2-migration preferentially occurs, while unbiased internal alkynes ($R^2 \neq H$) undergo a 1,3-acyloxy rearrangement.[48,49] However, other aspects, such as the type of catalyst, the substitution pattern at the propargyl moiety as well as the temperature can influence the reaction outcome.

The formation of a carbene-like intermediate through 1,2-migration with alkenes **57** was exploited by Toste and coworkers in the intermolecular cyclopropanation reaction of propargyl esters **56**.[49] In the presence of cationic gold(I) catalyst, cyclopropans **58** were prepared with high

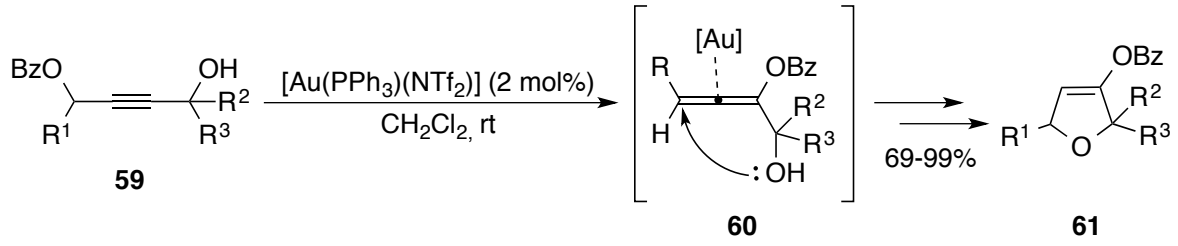
[46] For some recent reviews on this topic see: a) Ref. 9e; b) J. Marco-Contelles, E. Soriano, *Chem. Eur. J.* **2007**, *13*, 1350-1357; c) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692-706; d) X.-Z. Zhu, D. Shu, C. M. Schienebeck, W. Tang, *Chem. Soc. Rev.* **2012**, *41*, 7698-7711; e) R. K. Shiroodi, V. Gevorgyan, *Chem. Soc. Rev.* **2013**, *42*, 4991-5001.
[47] V. Rautenstrauch, *J. Org. Chem.* **1984**, *49*, 950-952.
[48] E. Soriano, J. Marco-Contelles, *Chem. Eur. J.* **2008**, *14*, 6771-6779.
[49] M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

diasteroselectivity. The reaction tolerated a wide range of olefin substitution and common esters such as pivaloate, acetate and benzoate could be employed (Scheme 1.24).



Scheme 1.24

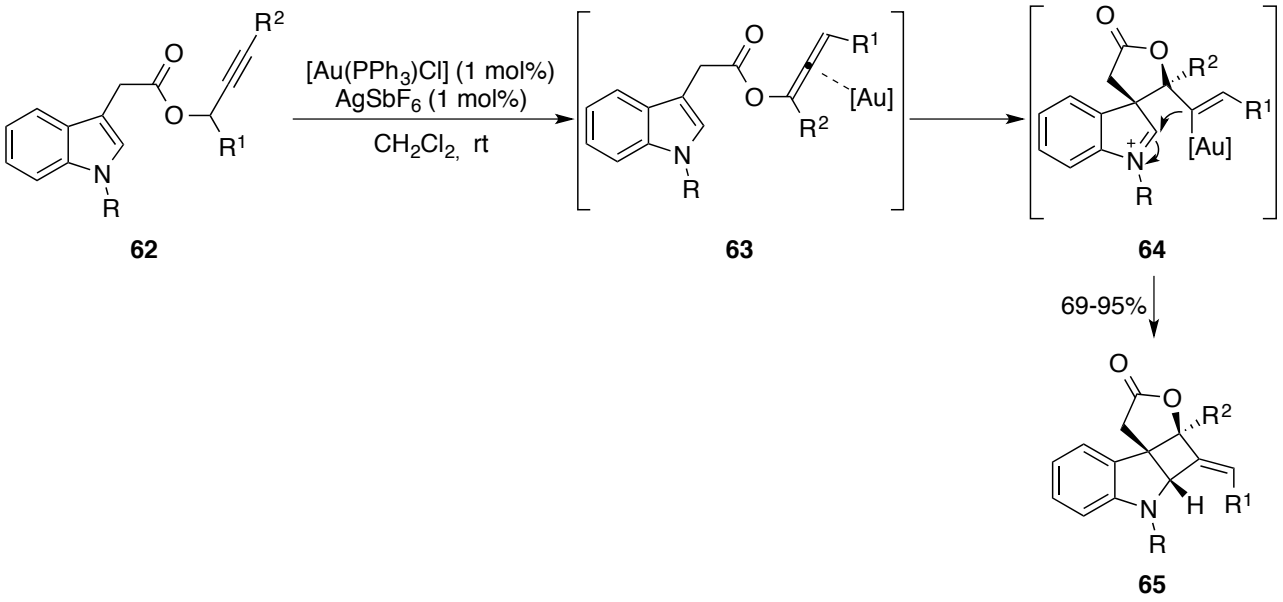
On the other hand, starting from butynediol monobenzoate **59**, Gagosz described an efficient synthesis of functionalized 2,5-dihydrofurans **61** through 1,3-shift of the ester and formation of allene **60** as intermediate.[50] Then, activation of the allene by coordination to gold enabled the nucleophilic attack of the alcohol to form the final products (Scheme 1.25).



Scheme 1.25

Another interesting example of 1,3-acyloxy migration, that involves indole derivatives, was reported by Zhang in 2005.[51] During the study of the general reactivities of propargylic carboxylates in the presence of Au salts, indoles **62** were treated with cationic gold(I) complex generated *in situ* by the reaction of [Au(PPh_3)Cl] and $AgSbF_6$ observing a complete conversion into compounds **65** at room temperature (Scheme 1.26).

[50] A. Buzas, F. Istrate, F. Gagosz, *Org. Lett.* **2006**, *8*, 1957-1959.
[51] L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804-16805.

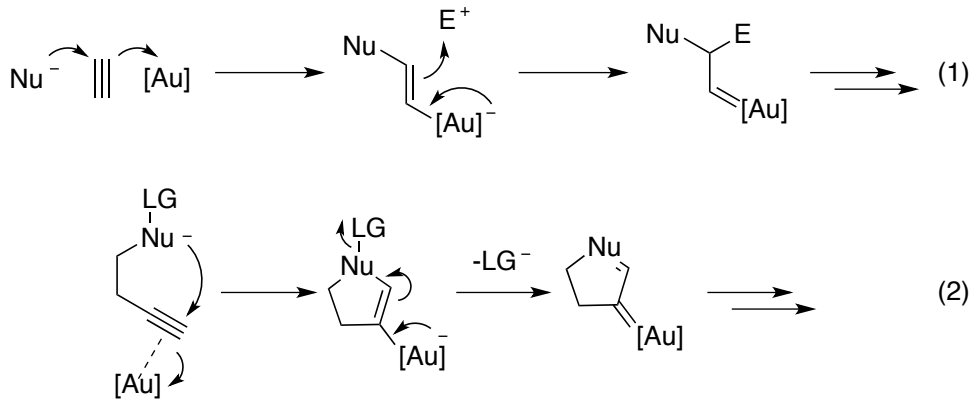


Scheme 1.26

Compound **62** by a first [3,3]-rearrangement led to allenyl intermediate **63**, which, in a second catalytic cycle, is activated by the same gold(I) species. Subsequent electrophilic attack on indole lead to spiro intermediate **64**, which then cyclize to final product **65**. Only exocyclic *E* double bond was observed in the product structure probably because of steric reasons.

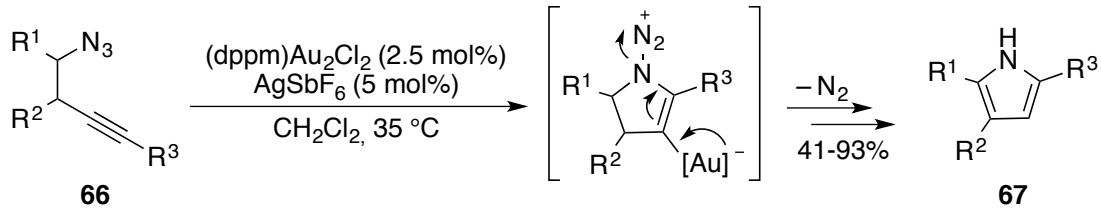
1.3.5 Addition of Nucleophiles with Leaving Groups

The reactivity of gold is not limited to the electrophilic activation of multiple bonds. In fact, this metal could react as a π-acid, and after it could behave as electron-donor, as reported in literature.[14c] In particular, a metal-carbenoid behavior could be derived from the back-bonding from gold to an electron-deficient intermediate, leading to the formation of an active species that could evolve in several ways (Scheme 1.27, Eq. 1). Making use of this idea, Toste and coworkers envisioned that the use of a nucleophile bearing a leaving group could be employed for the generation of a gold carbenoid intermediate. Thus, after an attack of the nucleophile onto the activate alkyne, gold might assist the loss of the leaving group, which finally should lead to the formation of a gold carbenoid intermediate (Scheme 1.27, Eq. 2).[52]



Scheme 1.27

This strategy was employed in the synthesis of pyrroles **67** from homopropargyl azides **66**, which reacted in the presence of a cationic gold(I) catalyst. The gold-assisted extrusion of molecular nitrogen enables an access to the pyrrole derivatives (Scheme 1.28).[53c]

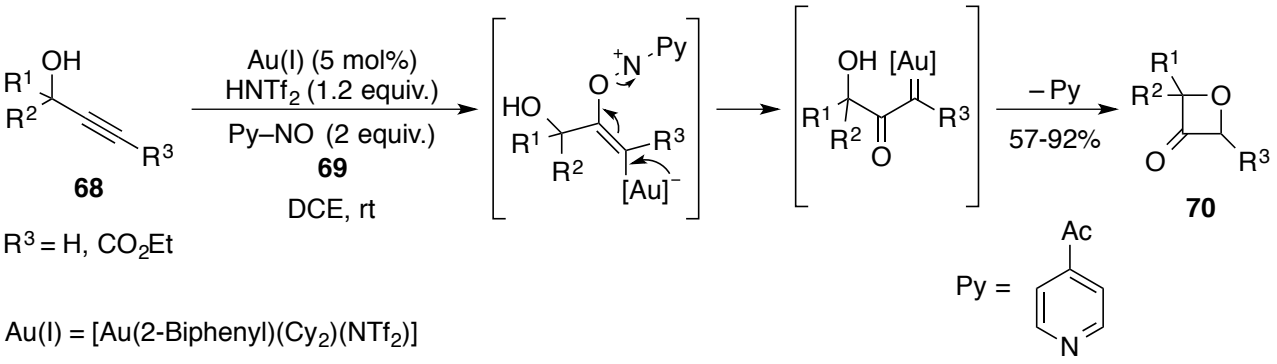


66 **67**

Scheme 1.28

[52] a) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859, b) X. Shi, D. J. Gorin, D. F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802-5803; c) D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260-11261.

An intermolecular approach was exploited for the efficient synthesis of oxetan-3-ones **70** starting from ready available propargyl alcohols **68**, as reported by Zhang. In this transformation, the gold-activated alkyne is converted into a reactive α-oxo carbene intermediate by oxidation with the pyridine *N*-oxide derivative **69**. Subsequent intramolecular nucleophilic attack of the alcohol and protodemetallation led to the final products in high yield (Scheme 1.29).[53]

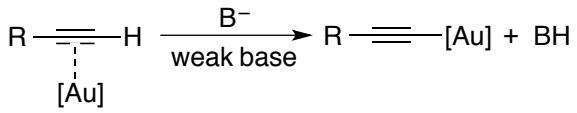


Scheme 1.29

[53] L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8550-8551.

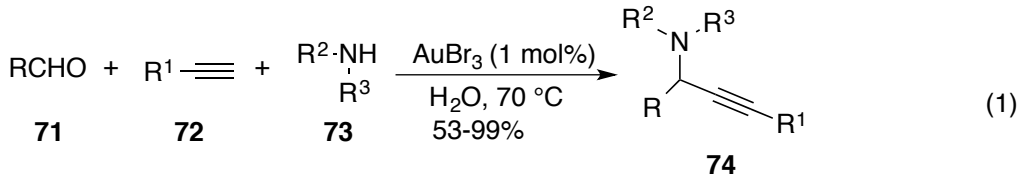
1.3.6 Formation of Gold Acetylides and New Activation Modes of Terminal Alkynes by Gold

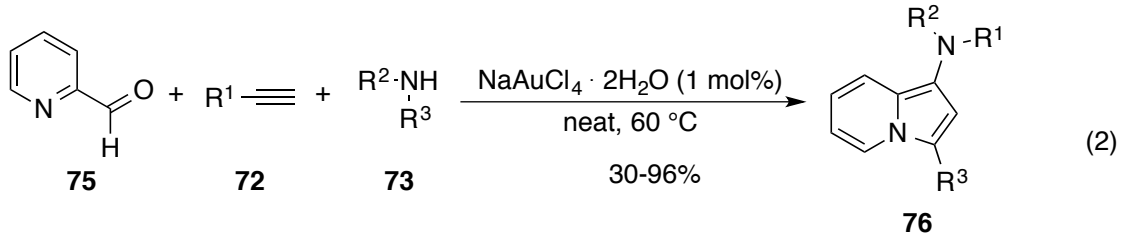
In addition to the previously disclosed gold-catalyzed transformations, the coordination of gold to terminal alkynes translates into an enhancement of the acidity of the C–H bond. Thus, in the presence of a mild base, the formation of a gold acetylide species can occur, as with other transition metals (Scheme 1.30). These new species can either react as organometallics in nucleophilic addition and substitution reactions or participate in catalytic redox processes.[54]



Scheme 1.30

Among the first studies exploiting the reactivity of gold acetylides, in 2003 Li and coworkers reported their use for the synthesis of propargyl amines **74** by a multicomponent reaction between aldehydes **71**, terminal alkynes **72** and secondary amines **73** (Scheme 1.31, Eq. 1).[55] In this transformation, the gold acetylide reacted with the in-situ generated iminium species. Lin and Yan applied this reactivity for the synthesis of relevant aminoindolizines **76** by using picolinaldehyde (**75**) (Scheme 1.31, Eq. 2).[56]

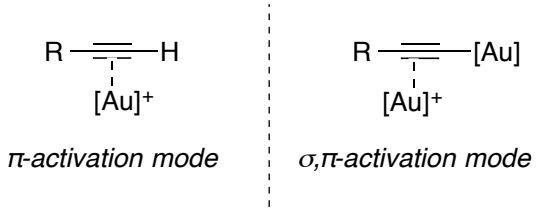




Scheme 1.31

[54] For some recent reviews including the formation of gold acetylides see a) T. de Haro, C. Nevado, *Synthesis* **2011**, 2530-2539; b) T. C. Boorman, I. Larrosa, *Chem. Soc. Rev.* **2011**, *40*, 1910-1925.
[55] C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125,* 9584-9585.
[56] B. Yan, Y. Liu, *Org. Lett.* **2007**, *9*, 4323-4326.

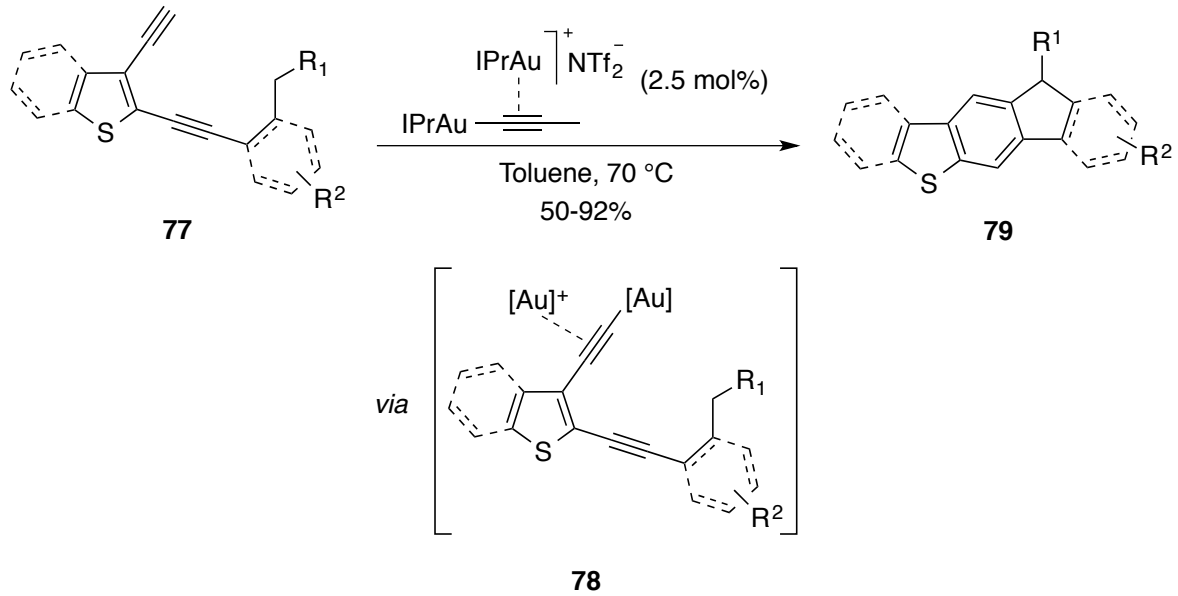
Notably, these transformation take place using gold(III) catalysts in spite of that the formation of gold(I) acetylides has been also reported.[57] Moreover, a new mode of alkyne activation beyond the π-activation and according to the capability of gold to form acetylides has been recently proposed and demonstrated.[58] This recent studies enabled the establishment of the new concept of activation, which consist of a dual σ,π-activation (Scheme 1.31).



Scheme 1.32

This activation mode has opened new pathways in gold catalysis, named as gold-catalysis 2.0 by Hashmi,[59] and it is currently being exploited in synthesis. For example, the same author recently reported a gold-catalyzed cycloisomerization of 2,3-diethynylthiophenes **77** with a terminal triple bond affording indanothiophenes and fluorenothiophenes **79**. The reaction seems to proceed by first formation of gold acetylide and π-coordination, intermediate **78**, followed by cyclization and C–H insertion processes (Scheme 1.33).[60]

[57] a) E. Vergara, E. Cerrada, A. Casini, O. Zava, M. Laguna, P. J. Dyson, *Organometallics* **2010**, *29*, 2596-2603; b) K. J. Kilpin, R. Horvath, G. B. Jameson, S. Telfer, K. C. Gordon, J. D. Crowley, *Organometallics* **2010**, *29*, 6186-6195; c) M. C. Blanco, J. Camara, M. C. Gimeno, P. G. Jones, A. Laguna, J. M. de-Luzuriaga, M. E. Olmos, M. D. Villacampa, *Organometallics* **2012**, *31*, 2597-2605.
[58] P. H.-Y. Cheong, P. Morganelli, M. R. Luzung, K. N. Houk, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 4517-4526.
[59] I. Braun, A. M. Asiri, A. S. K. Hashmi, *ACS Catal.* **2013**, *3*, 1902-1907.
[60] M. M. Hansmann, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, *52*, 2593-2598.

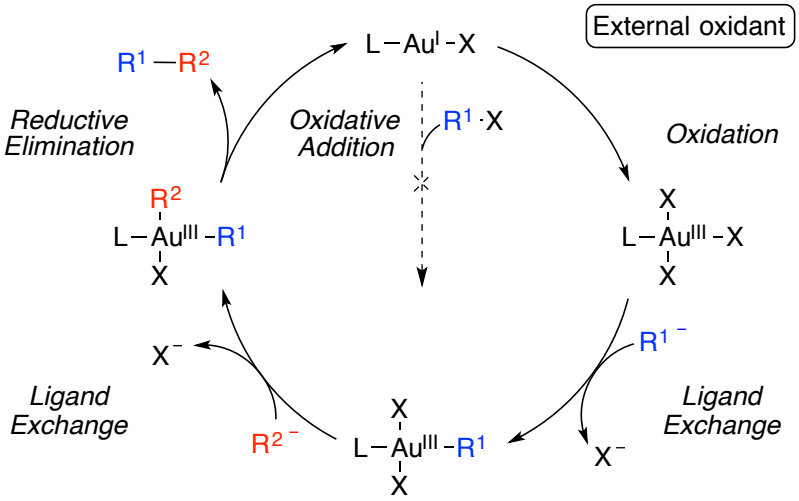

R1
S
R2
IPrAu
NTf2−
(2.5 mol%)
IPrAu
Toluene, 70 °C
50-92%
R1
S
R2
77
79
via
[Au]+
[Au]
R1
S
R2
78

Scheme 1.33

1.4 Au(I)/Au(III) Catalysis

Another interesting field of current research in gold catalysis involves the viability to develop synthetic procedures based on redox reactions of the species Au(I)/(III).[61] Under homogeneous catalysis conditions, gold may exist in the +1 or +3 oxidation states but rarely switches between the two during the course of a reaction due to the high redox potential of the Au(I)/(III) couple (E_0 = +1.41 V)[62] that makes the oxidation of gold(I) to gold(III) a challenging process. To achieve redox Au(I)/(III) catalytic cycle under homogeneous conditions the use a sacrificial external oxidant is required, being $PhI(OAc)_2$ or Selectfluor commonly employed to achieve this goal.

In gold-catalyzed reactions involving a Au(I)/Au(III) redox process, oxidative addition is nor responsible for the oxidation of gold.[63] In contrast, the formation of the Au–C bond occurs through ligand exchange processes prior the reductive elimination, as indicated in Scheme 1.34.



Scheme 1.34

An early example of a gold-catalyzed C–C coupling reaction involving a redox Au(I)/(III) cycle was reported by Tse and coworkers in 2008.[64,65] In this work, the homodimerization of arenes **80** is described. The transformation is accomplished using $HAuCl_4$ as the catalyst and $PhI(OAc)_2$ as the oxidant, affording the corresponding biaryls **81** in moderate to good yields (Scheme 1.35).

---

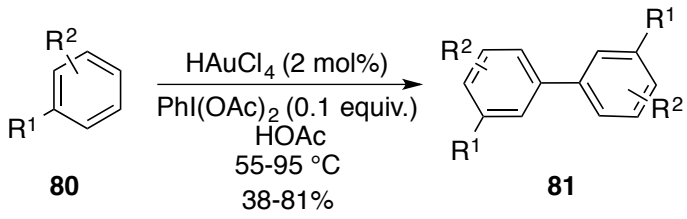
[61] For recent reviews see: a) H. A. Wegner, *Chimia* **2009**, *63*, 44-48; b) M. N. Hopkinson, A. D. Gee, V. Gouverneur, *Chem. Eur. J.* **2011**, *17*, 8248-8262; c) M. Livendahl, A. M. Echavarren, *Chimica Oggi* **2012**, *30*, 19-21.

[62] S. G. Bratsch, *J. Phys. Chem. Ref. Data* **1989**, *18*, 1-21.

[63] In fact, the oxidative addition of organic halides is non-trivial for gold(I) and to the date has been demonstrated only for alkylgold(I) complexes with simple alkyl iodides. For selected examples see: a) A. Tamaki, J. K. Kochi, *J. Chem. Soc. Dalton Trans.* **1973**, 2620-2626; b) A. Johnson, R. J. Paddephatt, *Inorg. Nucl. Chem. Lett.* **1973**, *9*, 1175-1177; c) A. Tamaki, J. K. Kochi, *J. Organomet. Chem.* **1973**, *64*, 411-425.

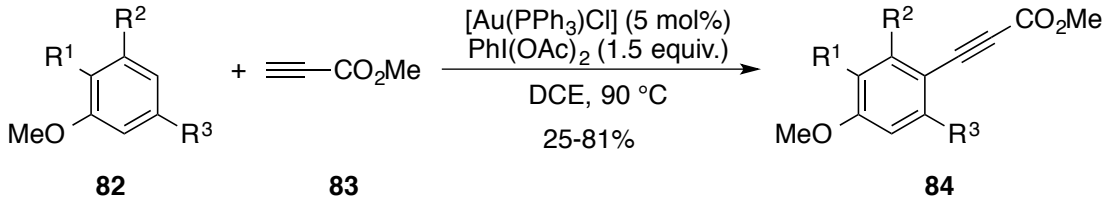
[64] A. Kar, N. Mangu, H. M. Kaiser, M. Beller, M. K. Tse, *Chem. Commun.* **2008**, 386-388.

[65] A. Kar, N. Mangu, H. M. Kaiser, M. K. Tse, *J. Organomet. Chem.* **2009**, *694*, 524-537.



Scheme 1.35

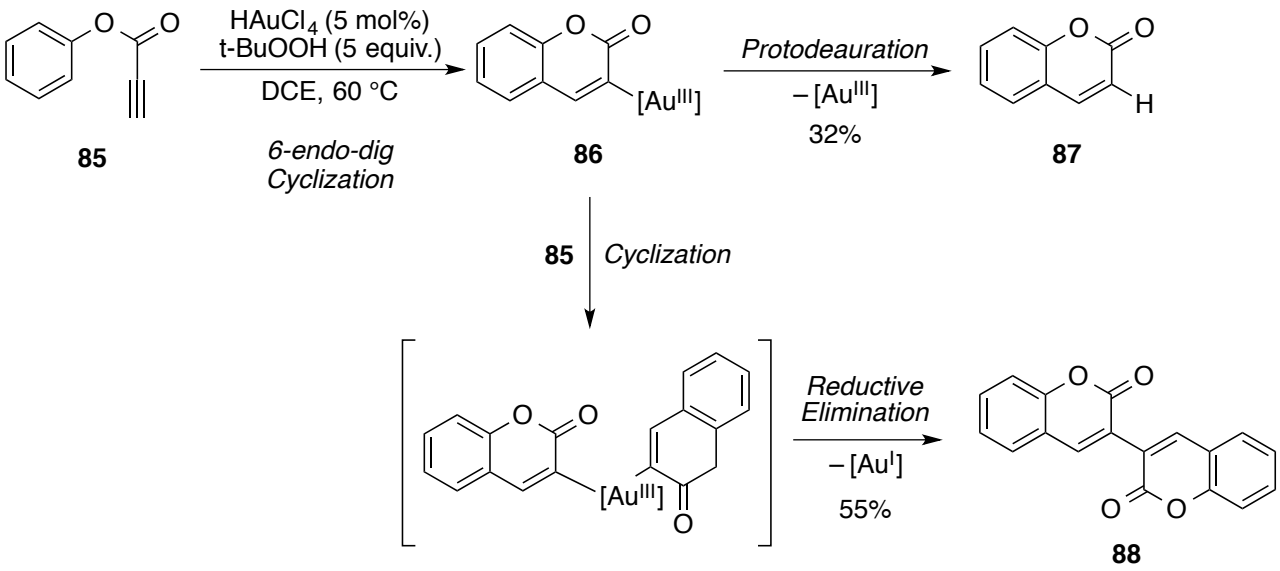
The extension of this methodology to cross-coupling reactions still remains challenging. A remarkable example was reported in 2010 by Nevado and coworkers.[66] Herein, a Sonogashira-like cross coupling of electron-rich arenes **82** with methyl propiolate **83** was described. In this case, a gold(I) catalyst was employed along with $PhI(OAc)_2$ as oxidant (Scheme 1.36). The gold-catalyzed coupling gave the corresponding ethynylarenes **84** in moderate to good yields. Interestingly, no biaryl or hydroarylation products where detected under the reported reaction conditions.



Scheme 1.36

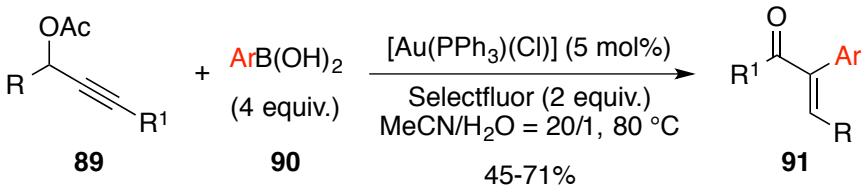
Organogold complexes involved in oxidative C–C coupling reactions are also accessible from gold-catalyzed nucleophilic addition processes. A gold-catalyzed nucleophilic addition-oxidative coupling sequence was reported by Wegner and coworkers in 2008.[67] Starting from phenyl propiolate **85**, along with the expected hydrofunctionalization product **87**, they isolated compound **88**, formed by an oxidative dimerization of the cyclization intermediate **86**. This reaction occurred in the presence of a strong oxidizing agent such as *tert*-butylhydroperoxide (Scheme 1.37).

[66] T. de Haro, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 1512-1513.
[67] H. A. Wegner, S. Ahles, M. Neuburger, *Chem. Eur. J.* **2008**, *14*, 11310-11313.



Scheme 1.37

More recently, it was demonstrated that the protodeauration of organogold complexes formed in these transformations could be completely avoided, as reported by Zhang.[68] Furthermore, when an alternative coupling partner, such as an arylboronic acid was added to the reaction mixture, it was possible to isolate the corresponding C–C cross-coupling product (Scheme 1.38). Thus, propargylic acetates **89** and arylboronic acids **90** underwent oxidative cross-coupling reaction giving rise to 2-arylenones **91** in moderate to good yields using [Au(PPh$_3$)Cl] as catalyst and Selectfluor as oxidant.

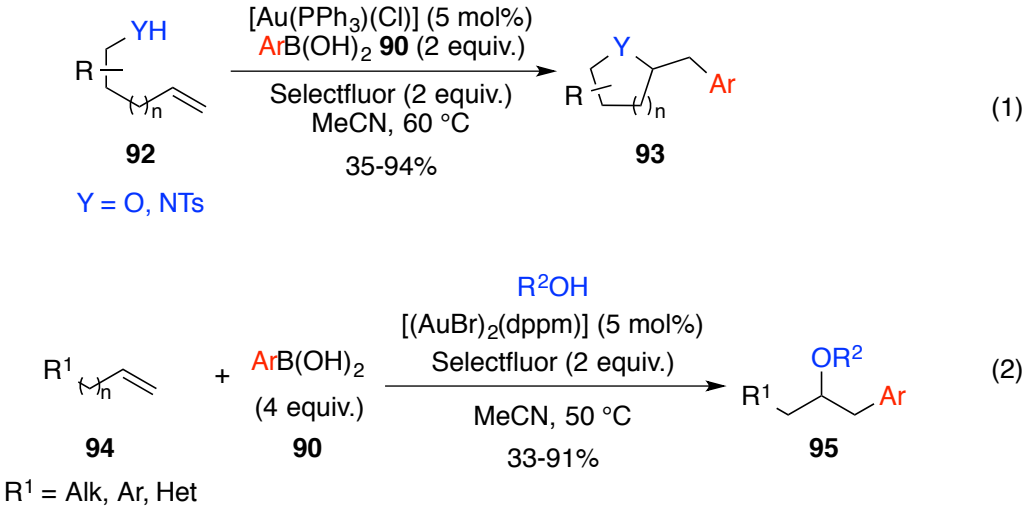


Scheme 1.38

Although more commonly reported for alkynes, gold can mediate also oxidative arylation reactions after a nucleophilic addition on alkenes. For example terminal alkenes **92** bearing an hydroxyl or tosylamide substituent reacted in the presence of gold(I), Selectfluor and aryl boronic acids **90** to yield benzyl tetrahydrofurans or tetrahydropyrrols **93** (Scheme 1.39, Eq. 1).[69] Similar reactivity was reported also by Toste using a bimetallic gold(I) catalyst able to stabilize gold(III) intermediates through aurophilic Au(I)–Au(III) interactions.[70] In addition the nucleophilic addition-oxidative

[68] G. Zhang, Y. Peng, L. Cui, L. Zhang, *Angew. Chem. Int. Ed.* **2009**, *48*, 3112-3115.
[69] G. Zhang, L. Cui, Y. Wang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 1474-1475.
[70] A. D. Melhado, W. E. Brenzovich, Jr., A. D. Lackner, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8885-8887.

arylation could be extended to intermolecular reactions with terminal alkenes **94** and aryl boronic acids **90** in the presence of alcohol yielding 4-oxoarylation compounds **95** (Scheme 1.39, Eq. 2).



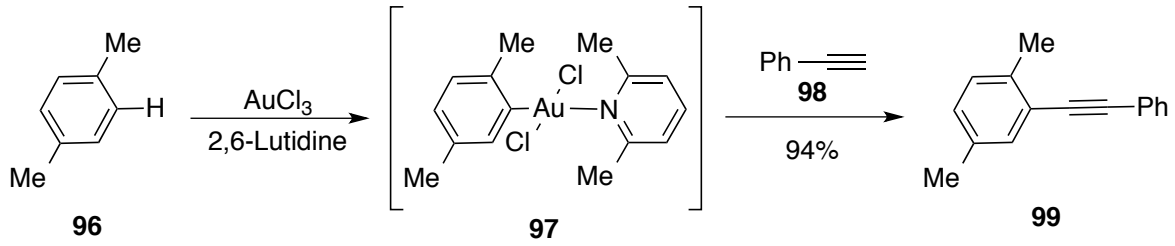
Scheme 1.39

1.5 Other Relevant Gold Transformations

This section includes some selected relevant transformations involving gold, on other unsaturated substrates, apart from reactions involving the activation of alkynes.

Gold(III) salts proved capable to activate arenes, as early established by Kharasch and Isbell in 1931.[71] Despite being known for long time, this ability was not explored until recent years, when some relevant processes for the synthesis of substituted arenes by functionalization of C–H bonds were reported.

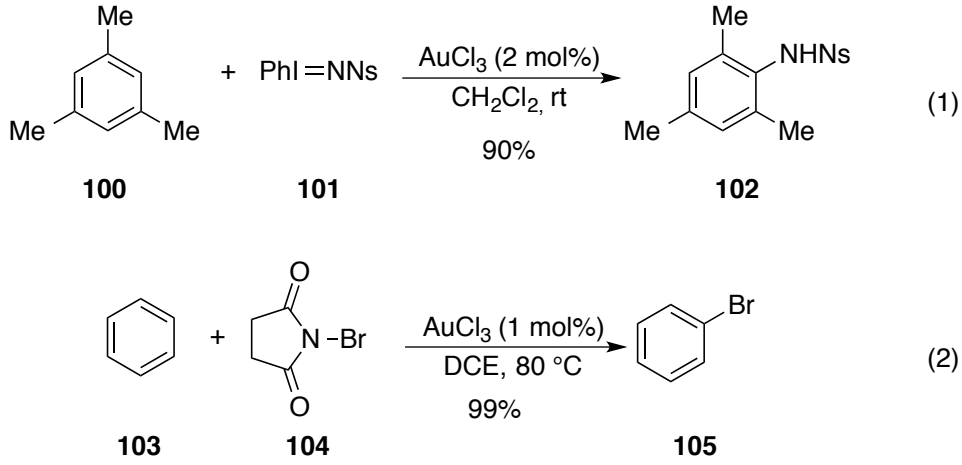
At the beginning of this century, Fuchita and coworkers[72] described the isolation of complexes such as **97**, which arise from the direct functionalization of *p*-xylene (**96**). Gold complex **97** was further transformed into alkyne **99** by a reaction with phenylacetylene (**98**) (Scheme 1.40).



Scheme 1.40

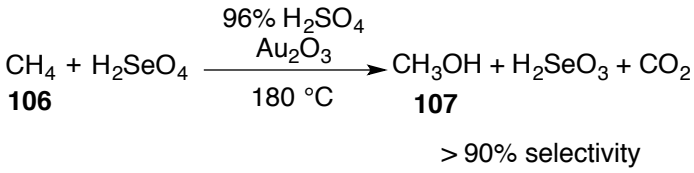
The ability of gold(III) to functionalize aromatic Csp^2–H bonds has also been exploited for the formation of Csp^2–N and Csp^2–Br bonds as illustrated in Scheme 1.41. Gold(III)-catalyzed nitrene insertions into aromatic and benzylic C–H bond by the use of [(nosylimino)iodo]benzene (**101**) were described by He.[73] For example, mesitylene (**100**), afforded sulfonylamide **102** when treated with **101** in dichloromethane at room temperature and using 2 mol% of $AuCl_3$ as catalyst (Scheme 1.42, Eq. 1). Besides, bromination of arenes with *N*-bromosuccinimide (**104**) in the presence of $AuCl_3$ was reported by Wang.[74] Benzene (**103**) reacted with **104** in dichloroethane at 80 °C giving rise to bromobenzene (**105**) in quantitative yield (Scheme 1.41, Eq. 2).

[71] M. S. Kharasch, H. S. Isbell, *J. Am. Chem. Soc.* **1931**, *53*, 3053-3059.
[72] Y. Fuchita, Y. Utsunomiya, M. Yasutake, *J. Chem. Soc. Dalton Trans.* **2001**, 2330-2334.
[73] Z. Li, D. A. Capretto, R. O. Rahaman, C. He, *J. Am. Chem. Soc.* **2007**, *129*, 12058-12059.
[74] F. Mo, J. M. Yan, D. Qui, F. Li, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2010**, *49*, 2028-2032.



Scheme 1.41

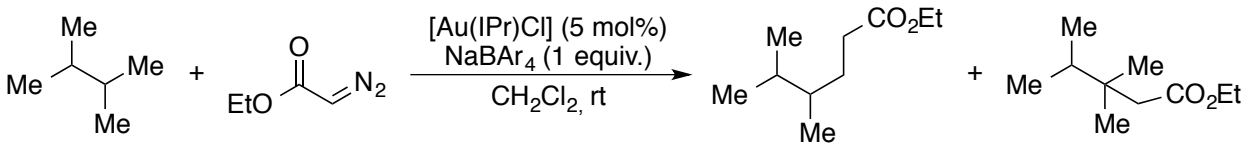
Gold catalysis has been also employed in the direct functionalization of hydrocarbons. The first example involving Csp_3–H activation was reported by Periana and coworkers in 2004.[75] Hence, the oxidation of methane (**106**) to methanol (**107**) in the presence of Au_2O_3, concentrated sulfuric acid and a selenic acid oxidizing agent at 180 °C was accomplished with high selectivity (Scheme 1.42).



Scheme 1.42

Functionalization of Csp^3–H bonds by the insertion of gold-carbene intermediates proved also feasible.[76] Diazocompounds served as source of carbene fragment, which in the presence of cationic gold(I) catalyst enable the functionalization of alkanes. For instance, Nolan and Pérez, reported the insertion of ethyldiazoacetate into alkane **108** to afford a mixture of products with selectivity towards primary C–H bonds (Scheme 1.43).[77]

[75] C. J. Jones, D. Taube, V. R. Ziatdinov, R. A. Periana, R. J. Nielsen, J. Oxgaard, W. A. Goddard III, *Angew. Chem. Int. Ed.* **2004**, *43*, 4626-4629.
[76] For some selected examples of gold-carbene on Csp_3–H: a) Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda, D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2809-2811; b) A. Escribano-Cuesta, V. López-Carillo, D. Janssen, A. M. Echavarren, *Chem. Eur. J.* **2009**, *15*, 5646-5650; c) S. Bhunia, R. -S. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 16488-16489.
[77] M. R. Fructos, P. de Frémont, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez, *Organometallics* **2006**, *25*, 2237-2241.



108 **109** **110** **111**

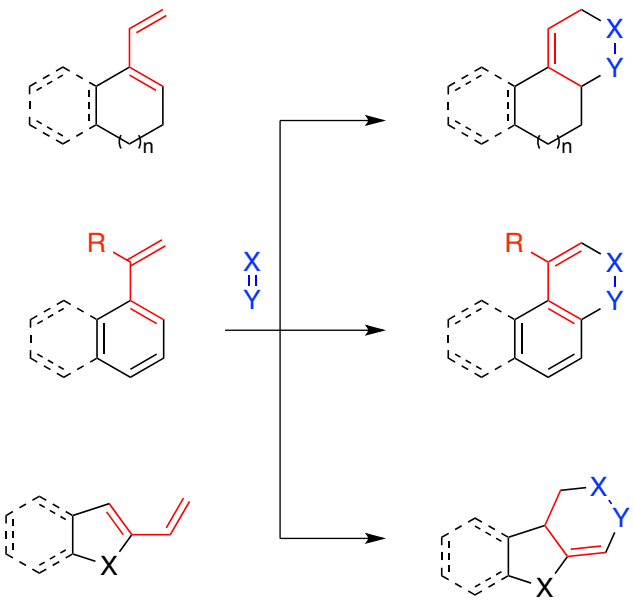
83% 17%

Scheme 1.43

Chapter 2. Diels-Alder reactions of 2-vinylindoles with enones

2.1 Introduction

The Diels-Alder reaction is one of the most fundamental and useful transformations in synthetic organic chemistry.[78] It is a widely used method for the assembly of simple and complex six-membered carbo- and heterocyclic compounds *via* the simultaneous formation of two new carbon-carbon and/or carbon-heteroatom bonds. In addition to these basic concepts, the success of DA methodologies is predominantly due to the high degree of regio-, diastereo- and enantioselectivities observed. The reaction outcome, related to the reaction mechanism, are modulated by the substituents on both the diene and the dienophile partners and by the design and use of different catalytic species. In particular, among dienes, internal-external ring dienes represent a class of very useful and versatile molecules. Their participation as 4π components in DA reactions allows for the construction of complex polycyclic compounds, often hardly derivable from other synthetic methodologies. However, their mode of participation in the DA reactions depends on the type of ring (carbo-, heterocyclic, aromatic) that bears the ethenyl group, on the electronic effects of the substituents and on the reaction conditions employed (catalyzed *vs* uncatalyzed DA reactions) (Scheme 2.1).

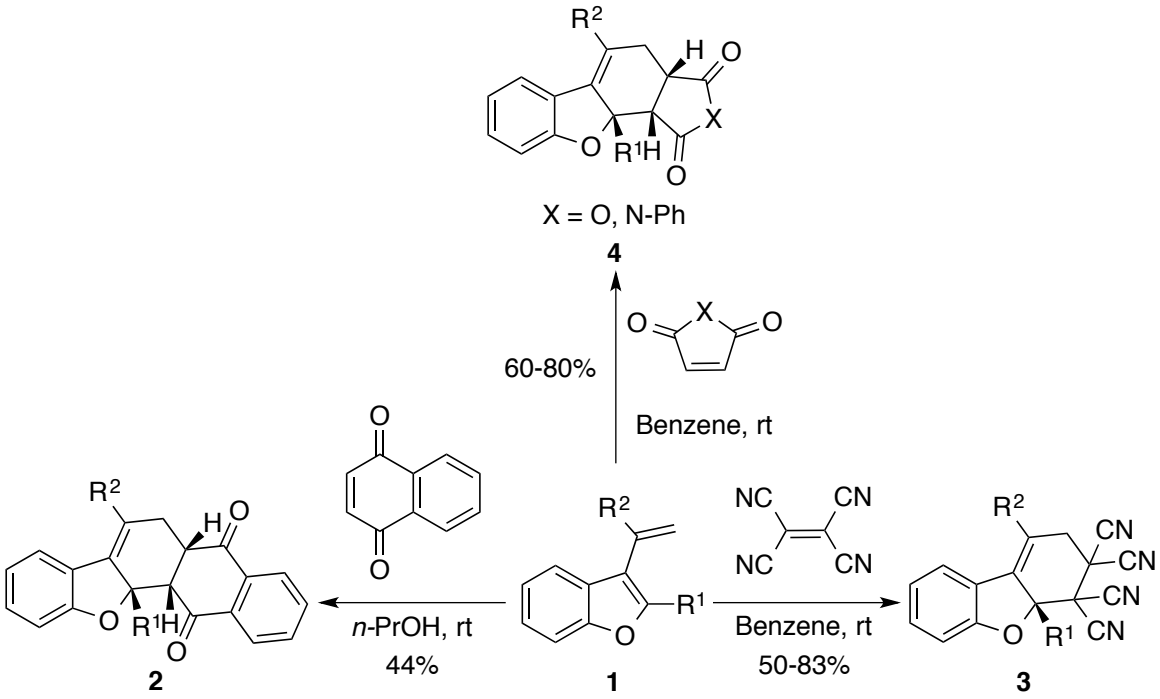


Scheme 2.1

[78] a) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, **1990**; b) F. Fringuelli, A. Taticchi, *Dienes in the Diels–Alder Reaction*, John Wiley & Sons, New York, **1990**; c) J. Sepúlveda-Arques, B. Abarca-González, M. Medio-Simón, *Adv. Heterocycl. Chem.* **1995**, *63*, 339-401; d) S. Kobayashi, K. A. Jorgensen, *Cycloaddition Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2002**; e) F. Fringuelli, A. Taticchi, *The Diels-Alder Reaction: Selected Practical Methods*, John Wiley & Sons, New York, **2002**; f) E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724-1741; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650-1667.

In particular, the introduction of an ethenyl group on a heterocyclic ring results in the construction of a particular and useful class of internal-external ring dienes and their reactions with various dienophiles provide an easy access to polyheterocycles. However, the reported examples are limited to vinyl substituted π-excessive hetroarenes. Vinylpyrroles, furans, thiophenes and their benzoderivatives are the most representative and the most studied examples.[1c]

For example, starting from 3-vinylbenzofurans **1** a large variety of derivatives **2**-**4** could be prepared through termal [4+2] cycloaddition reaction (Scheme 2.2).[79]



Scheme 2.2

Among internal-external ring dienes embedded into a heterocyclic ring, 2-vinylindoles and 3-vinylindoles represent synthetically attractive starting materials for the regio- and stereocontrolled construction of [*b*]annelated indoles, which serve as lead substances and as building blocks for the synthesis of several alkaloid families.[80]

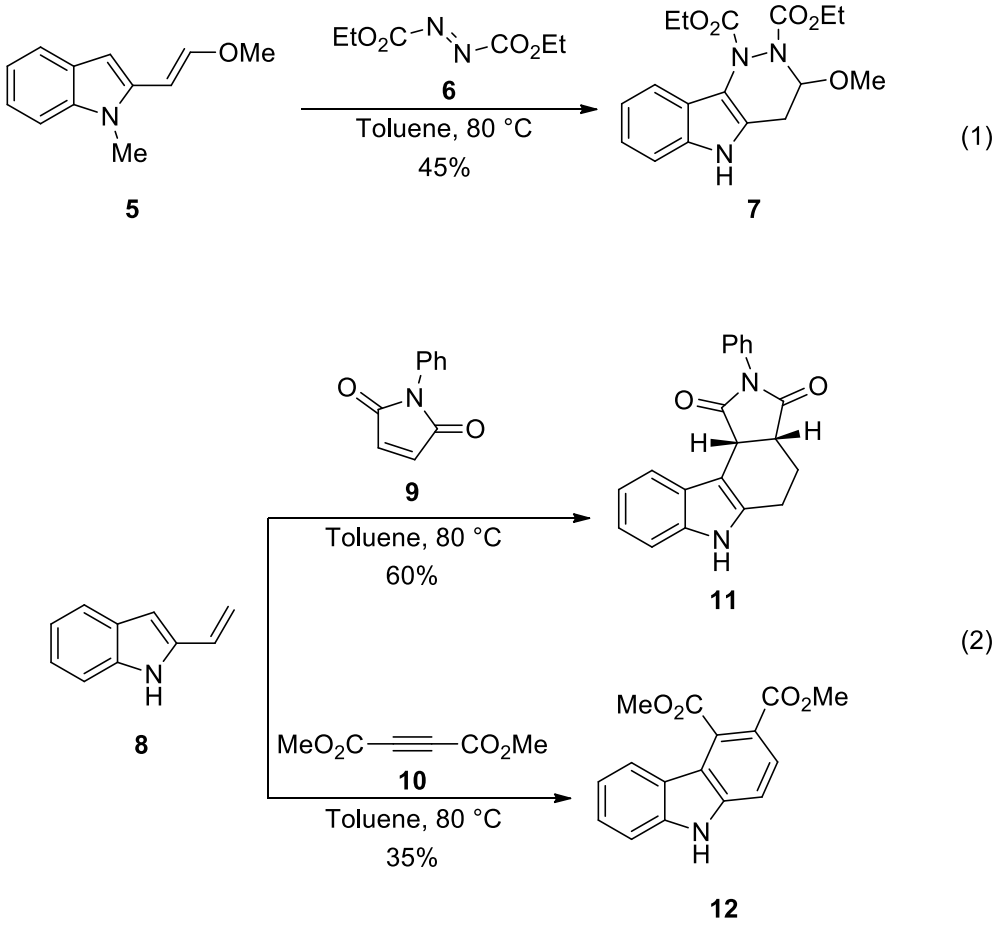
The scope of this introduction will be to highlight the chemistry of these compounds, in particular of 2-vinylindoles, with special attention to their use in Diels-Alder reactions for the preparation of tetrahydrocarbazole derivatives and in total synthesis of bioactive carbazole alkaloids.

[79] J. R. Pearson, Q. N. Porter, *J. Aus. Chem.* **1991**, *44*, 907-917.

[80] For selected reviews on the use of vinylindole, see: a) U. Pindur, *Heterocycles* **1988**, *37*, 1253-1268; b) U. Pindur, *Adv. Nitrogen Hetrocycl.* **1995**, *1*, 121-172; c) R. F. Kester, S. J. Berthel, F. Firooznia, *Top. Heterocycl. Chem.* **2010**, *26*, 327-396.

2.1.1 Diels-Alder reactions of 2-vinylindoles for the synthesis of carbazole derivatives

The synthetic potential of 2-vinylindoles as 4π-component for Diels-Alder reactions was not widely investigated up to 90s, since the access to this structural class was associated with a relatively high synthetic effort.[81] Early reports on the reactivity of 2-vinylindoles **5** and **8** included the reaction with azodienophiles such as diethyl azodicarboxylate **6** (Scheme 2.3, Eq. 1), and with carbon dienophiles like *N*-phenylmaleimide **9** and dimethyl acetylendicarboxylate **10** (Scheme 2.3, Eq. 2) giving rise to carbazole derivatives **7** and **11**, **12** in moderate yields.[3a]

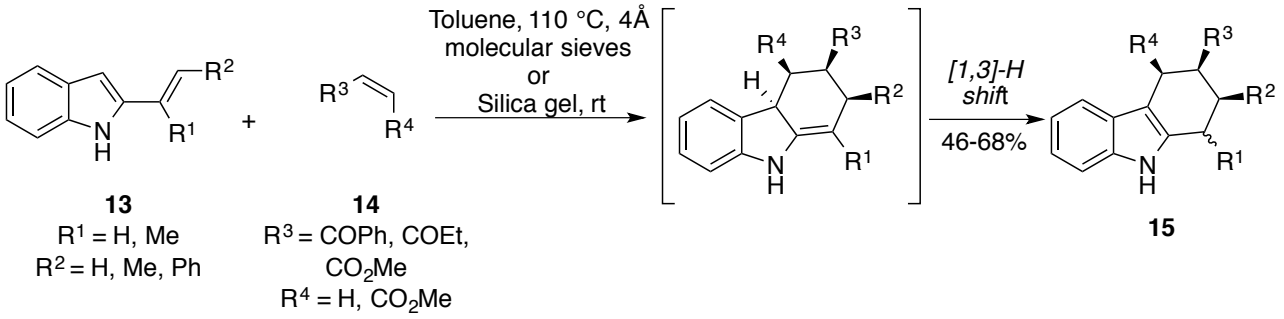


Scheme 2.3

Pindur and coworkers accomplished the synthesis of several *N*,3-unsubstituted 2-vinylindoles **13** and investigated their participation in Diels-Alder reactions with different carbodienophiles **14**.[82] The reactions were conducted in toluene at reflux and in the presence of 4 Å molecular sieves or at

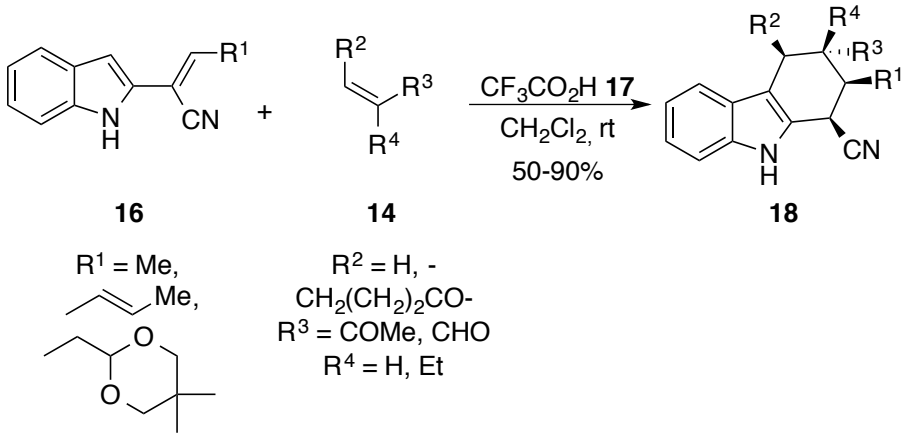
[81] E. Akgün, U. Pindur, *Liebigs Ann. Chem.* **1985**, 2472-2476.
[82] M. Eitel, U. Pindur, *J. Org. Chem.* **1990**, *55*, 5368-5374.

room temperature and in the presence of silica gel using the dienophile as solvent. Thus, the corresponding tetrahydrocarbazoles **15** were prepared in moderate to good yields and with high regio- and *endo* diasteroselectivity (Scheme 2.4). This regio- and stereochemical outcomes were in agreement with the prediction of the FMO theory and with a concerted $HOMO_{diene}$–$LUMO_{dienophile}$-controlled Diels-Alder process.



Scheme 2.4

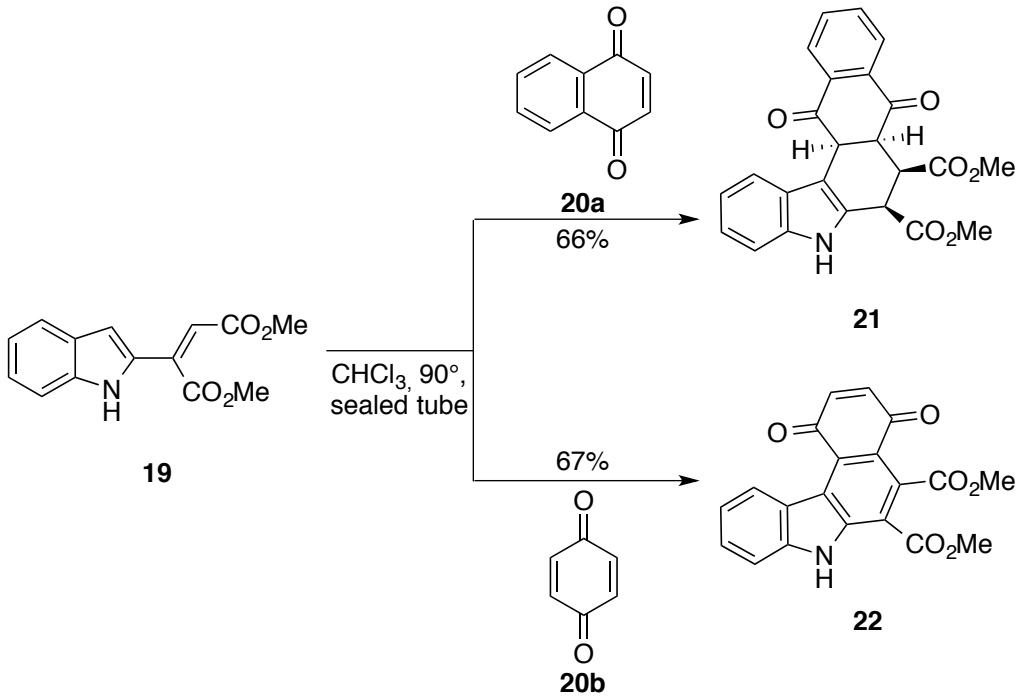
In 1995, Blechert and coworkers tested the reactivity of 2-vinylindoles derivatives **16** with enones **14** and they found that the Diels-Alder reactions did not proceed under thermal conditions, whereas products **18** were obtained in the presence of a stoichiometric amount of trifluoroacetic acid (**17**) (Scheme 2.5).[83] These reactions were found to proceed with high *endo* selectivity and the tetrahydrocarbazoles could be then oxidized with DDQ to form the corresponding carbazoles in good yield.



Scheme 2.5

[83] S. Blechert, R. Knier, H. Schroers, T. Wirth *Synthesis* **1995**, 592-604.

More recently, Saracoglu and Cavdar investigated the cycloaddition reactions of 2-vinylindoles with various quinones.[84] Thus, 2-vinylindole methylester **19** was reacted with naphthoquinone **20a** to yield the corresponding tetrahydrocarbazole **21** as sole product. The stereochemical outcome was in agreement with the results of Pindur[5] and explained by the presence of additional secondary orbital interactions between diene and dienophile in the *endo* Diels-Alder transition state. Furthermore, they proved the reaction of **19** with *p*-benzoquinone **20b**, which afforded directly the aromatized product **22** in moderate yield (Scheme 2.6). Both reactions were thermally induced and were performed in chloroform at 90°C and required long reaction times, especially using naphthoquinone **20a** (9 days).



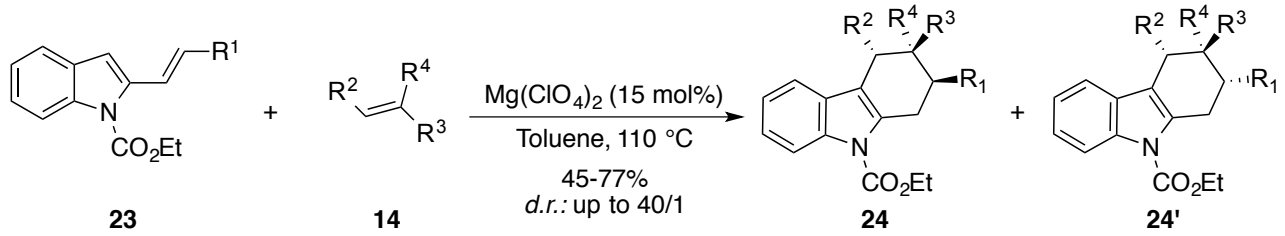
Scheme 2.6

An in-depth analysis of these reports reveals two main drawbacks for these reactions. First, the synthesis of the starting materials is somewhat difficult and requires multistep sequences. Moreover, all reported reactions are thermally induced or require the use of stoichiometric amounts of an acidic promoter.

Starting from these results, our research group decided to investigate the reactivity of 2-vinylindoles, in particular of (*E*)-2-vinylindole-1-carboxylic acid ethyl esters **23**, which could be easily obtained in multigram quantities through an approach based on palladium-catalyzed cross-

[84] H. Cadvar, N. Saracoglu, *J. Org. Chem.* **2006**, *71*, 7793-7799.

coupling reactions.[85] Under the conditions reported by Eitel and Pindur[5] (see Scheme 2.4) the reactions were extremely slow or did not proceed at all. In contrast, the use of a Lewis acid as catalyst promoted the cycloadditions as was anticipated considering the efficiency of these species in improving the reaction outcome of DA reactions.[86] Thus, the [4+2] cycloadditions of 2-vinylindoles **23** and enones **14** were performed in toluene at 110 °C and in the presence of 15 mol% of magnesium perchlorate as catalyst. After completion of the reaction, purification over silica gel yielded the corresponding diasteroisomeric tetrahydrocarbazoles **24** and **24'**, which formation could be explained by Diels-Alder reaction followed by 1,3-proton shift (Scheme 2.7).[87]



23 **14** **24** **24'**

R^1 = *p*-Tol, Me, *n*-Bu R^2 = H, CO_2Me, Me, Ph
R^3 = CO_2Me, COMe, CO_2Et, CHO
R^4 = H, Me

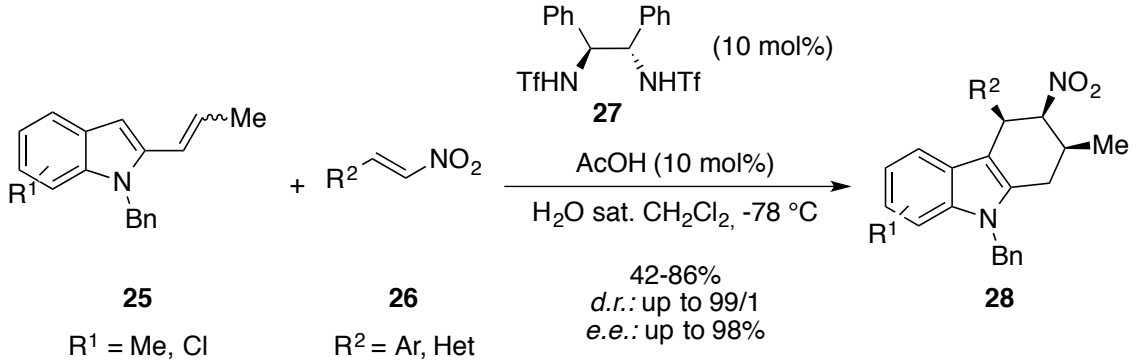
Scheme 2.7

The regiochemical outcome of all these cycloadditions can be easily understood by applying the FMO concept concerning the interactions between a 1,2,4-trisubstituted diene containing in position 2 an electron-donating group and an electron-withdrawing substituted dienophile.[88] On the other hand, in contrast to the results obtained by Pindur for the cycloaddition reactions performed between the *N*-unsubstituted 2-vinylindoles **13** and open chain carbodienophiles **14** (scheme 2.4), which afford exclusively the *endo* carbazole adducts, the (*E*)-2-vinylindole-1-carboxylic acid ethyl esters **23** provide *endo*:*exo* ratios ranging from 1:2.2 to 54:1, in the presence of magnesium perchlorate as catalyst, according to the nature of substituents both on diene and dienophile.

A completely different catalytic approach to realize these cycloaddition reactions makes use of organocatalytic methodologies. In particular the use of optically active organocatalysts has permitted the development of enantioselective intermolecular preparation of these compounds. Xiao

[85] E. Rossi, G. Abbiati, V. Canevari, G. Celentano, *Synthesis* **2006**, 299-304.
[86] a) H. Yamamoto, *Lewis Acids in Organic Synthesis*, Wiley-VCH, Weinheim, **2000**, vol. 1-2; b) K. Ishihara, A. Sakakura, *Science of Synthesis, Stereoselective Synthesis* (Eds.: J. G. de Vries, G. A. Molander, P. A. Evans), Georg Thieme Verlag, Stuttgart, **2011**, vol. 3, p. 67.
[87] G. Abbiati, V. Canevari, D. Facoetti, E. Rossi, *Eur. J. Org. Chem.* **2007**, 517-525.
[88] F. Carey, R. J. Sundberg, *Advanced Organic Chemistry*, Plenum Press, New York, **1990**, vol. A, p. 625-640.

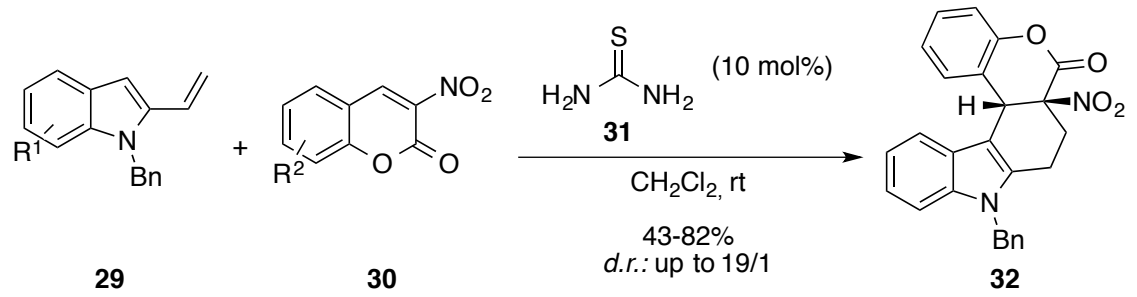
and coworkers gave a first example of this reactivity in 2010 using the chiral bis-sulfonamide **27** as catalyst for the reaction between 2-propenylindoles **25** and nitroolefins **26** (Scheme 2.8).[89].



Scheme 2.8

The reaction affords the corresponding thetrahydrocarbazoles **28** in moderate to good yields and with good to excellent enantio- and diastereoselectivities. The authors claimed for a mechanism involving only a formal [4+2] cycloaddition reaction and proposed a catalytic cycle involving electrophilic activation of the dienophile 2**6** by the chiral hydrogen bonding donor **27** followed by a sequential inter- and intramolecular Michael addition reactions. The reaction scope is limited to the use of nitro activated alkenes and 2-propenyl-*N*-methyl indole derivatives. Simple Michael adduct were isolated when 2-vinyl or *N*-unsubstituted indoles were employed as substrates.

The same group studied also the reaction between **29** and 2-nitrocoumarins **30** using thiourea **31** as catalyst.[90] Using this method a series of diversified coumarin-fused polycyclic indoles **32** could be obtained with diasteroisomeric ratios up to 19/1 in favor to the *endo* adduct (Scheme 2.9).

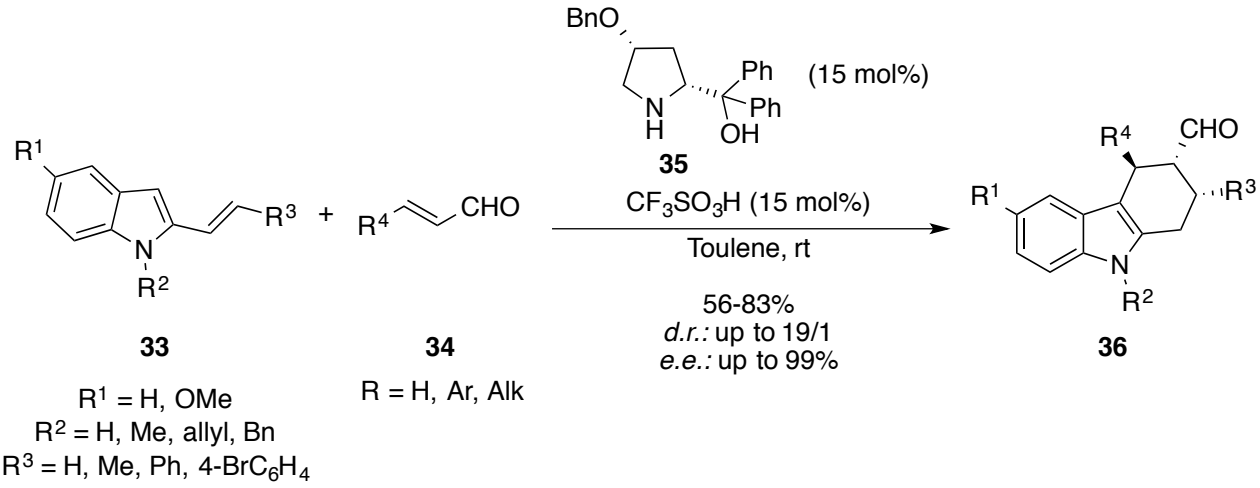


Scheme 2.9

Also α,β-unsaturated carbonyl compounds can participate in DA reactions with 2-vinylindoles under organocatalysis. Between 2000 and 2005, MacMillan developed the use of organocatalysts

[89] X.-F. Wang, J.-R. Chen, Y.-J. Cao, H.-G. Cheng, W.-J. Xiao, *Org. Lett.* **2010**, *12*, 1140-1143.
[90] F. Tan, F. Li, X.-X. Zhang, X.-F. Wang, H.-G. Cheng, J.-R. Chen, W.-J. Xiao, *Tetrahedron* **2011**, *67*, 446-451.

for the construction of six-membered cyclic compounds by using iminium formation from α,β-unsaturated carbonyl compounds and prolinol derivatives.[91] More recently, Zhao and coworkers applied this approach using prolinol **35** as catalyst for the reaction between 2-vinylindoles **33** and α,β-unsatured aldehydes **34** giving rise to tetrahydrocarbazoles **36**.[92] In general, moderate to high yields were observed with good diasteromeric ratios and enantiomeric excess up to 99% (Scheme 2.10).



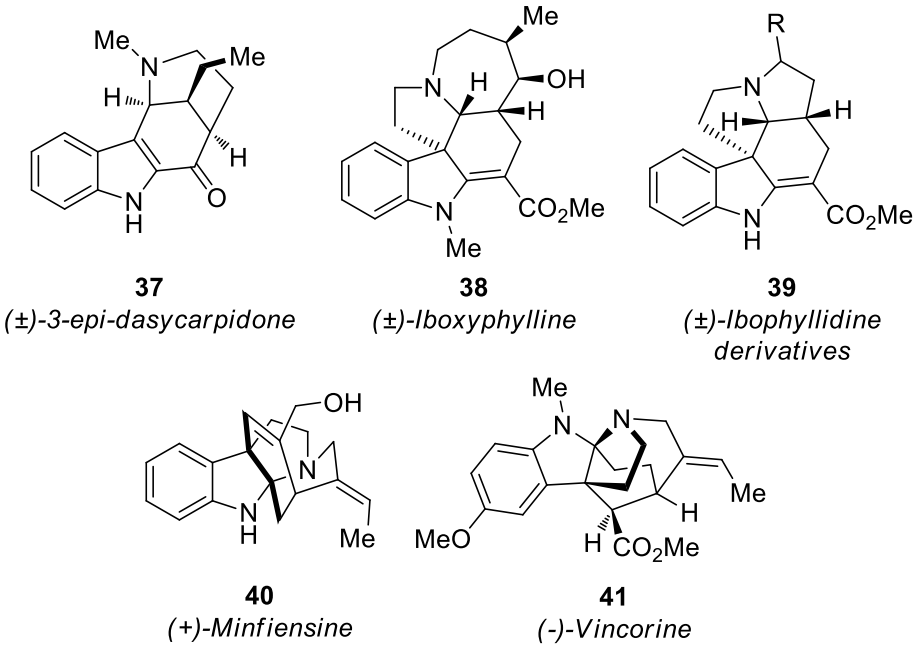
Scheme 2.10

In particular, prolinol **35** gave the best results in terms of diastereo- and enantioselectivity avoiding the formation of undesired Michael-type adduct observed in the presence of prolinol trimethylsilyl ether. The reaction mechanism fulfill with the previously reported achievement by MacMillan.

[91] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458-2460; c) R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 11616-11617.
[92] C. Zheng, Y. Lu, J. Zhang, X. Chen, Z. Chai, W. Ma, G. Zhao, *Chem. Eur. J.* **2010**, *16*, 5853-5857

2.1.2 Application of [4+2] cycloaddition reactions of 2-vinylindoles to the synthesis of active molecules

The use of 2-vinylindole species has played a large role in the total synthesis of a series of indole alkaloids.[3c] The most recent findings include the application of these substrates in cycloaddition reactions for the preparation of (±)-3-epi-dasycarpidone **37**,[6] *Vinca* alkaloids from the family of ibophyllidine **38** and iboxyphylline **39**,[93] (+)-minfiensine **40**[94] and (-)-vincorine **41**[95] (Figure 2.1).



37 *(±)-3-epi-dasycarpidone* | **38** *(±)-Iboxyphylline* | **39** *(±)-Ibophyllidine derivatives*

40 *(+)-Minfiensine* | **41** *(-)-Vincorine*

Figure 2.1

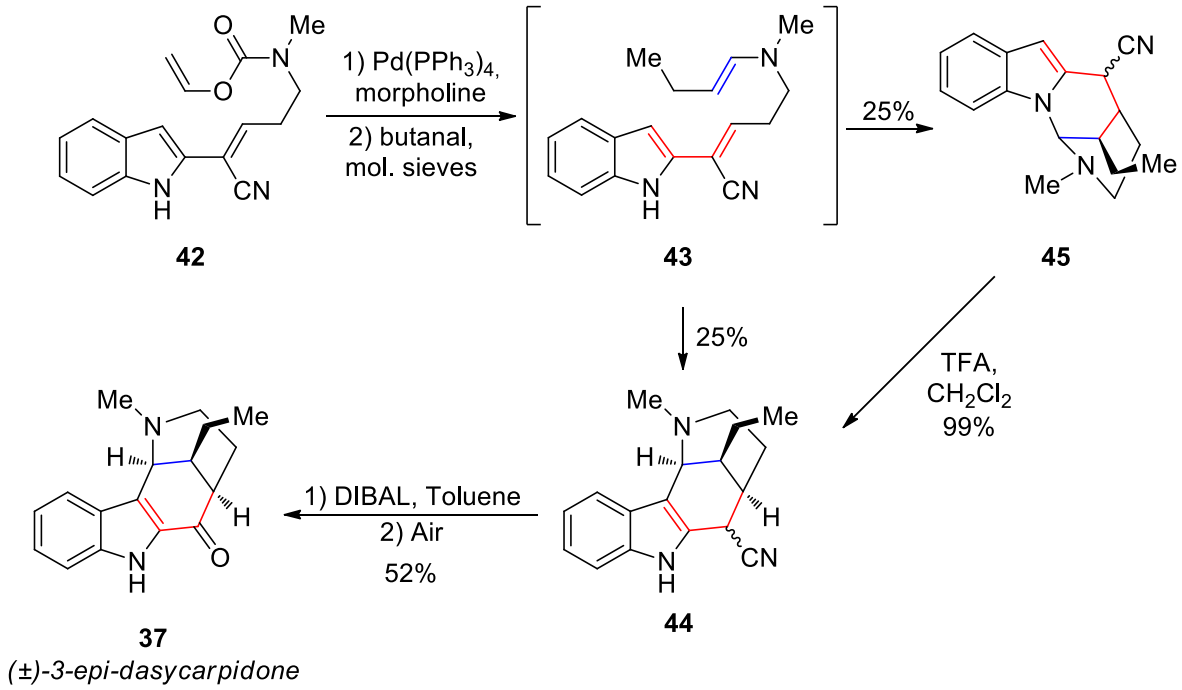
The synthesis of (±)-3-epi-dasycarpidone **37**, an uleine alkaloid, was described in 1995 by Blechert and coworkers using as starting material vinyl indole **42**, prepared according to a four-steps procedure reported in the same work.[6] A deprotection of the amine by Pd-catalyzed cleavage of the carbamate moiety and condensation with butanal led to intermediate **43** and set the stage for the in-situ [4+2] cycloaddition, which occurred at room temperature and in the presence of molecular sieves. Purification of the reaction crude yielded the diastereomeric Diels-Alder adducts **44**, formed in 1:1 ratio. The ring closure of the intermediate iminium salt with the indole nitrogen led to the undesired product **45**, which could be transformed quantitatively in **44** by treatment with

[93] F. Toth, G. Kalaus, G. Pipa, I. Greiner, A. Szollosy, A. Rill, A. Gomory, L. Hazai, C. Szantay, *Heterocycles* **2008**, *75*, 65-76 and references cited therein.

[94] S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606-13607.

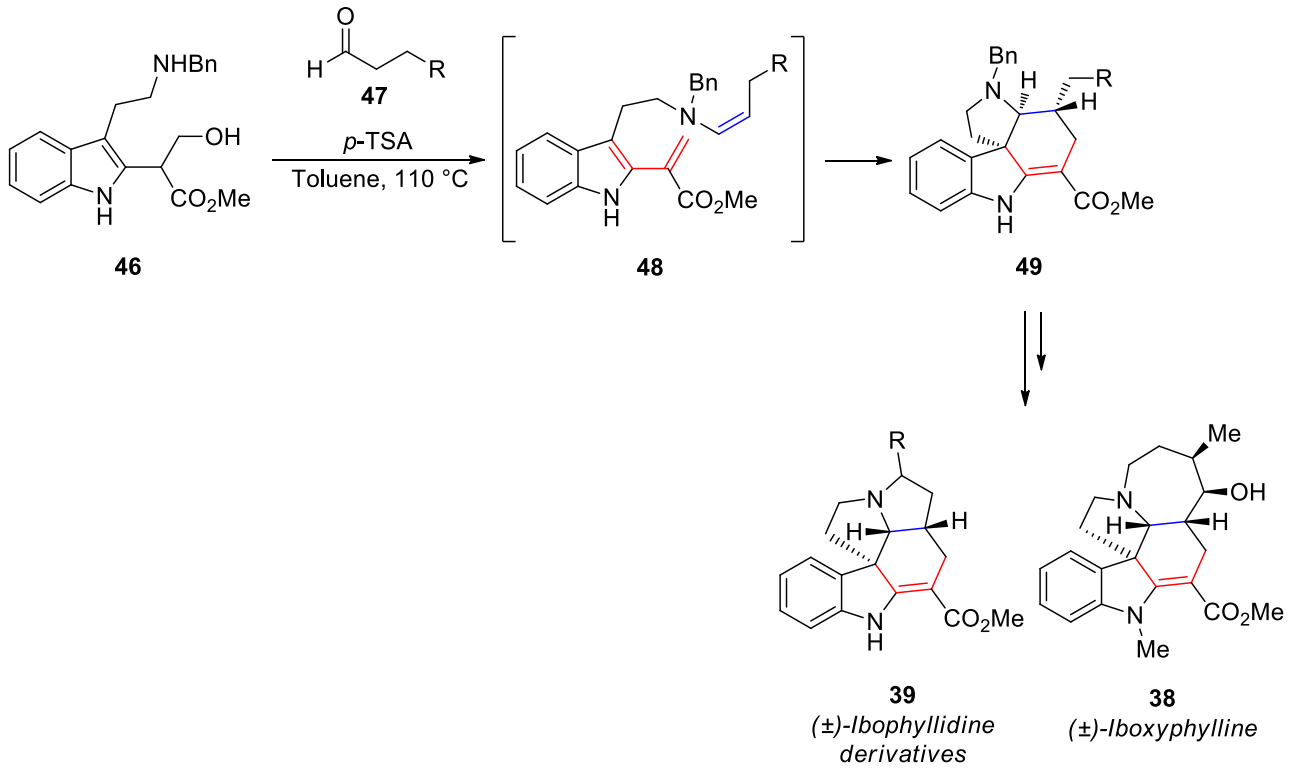
[95] D. B. Horning, W. C. D. MacMillan, *J. Am. Chem.Soc.* **2013**, *135*, 6442-6445.

trifluoroacetic acid. Final oxidative decyanation of **44** yielded (±)-3-epi-dasycarpidone **37** in moderate yield (Scheme 2.11).



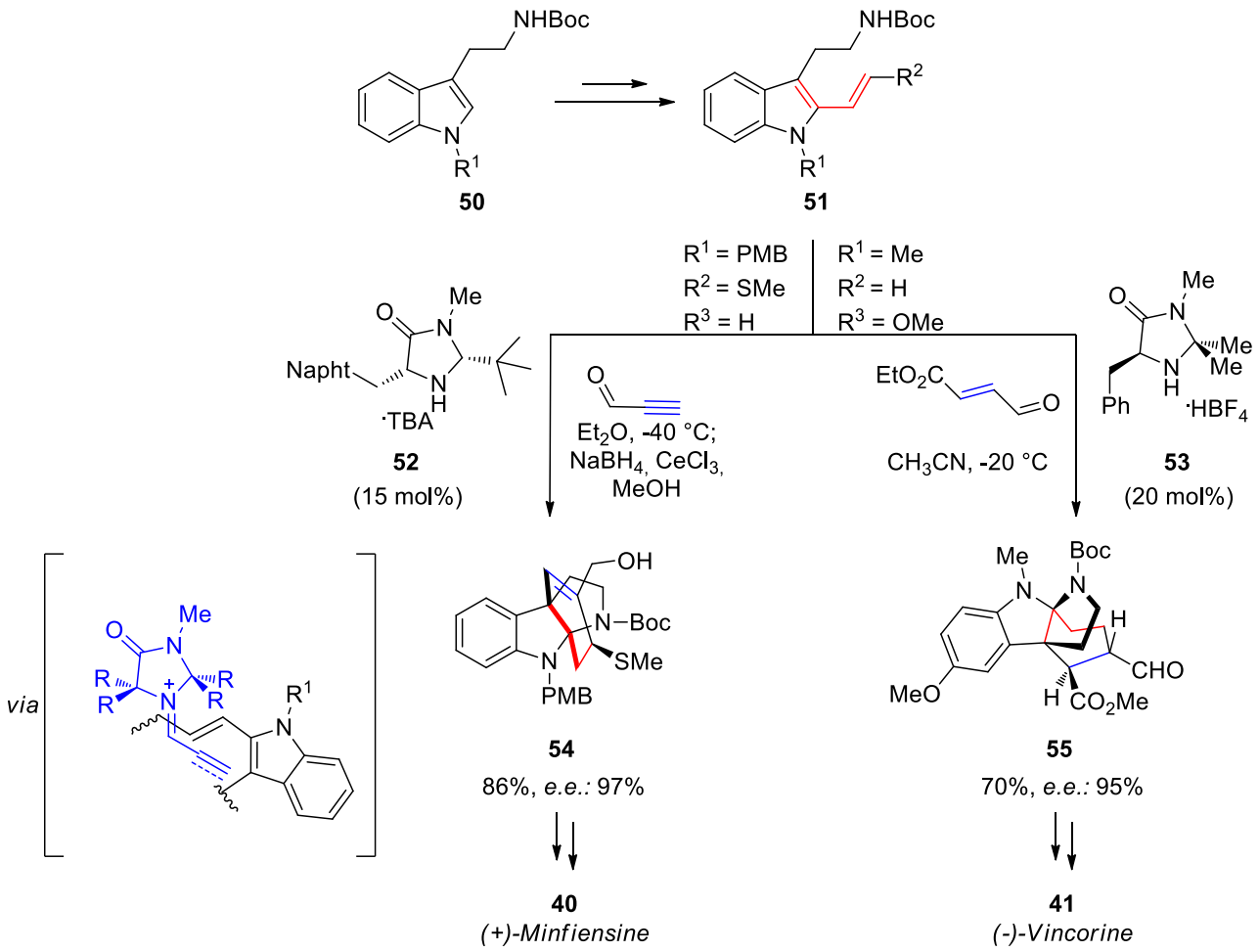
Scheme 2.11

Kalaus and Szantay used the 2-vinylindole Diels-Alder strategy to synthetize representative structures from the ibophyllidine and iboxyphylline familes.[16] These syntheses relied on intermediates **48**, obtained by the reaction between indol derivative **46** and aldehyde **47**, as key precursors for the intramolecular cycloaddition that led to the formation of adducts **49**. Further functional group modifications enabled the access to compounds **38**, **39** (Scheme 2.12). Simple modification of the substituents on aldehyde **47** made possible the preparation of a series of these alkaloid derivatives.



Scheme 2.12

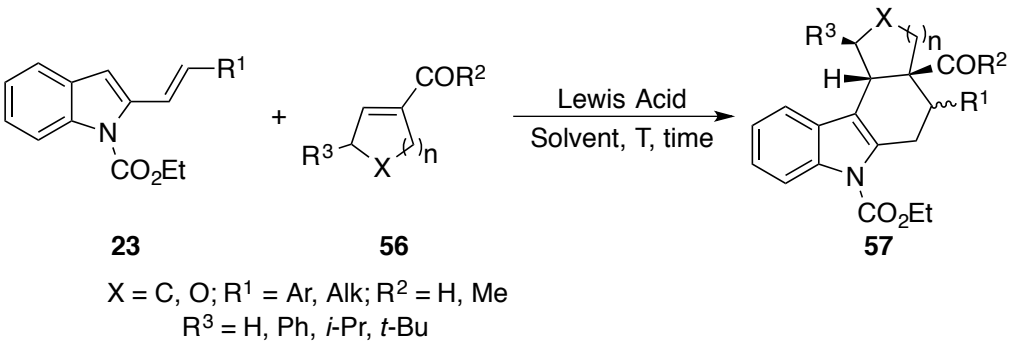
The total syntheses of indole alkaloids (+)-minfiensine **40** and (-)-vincorine **41** were described by MacMillan and coworkers very recently.[17, 18] Key step for the preparation of both molecules is a organocatalytic iminium Diels-Alder/amine cyclization sequence that allowed an efficient and enantioselective access to the tetracyclic carbazole framework in one pot. The synthesis started from commercially available tryptamine derivative **50**, which could be easily transformed in diene **51**. Then, the condensation of the chiral secondary amine organocatalysts **52** or **53** would form an activated iminium ion. In the proposed transition state, orientation of the reactive π-system would allow the shielding of one π-face by the substituents of the chiral catalyst, thereby enabling a high stereoselective Diels-Alder reaction with the diene, to deliver enamine cycloadducts. Subsequent Brønsted acid-catalyzed amine cyclization would lead to the high-functionalized carbazole derivatives **54** and **55**. Further transformations of **54** and **55** afforded the natural **40** and **41**, respectively (Scheme 2.13).


NHBoc
R1
50
NHBoc
R2
R1
51
R1 = PMB
R2 = SMe
R3 = H
R1 = Me
R2 = H
R3 = OMe
Napht
Me
N
O
N
H
·TBA
52
(15 mol%)
Et2O, -40 °C;
NaBH4, CeCl3,
MeOH
EtO2C
O
CH3CN, -20 °C
Me
N
O
N
Me
Me
H
Ph
·HBF4
53
(20 mol%)
via
R
R
R
R1
OH
N–Boc
N
SMe
PMB
54
86%, e.e.: 97%
Me
N
Boc
N
H
CHO
MeO
H
CO2Me
55
70%, e.e.: 95%
40
(+)-Minfiensine
41
(-)-Vincorine

Scheme 2.13

2.2 Objectives

Starting from our previous investigations on the reactivity of 2-vinylindoles in [4+2] cycloaddition reactions with open-chain carbon-carbon dienophiles[10] and taking into account the excellent reported σ- and π-philic catalytic properties of gold salts and complexes,[96] we became interested in testing the catalytic activity of this of coinage metal in our intermolecular transformations. In parallel, we decided to extend the scope of the [4+2] cycloaddition reactions to cyclic dienophiles such as α,β-unsatured carbo- and heterocyclic aldehydes and ketones **56** (Scheme 2.14). In this way it would be possible to obtain highly functionalized tetracyclic indole derivatives **57** in a regio- and stereospecific manner. Polycyclic structures bearing a carbonyl substituent in an angular position could be accessed with this approach. This structural feature is relevant as it is pretty uncommon but is present in some alkaloids. Thus, the research work was planned in two stages. Firstly, to gain several insights on the behavior of cyclic dienophiles in [4+2] cycloaddition reactions, we tested the reactivity of 2-vinylindoles **23** with α,β-unsatured carbo- and heterocyclic aldehydes or ketones **56** in the presence of classical Lewis acids as catalysts (Scheme 2.14.)



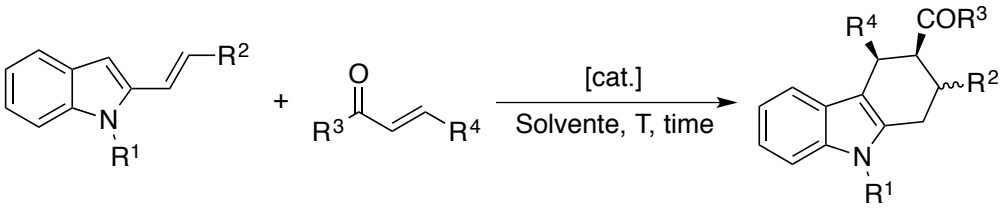
23 **56** **57**

X = C, O; R^1 = Ar, Alk; R^2 = H, Me
R^3 = H, Ph, *i*-Pr, *t*-Bu

Scheme 2.14

Furthermore, a second study focused on the search of new reaction conditions, *i.e.* gold catalysis, that would allow the improvement of both yield and diasteroselectivity in the reaction between various 2-vinylindoles and both acyclic and cyclic α,β-enones (Scheme 2.15).

[96] For a description of general gold reactivity see Chapter 1.



23 **14** **24**

R^1 = H, Me, CO_2Et, R^2 = Ar, Alk
R^3 = H, Me, Ph; R^4 = H, Me, Ph

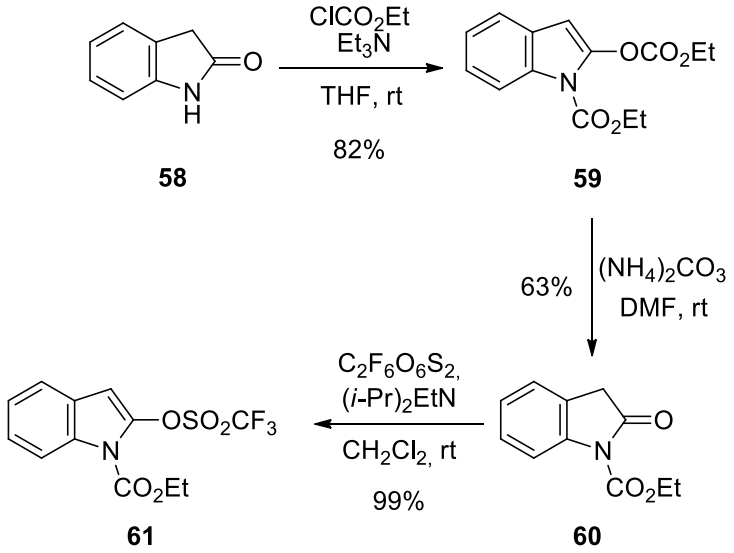
Scheme 2.15

2.3 Results and discussion

2.3.1 Synthesis of starting materials

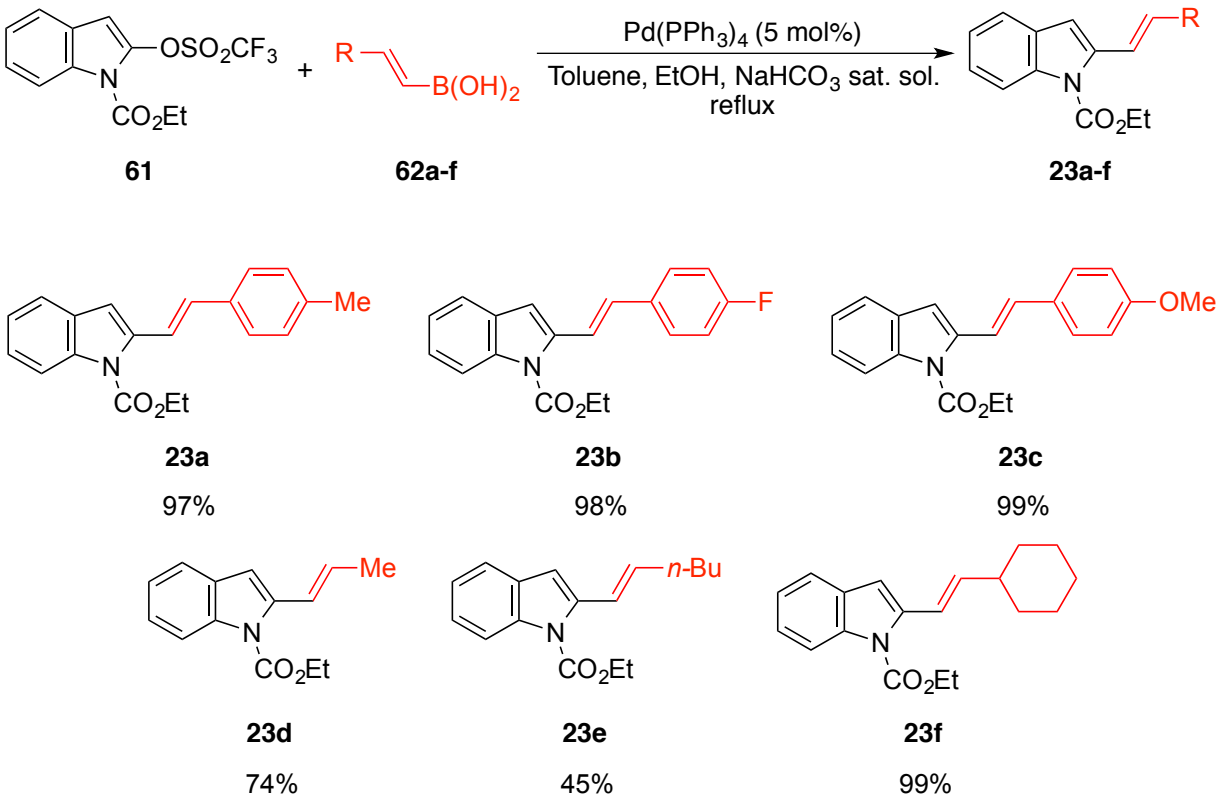
2.3.1.1 Synthesis of 2-vinylindoles **23a-h** and 2-vinylbenzofuran **68**

The procedures for the synthesis of 2-vinylindoles generally are based on functionalization of indole moiety through Michael addition[7] and Wittig reaction[12-15] from the corresponding aldehydes. In 2006, we proposed a new synthetic route for the preparation of these substrates.[8] The key step for the formation of the C–C bond between the indole and the vinyl moiety is a palladium-catalyzed cross-coupling reaction of 2-trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester (**61**), whose preparation is described in Scheme 2.16.



Scheme 2.16

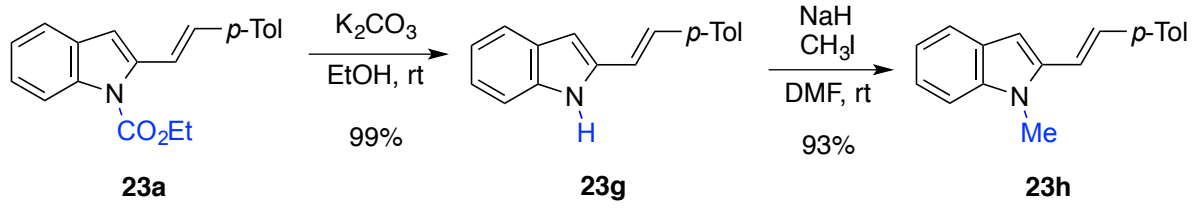
Treatment of 2-indolinone **58** with ethylchloroformate in the presence of triethylamine at room temperature led to **59** in 82% yield. The partial hydrolysis of **59** with ammonium carbonate in DMF yielded ethyl 2-oxoindoline-1-carboxylate **60**. Treatment of **60** with trifluoromethansulfonic anhydride in anhydrous dichloromethane and in the presence of Hünig base (diisopropylethylamine) afforded **61**. Once that **61** was prepared, it could be employed in Suzuki cross-coupling reactions catalyzed by $Pd(PPh_3)_4$ with various boronic acids **62a-f**, in a mixture of solvents consisting of toluene, ethanol and of an aqueous saturated solution of $NaHCO_3$ (Scheme 2.17).



Scheme 2.17

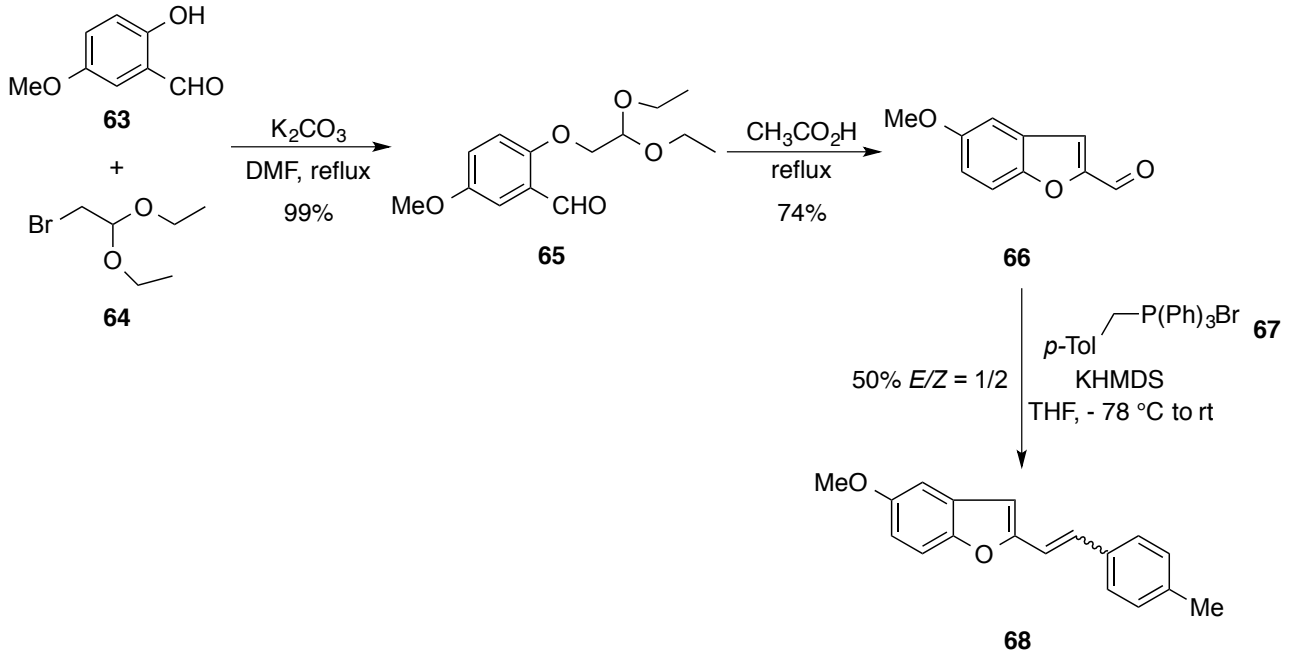
This synthetic approach allows for the construction of a small library of 2-vinylindoles **23a-f** in moderate to quantitative yields starting from a single precursor and, more importantly, the geometry of the vinylboronic acid was unaltered under these reaction conditions enabling the access to a single isomer, in contrast with the results observed when trying Wittig-type reactions.

N-H free and *N*-methyl 2-vinyl indoles **23g** and **23h** were prepared starting from (*E*)-ethyl 2-(4-methylstyryl)-1*H*-indole-1-carboxylate (**23a**). Deprotection of **23a** with potassium carbonate in methanol at room temperature yielded **23g** quantitatively. Subsequent deprotonation with NaH at 0 °C in DMF and reaction with iodomethane at room temperature afforded the methylated vinyl indole **23h** in excellent yield (Scheme 2.18).



Scheme 2.18

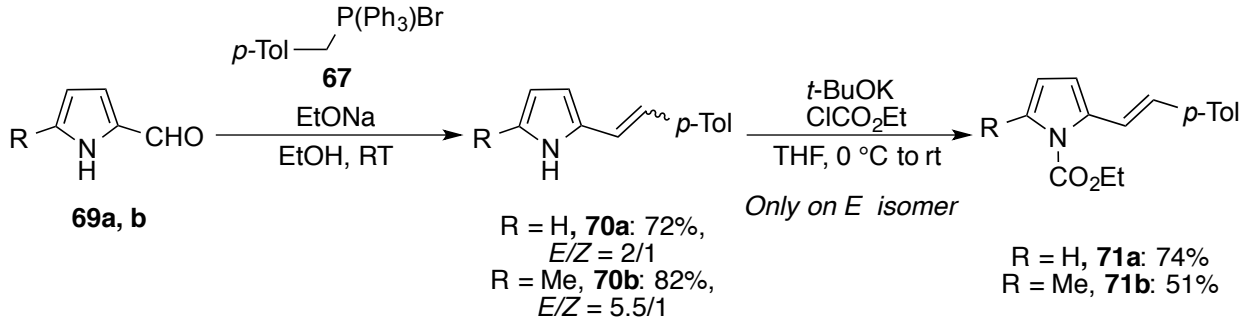
Besides 2-vinylindoles, also 2-vinylbenzofuran **68** was prepared following the reactions sequence reported in Scheme 2.20. Nucleophilic substitution reaction between 2-hydroxy-5-methoxybenzaldehyde (**63**) and 2-bromo-1,1-diethoxyethane (**64**) in the presence of K_2CO_3 in refluxing DMF provided **65** in excellent yield, while the subsequent addition of acetic acid allowed the cyclization to 5-methoxybenzofuran-2-carbaldehyde (**66**). Finally, through Wittig reaction between **66** and (4-methylbenzylidene)triphenylphosphorane, generated *in situ* from **67**, 5-methoxy-2-(4-methylstyryl)benzofuran (**68**) was obtained as a separable mixture of *E* and *Z* isomers in moderate yield (Scheme 2.19).



Scheme 2.19

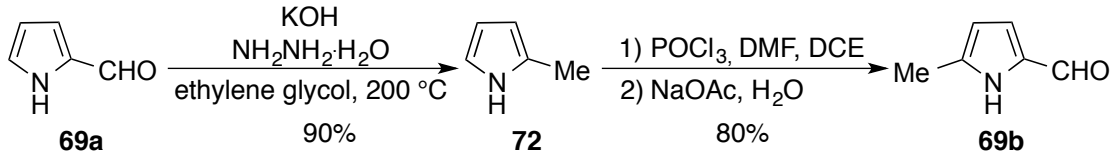
2.3.1.2 Synthesis of 2-vinylpyrroles **70** and **71a,b**

The synthesis of 2-viny pyrroles was achieved through a Wittig reaction between pyrrole-2-carbaldehydes **69a,b** and bromo(4-methylbenzyl)triphenylphosphorane **67**. The reaction afforded **70a,b** as a separable mixture of *E* and *Z* isomers in good yield.[97] Subsequent treatment of **70a,b** with *t*-BuOK at 0 °C in THF and then with ethyl chloroformate at room temperature yielded protected 2-vinyl pyrroles **71a,b** (Scheme 2.20).



Scheme 2.20

5-Methyl-1*H*-pyrrole-2-carbaldehyde (**69b**) was obtained in good quantities by a two-step process. (Scheme 2.21). First, 1*H*-pyrrole-2-carbaldehyde (**69a**) was reduced to 2-methyl-1*H*-pyrrole **72** by heating at 200 °C during 1 hour in the presence of potassium hydroxide and hydrazine hydrate.[98] Then, formylation reaction performed on **72** yielded final aldehyde **69b** in high yield.[99]

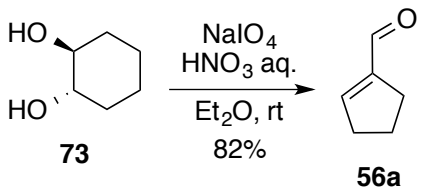


Scheme 2.21

[97] J. McNulty, P. Das, D. McLeod, *Chem. Eur. J.* **2010**, *16*, 6756-6760.
[98] D. O. A. Garrido, G. Buldain, B. Frydman, *J. Org. Chem.* **1984**, *49*, 2619-2622.
[99] P. A. Liddell, T. P. Forsyth, M. O. Senge, Kevin M. Smith, *Tetrahedron*, **1993** , *49*, 1343-1350.

2.3.1.3 Synthesis of α,β-unsatured aldehydes and ketones **56a-f**

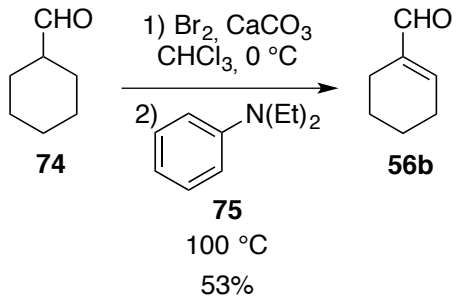
1-(Cyclopenten-1-yl)ethan-1-one **56c** is commercially available. Cyclopent-1-ene-1-carboxaldehyde (**56a**) was prepared from *trans*-1,2-cyclohexanediol (**73**) by addition of an acidic solution of $NaIO_4$. Final product **56a** was isolated in 82% yield without any further purification (Scheme 2.22).[100]



73 **56a**

Scheme 2.22

Cyclohex-1-ene-1-carbaldehyde (**56b**) was prepared by treatment of cyclohexanecarbaldehyde (**74**) with bromine and $CaCO_3$ at 0 °C. The corresponding α-bromoaldehyde was then dehydroalogenated in the presence of diethylaniline (**75**) at 100 °C (Scheme 2.23).[101]



74 **75** **56b**

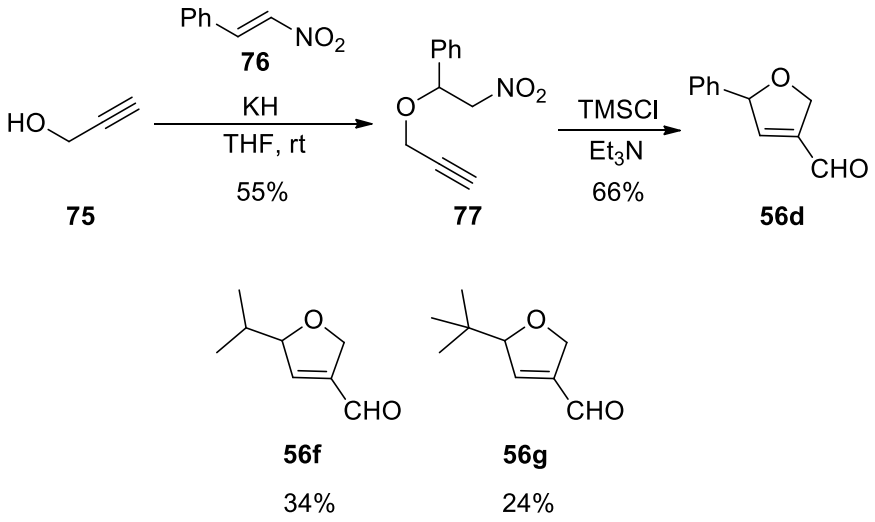
100 °C

53%

Scheme 2.23

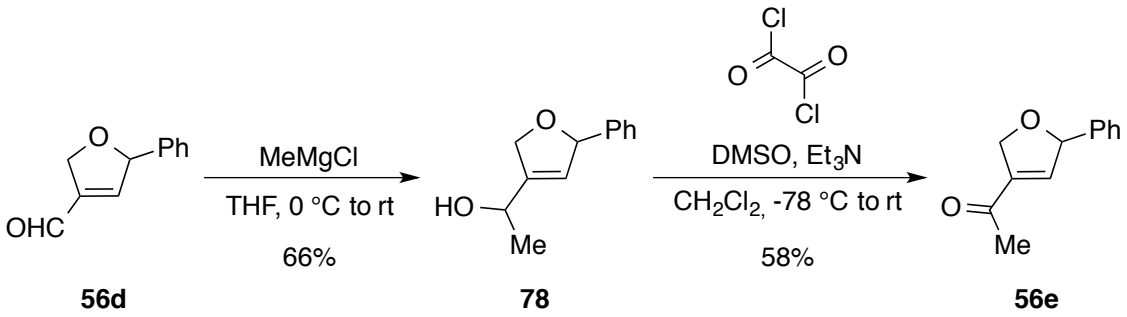
The synthesis of dihydrofurancarbaldehydes **56d,f-g** was accomplished as described in literature for compound **56d**,[102] and shown in Scheme 2.24. Reaction of propargyl alcohol (**75**) with potassium hydride and β-nitrostyrene **76** led to the formation of the corresponding propargyl ether **77**. Treatment of **77** with triethylamine and trimethylsilyl chloride afforded the corresponding dihydrofurancarbaldehyde **56d**. Compounds **56f-g** were prepared by the same procedure, however in lower yields.

[100] B. Brown, H. B. Henbest, E. R. H. Jones *J. Chem. Soc.* **1950**, 3634-3641.
[101] I. Heibron, E. R. H. Jones, R. W. Richardson, F. Sondheimer *J. Chem. Soc.* **1949**, 737-741.
[102] a) J. L. Duffy, J. A. Kurth, M. J. Kurth *Tetrahedron Lett.* **1993**, *34*, 8, 1259-1260; b) J. L. Duffy, M. J. Kurth, *J. Org. Chem.* **1994**, *59*, 3783-3785; c) H. J. Kim, Y. J. Lee *Synth. Commun.* **1998**, *28*, 3527-3537.



Scheme 2.24

Finally, 1-(5-phenyl-2,5-dihydrofuran-3-yl)ethan-1-one (**56e**) was obtained in two steps from **56d**. First addition of methyl magnesium chloride at 0° C in THF, followed by aqueous work-up led to **78** in 66% yield. Then a Swern oxidation of the alcohol afforded **56e** in moderate yields (Scheme 2.25).



Scheme 2.25

2.3.2 Diels-Alder reactions of 2-vinylindoles with cyclic dienophiles under Lewis acid catalysis

Cyclic dienophiles have been described as useful partners in Diels-Alder reactions even though their use is less common with respect to acyclic compounds.[103] A cycloaddition reaction involving these compounds and 2-vinylindoles would lead to polycyclic products bearing a carbonyl group in an angular position suitable for further transformations. Among natural products, aflavazole is the only [*c*]-carboannulated carbazole alkaloid isolated so far.[104] Besides, carbazole alkaloids [*c*]annulated with oxygen-containing rings fall in two main categories: carbazolelactones and furocarbazole alkaloids.[105] The clausamines, clausevatines and furanoclausamines are representative for [*c*]annulated δ-lactone carbazole alkaloids[106] whereas eustifoline D represents the only furo[2,3-*c*]carbazole alkaloid isolated till now (Figure 2.2).[107]

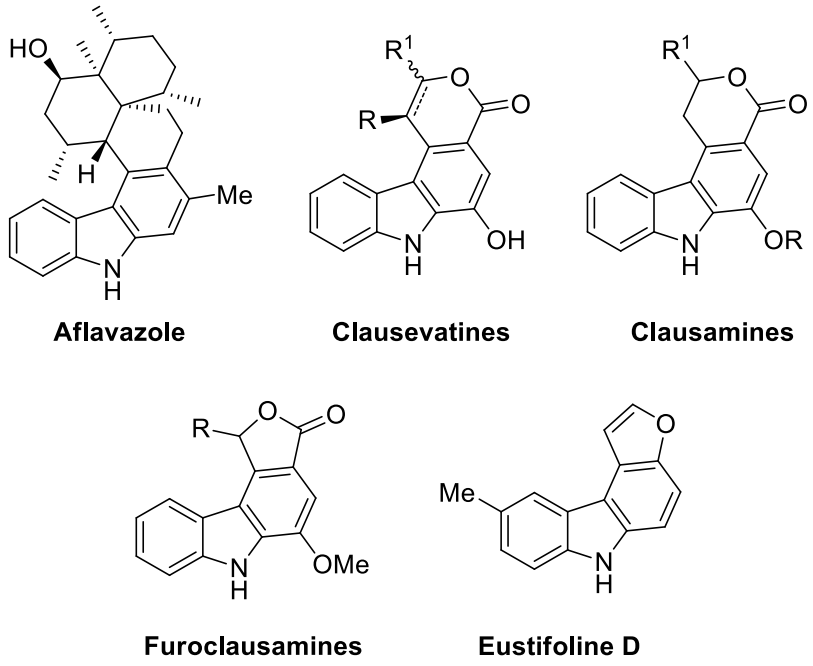


Figure 2.2

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[103] a) K. Ishihara, H. Kurihara, M. Matsumoto, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 6920-6930; b) Y. Huang, T. Iwama, V. H. Rawal, *J. Am. Chem. Soc.* **2000**, *122*, 7843-7844; c) E. Canales, E. J. Corey, *Org. Lett.* **2008**, *10*, 3271-3273.

[104] M. R. Te Paske, J. B. Gloer, D. T. Wicklow, P. F. Dowd, *J. Org. Chem.* **1990**, *55*, 5299-5301.

[105] A. W. Schmidt, K. R. Reddy, H.-J. Knoelker, *Chem. Rev.* **2012**, *112*, 3193-3328.

[106] a) C. Ito, S. Katsuno, N. Ruangrungsi, H. Furukawa, *Chem. Pharm. Bull.* **1998**, *46*, 344-346; b) T.-S. Wu, S.-C. Huang, P.-L. Wu, *Chem. Pharm. Bull.* **1998**, *46*, 1459-1461; c) C. Ito, M. Itoigawa, K. Aizawa, K. Yoshida, N. Ruangrungsi, H. Furukawa, *J. Nat. Prod.* **2009**, *72*, 1202-1204; d) T. P. Lebold, M. A. Kerr, *Org. Lett.* **2008**, *10*, 997-1000; e) A. K. Jana, D. Mal, *Chem. Commun.* **2010**, *46*, 4411-4413.

[107] a) R. Forke, M. P. Krahl, T. Krause, G. Schlechtingen, H.-J. Knoelker, *Synlett* **2007**, 268-272; b) T. P. Lebold, M. A. Kerr, *Org. Lett.* **2007**, *9*, 1883-1886.

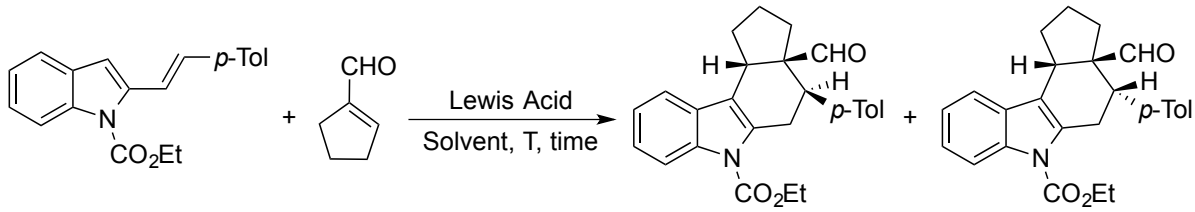
The reported syntheses of the naturally occurring derivatives mainly entail the construction of the [*c*]-ring through manipulation of 3,4-disubstituted carbazole derivatives.[108] Moreover, recently reported synthesis of unnatural [*c*]-carbo- and furoannulated carbazoles (cyclopenta-, hexa- and hepta[*c*]carbazoles and furo[3,4-*c*]carbazole derivatives) via Fischer indole synthesis suffers from the lack of regioselectivity (angular *vs* linear annulation) depending on the substitution and relative configuration of starting materials.[109] Therefore, we got interested in the application of [4+2] cycloaddition reaction of 2-vinylindoles with cyclic dienophiles in order to have an alternative access to this class of molecules. As reported in section 2.2, we tested the feasibility of these reactions under classical Lewis acid catalysis prior to extend our studies to the application of gold catalysis to the same transformations.

2.3.2.1 Screening of reaction conditions

2-Vinylindole **23a** and cyclopent-1-ene-1-carbaldehyde **56a** were selected as benchmark substrates to evaluate the feasibility of the devised [4+2] cycloaddition. A variety of reaction conditions were evaluated, whose results are summarized in the Table 2.1.[110]

[108] I. Bauer, H.-J. Knoelker, *Top. Curr. Chem.* **2012**, *309*, 203-253.
[109] a) C. L. Diedrich, W. Frey, J. Christoffers, *Eur. J. Org. Chem.* **2007**, 4731-4737; b) J. Christoffers, *Synlett* **2006**, 318-320; c) M. Bender, J. Christoffers, *Z. Naturforsch. B* **2011**, *66*, 1209-1218.
[110] V. Pirovano, G. Abbiati, M. Dell'Acqua, D. Facoetti, M. Giordano, E. Rossi, *Synlett* **2012**, *23*, 2913-2918.

Table 2.1: Screening of reaction conditions for the cycloaddition reaction between 23a and 56a



23a **56a** (±)-**57a** (±)-**57'a**

Entry	23a/56a	L.A., mol%	Solvent	T, ¡C	Time, h	Yield,[a] %	57a/57'a[b]
1	1:1	$MgClO_4$, 13	Toluene	110	24	–	–
2	1:1.2	$EtAlCl_2$, 13	Toluene	40	72	50	1:1
3	1:1.2	$Cu(OTf)_2$, 13	Toluene	40	24	53	1:1.5
4	1:1	$Sc(OTf)_3$, 13	CH_2Cl_2	40	24	91	1:2
5	1:1	$Sc(OTf)_3$, 13	Toluene	40	48	85	1:1.5
6	1:1.5	$BF_3{\cdot}OEt_2$, 13	CH_2Cl_2	rt	2	90	1:1.2
7	1:1.5	$BF_3{\cdot}OEt_2$, 13	Toluene	rt	2	92	1:2
8	1:1.5	$BF_3{\cdot}OEt_2$, 15	CH_2Cl_2	-20	4	90	1:1
9	1:1.5	$BF_3{\cdot}OEt_2$, 15	Toluene	-20	4	80	1:5
10	1:1.5	$BF_3{\cdot}OEt_2$, 15	CH_2Cl_2	-40	24	90	1:1
11	1:1.5	$BF_3{\cdot}OEt_2$, 15	Toluene	-40	24	59	1:3

Reaction conditions: To a N_2-flushed solution of **23a** and **56a** in the appropriate solvent (4 mL) the catalyst was added and the mixture was reacted at the stated temperature 2-72 h; for entries 8-11 the mixture was cooled prior to addition of the Lewis acid. **57a** and **57'a** were separated by column chromatography.
[a] Isolated yields. [b] Determined by ^1H NMR analysis of the crude mixture.

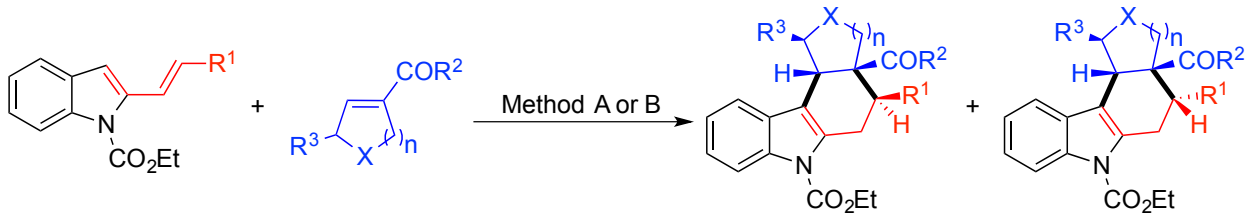
Firstly, the reaction conditions previously reported in our research group for the cycloadditions of 2-vinylindoles with acyclic dienophiles were tested, although proved ineffective.[10] Improved results were obtained with ethylaluminium dichloride and with copper(II) triflate at 40° C (entries 2-3) yielding the desired compounds (±)-**57a** and (±)-**57'a** in 50% and 53% yield and in a diastereomeric ratio of 1:1 and 1:1.5, respectively. Scandium(III) triflate gave better results both in dichloromethane and toluene as solvents, yielding (±)-**57a** and (±)-**57'a** in 91% and 85% yield with a diastereomeric ratio of 1:2 and 1:1.5, respectively (entries 4-5). Boron trifluoride was tested both in dichloromethane and in toluene as solvents, at temperatures ranging from -40 °C to room temperature (entries 6–11). In the presence of this Lewis acid, the best result was obtained when using toluene at -20 °C. Under these conditions tetrahydrocarbazoles (±)-**57a** and (±)-**57'a** were

obtained in 80% yield in a diastereomeric ratio of 1:5 (entry 9). On the basis of the obtained results, the best compromise between yields and diastereomeric ratios was obtained in the presence of $Sc(OTf)_3$ in CH_2Cl_2 at 40 °C (method A) or with $BF_3{\cdot}OEt_2$ in toluene at -20 °C (method B).

2.3.2.2 Scope of the reaction

With the best reaction conditions in hands, the scope of the transformation was the explored using the previously synthesized 2-vinylindoles **23** and cyclic α,β-unsaturated enone derivatives **56**. The results are shown in Table 2.2.

Table 2.2: Scope of the cycloaddition reaction between 23a-c,f and 56a-g

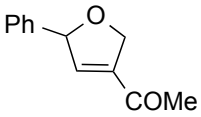
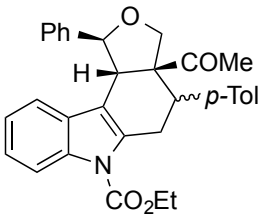
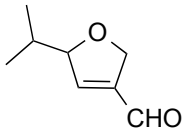
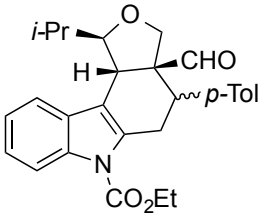
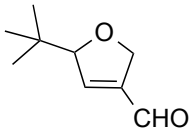
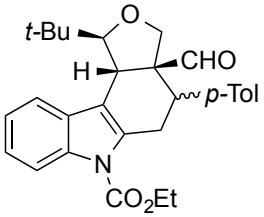
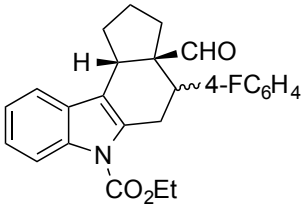
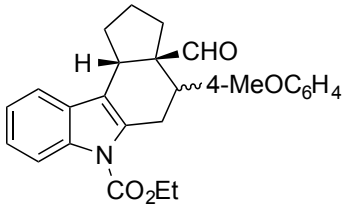
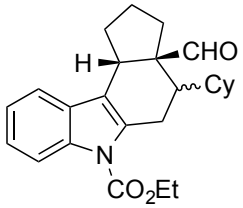


23a-c,f **56a-g** (±)-**57** (±)-**57'**

Entry	23, R^1	56	Products	Method	Yield,[a] %	57/57'[b]
1	*p*-Tol **23a**	CHO **56b**	**57b-57'b**	A	83	1:1.3
2				B	90	1.5:1
3	*p*-Tol **23a**	COMe **56c**	**57c-57'c**	B[c]	91	1.8:1
4	*p*-Tol **23a**	Ph, O, CHO **56d**	**57d-57'd**	A	92	1:1
5				B[d]	76[c]	9:1

continues on the next page

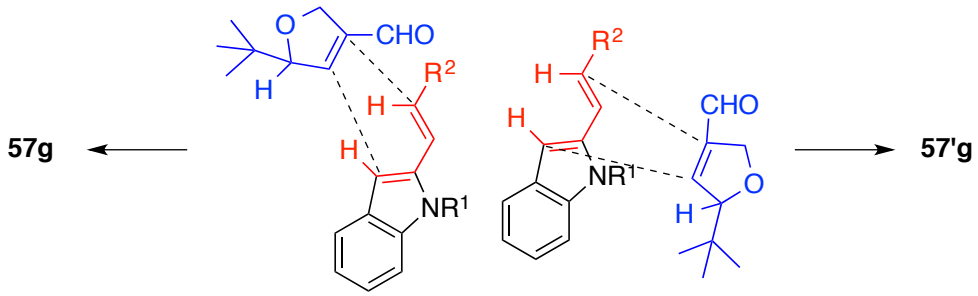
Table 2.2: Scope of the cycloaddition reaction between 23a-c,f and 56a-g

Entry	23, R^1	56	Products	Method	Yield,[a] %	57/57[b']
6	*p*-Tol **23a**	 **56e**	 **57e-57'e**	B[d]	99	1:1.1
7	*p*-Tol **23a**	 **56f**	 **57f-57'f**	A	97	2:1
8	*p*-Tol **23a**	 **56g**	 **57g-57'g**	A	73	3:1
9	4-FC_6H_4 **23b**	**56a**	 **57h-57'h**	B	81	1:3.2
10	4-$MeOC_6H_4$ **23c**	**56a**	 **57i-57'i**	B	83	1:1.8
11	Cy **23f**	**56a**	 **57j-57'j**	B	87	1:1.8

Reaction conditions: Method A: To a solution of $Sc(OTf)_3$ in CH_2Cl_2 (6 mL) **23a-c, f** and **56 a-g** were added and the mixture was stirred at 40 °C for 24 h. Method B: to a Solution of **23a,c-f** and **56a-g** in Toluene (6 mL) at -20 °C $BF_3{\cdot}OEt_2$ was added and the mixture was stirred for 4 h.

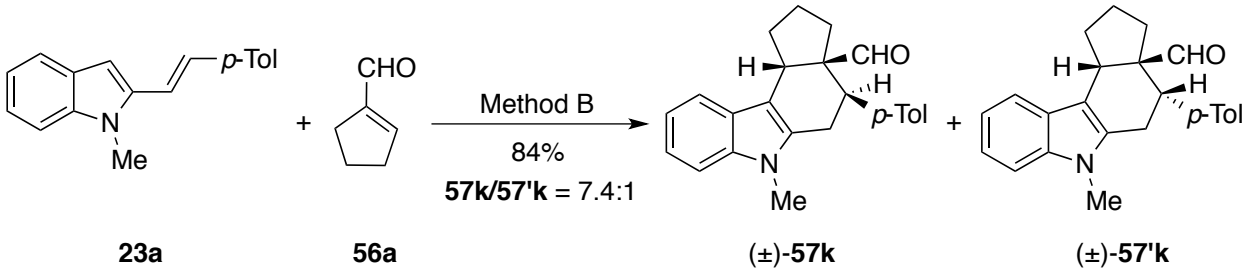
[a] Yields refer to pure isolated compounds. [b] Determined by ^1H NMR analysis of the crude mixture. [c] The reaction was performed at 0 °C for 96 h. [d] The reaction was performed at rt for 96 h.

Method B, giving the highest diastereomeric ratio in the model reaction, was selected for the reactions between *carbocyclic* enones **56a-c** and indoles **23a-c,f**. In this way, tetrahydrocarbazoles **57** and **57'** were prepared in good to excellent yields but with variable diastereomeric ratios (Table 2, entries 1, 3, 9-11). For comparison, the reaction of **23a** with *carbocyclic* enone **56b** was performed with both catalytic systems giving rise to similar results (*cf.* entries 1 and 2). Moving to *heterocyclic* enone **56d**, the reaction with **23a** was performed with both methods A and B yielding tetrahydrocarbazoles **57d** and **57'd** in higher diastereomeric ratio with method B but with higher yield with method A (*cf.* entries 4 and 5). Moreover, method B applied to *heterocyclic* enones seems to require higher temperature and prolonged reaction time (r.t., 96 h) if compared to the reactions performed with *carbocyclic* compounds (-20°C, 4 h) (*cf.* entries 1 and 5). In addition switching from *heterocyclic* enone **56d** to **56e** the diastereomeric ratio decreased drastically to give an almost equimolecular mixture of diastereoisomers (entry 6). Taking into account these latter results and the low yields against the long reaction time required for the reaction of **23a** with *heterocyclic* enones performed with method B, we chose to perform the reaction of **23a** with *heterocyclic* enones **56f,g** with method A (entries 7 and 8). It is worth noting that the cycloaddition reactions performed with racemic dienophiles **56f,g**, bearing a bulky group on the C-2 position, gave the derivatives **(±)-57f,g** and **(±)-57'f,g**, respectively, via addition to the less hindered side of the dienophiles, as exemplified in Scheme 2.26 for **57g** and **57'g**.



Scheme 2.26

Method B was applied also for the reaction between *N*-methyl 2-vinyl indole **23h** and **56a** obtaining the corresponding tetrahydrocarbazoles **57k** and **57'k** in high yield and with a ratio of 7.4/1 in favor to the *endo* adduct (Scheme 2.27).



23a **56a** **(±)-57k** **(±)-57'k**

Scheme 2.27

The *endo*/*exo* diastereoisomeric mixture of compounds **57**/**57'** could be separated by flash chromatography and each isomer was fully characterized as pure compound. The structures were established by combined 1D-(^{1}H NMR, APT) and 2D-NMR (COSY, HETCOR) experiments. For illustration, the ^{1}H- and ^{13}-C NMR spectra of compounds *endo*-**57c** and *exo*-**57'c** are shown in Figures 2.3a and b and 2.4a and b, respectively.

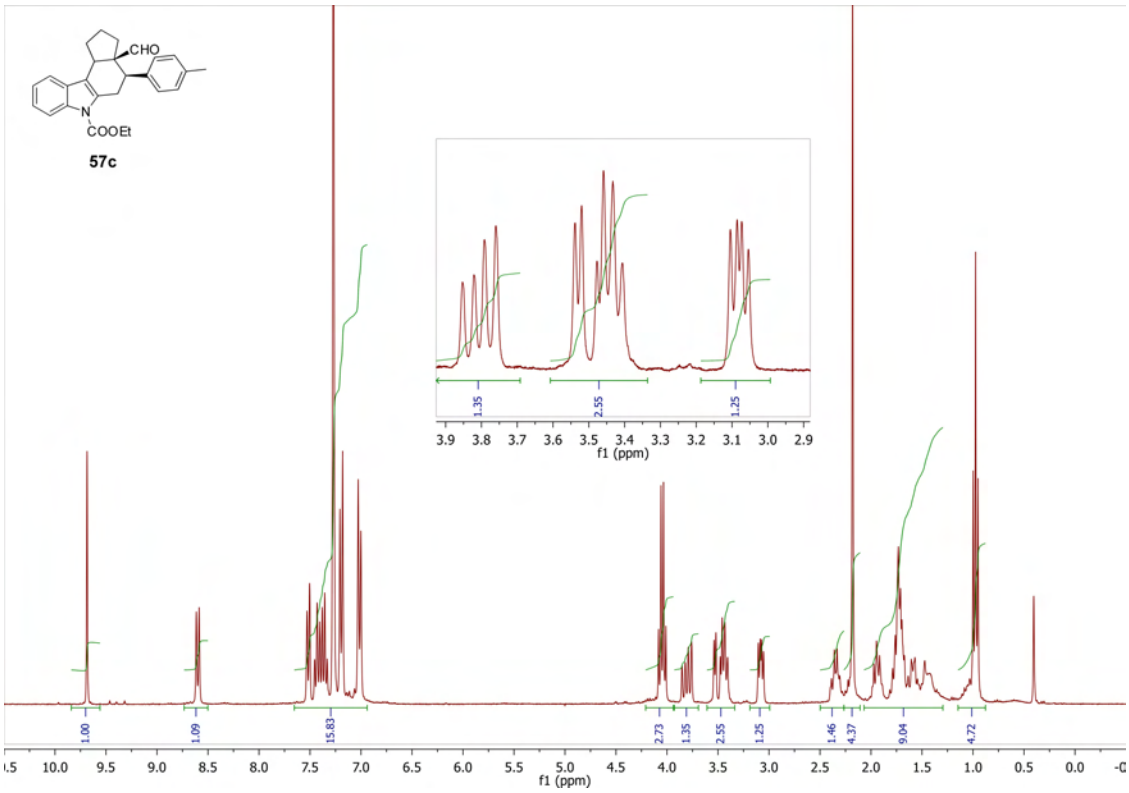


Figure 2.3a

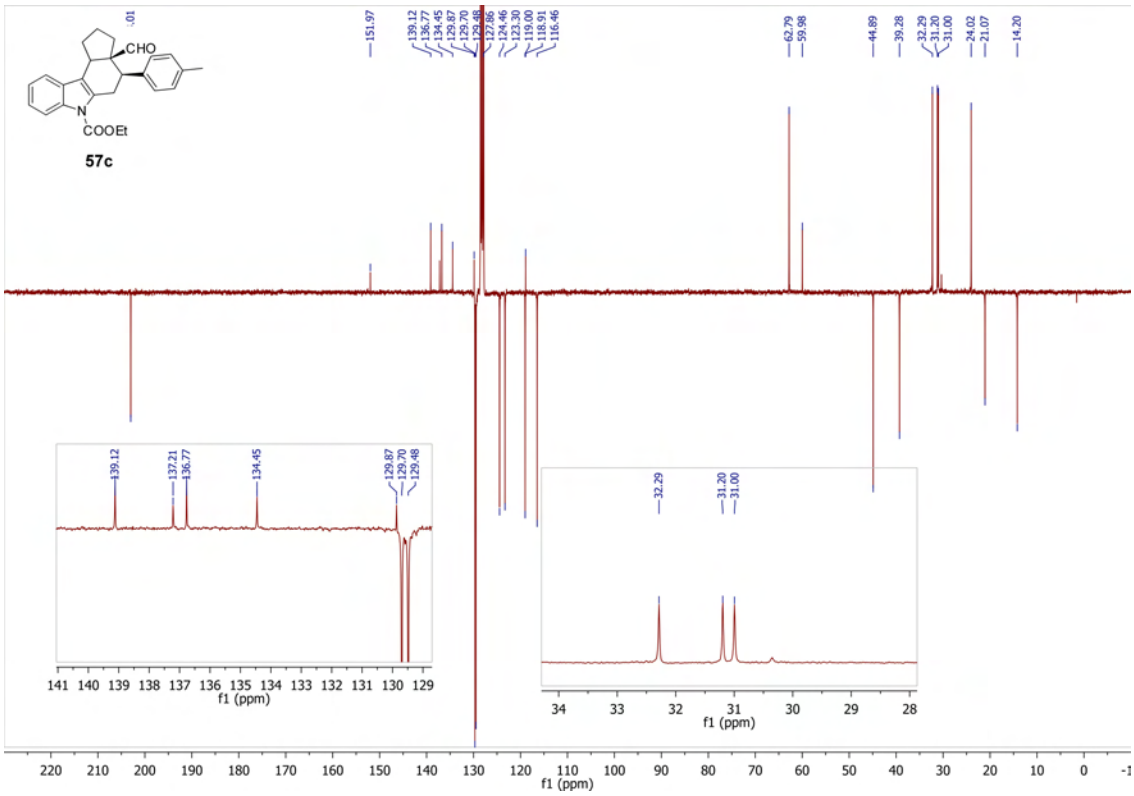


Figure 2.3b

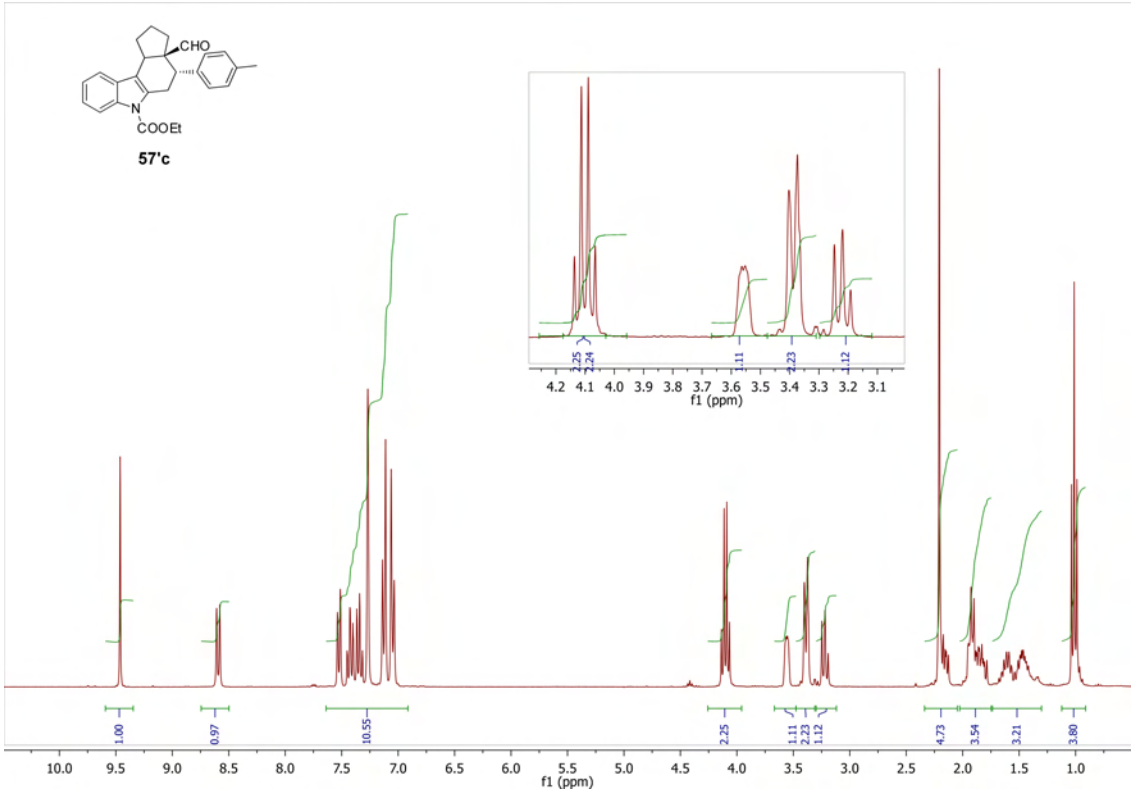


Figure 2.4a

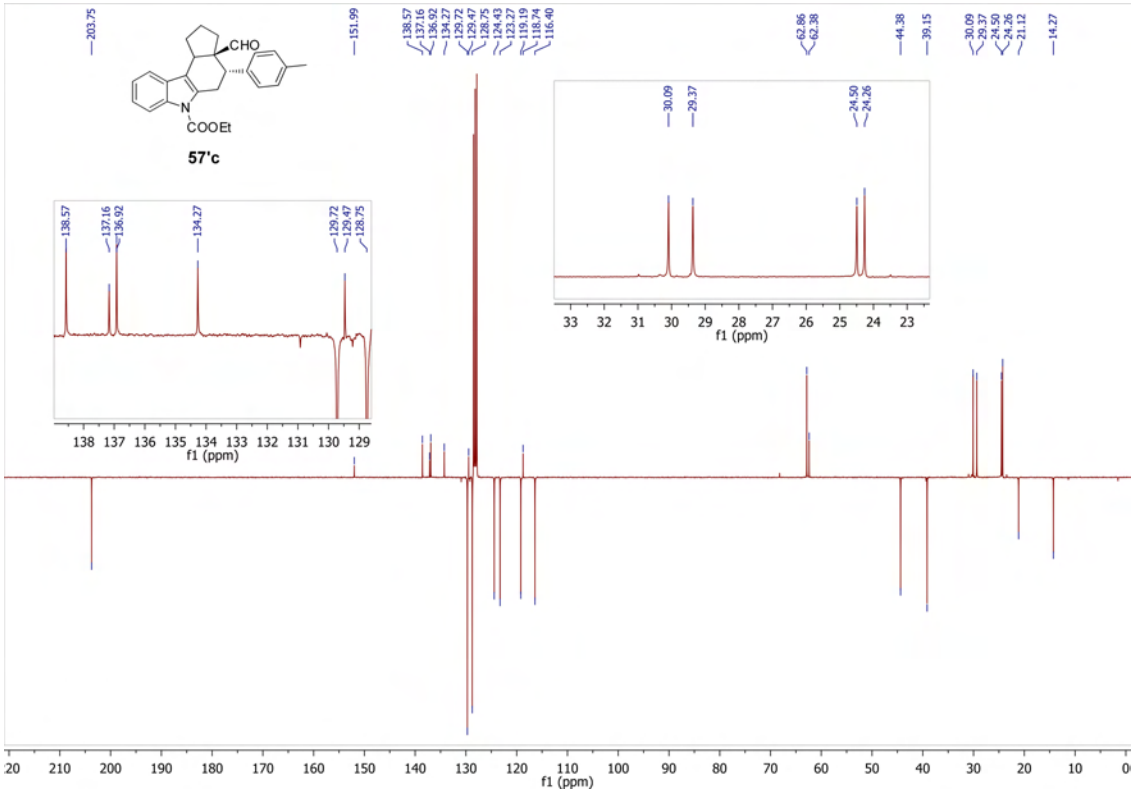


Figure 2.4b

The regio- and stereochemistry of Diels-Alder adducts were assigned on the basis of spatial coupling interactions, detected by 2D NOESY experiments as reported in Figure 2.5 for (±)-**57g** and (±)-**57'g**. The regiochemistry was assigned on the basis of NOE interactions between H-10 and both the hydrogen at C-10c and the substituent at C-1. The *cis* relationship between substituents at C-3a, C-10c and C-1 was established by the NOE interactions among these substituents.

The 3a,4-*cis*/*trans* relationships were assigned on the basis of diagnostic NOE interactions and computational investigations on both conceivable conformers ascribable to each isomer as exhaustively described in the literature[10,111] and reported in Figure 2.5.

[111] For further details see section 2.3.5.

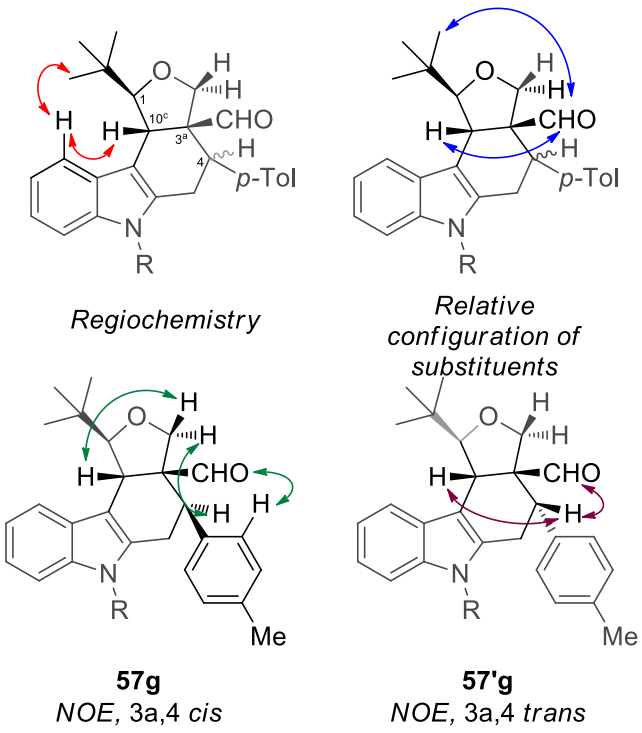

Regiochemistry
Relative configuration of substituents
57g
NOE, 3a,4 cis
57'g
NOE, 3a,4 trans

Figure 2.5

2.3.3 Gold-catalyzed [4+2] cycloaddition reactions of 2-vinylindoles and enones

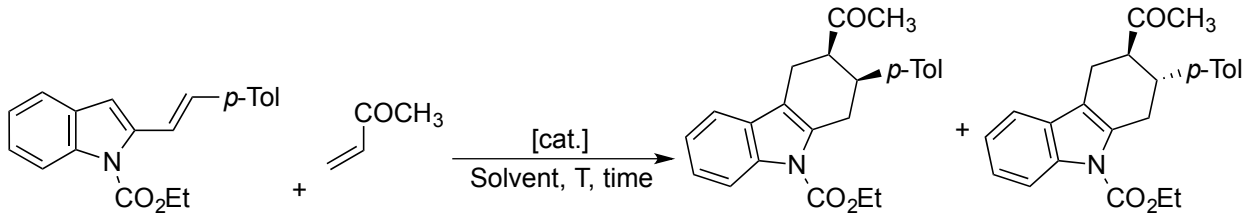
Taking in account the reported results for copper-catalyzed Diels-Alder reactions,[112] as well as the recent gain in popularity of both silver- and gold-based catalysts, we became interested in testing the catalytic activity of the entire series of coinage metals in the reactivity of 2-vinylindoles in cycloaddition reactions.[33] Coinage metal salts display σ- and π-philic properties to activate either the carbon–carbon or carbon–heteroatom multiple bonds.[113] Thus, testing their performance in our reactions appeared particularly attractive in order to study the influence on the yield and more importantly on the selectivity in the formation of tetrahydrocarbazole derivatives.

2.3.3.1 Screening of reaction conditions

By using 2-vinylindole **23a** and 3-buten-2-one (**14a**) as a model reaction, a series of conditions for the synthesis of the corresponding carbazoles **24a** were evaluated. The results obtained from the screening of catalysts are summarized in Table 2.3.[114]

[112] S. Reymond, J. Cossy, *Chem. Rev.* **2008**, *108*, 5359-5406.
[113] Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817-7831.
[114] V. Pirovano, M. Dell'Acqua, D. Facoetti, S. Rizzato, G. Abbiati, E. Rossi, *Eur. J. Org. Chem.* **2013**, 6267-6279.

Table 2.3: Screening of cycloaddition reaction between 23a and 14a



23a **14a** **(±)24a** **(±)24'a**

Entry	Catalyst, mol%	Solvent	T, °C	Time, h	Yield,[a] %	24/24'
1	$Mg(ClO_4)_2$,15	Toluene	110	24	77	2.5:1
2	$Sc(OTf)_3$, 15	CH_2Cl_2	rt	24	95	5.1:1
3	$BF_3{\cdot}OEt_2$, 15	Toluene	-20	1.5	92	12:1
4	CuOTf, 15l	Toluene	rt	24	–	–
5	CuOTf, 15	CH_2Cl_2	rt	120	95	4.6:1[a]
6	$Cu(OTf)_2$, 15	Toluene	rt	96	81	6:1[a]
7	$Cu(OTf)_2$, 15	CH_2Cl_2	rt	24	94	6:1
8	AgOTf, 2	Toluene	rt	24	88	8:1
9	$[Au(PPh_3)Cl]$, 2	Toluene	rt	24	–	–
10	$[Au(PPh_3)Cl]$/AgOTf, 2	Toluene	rt	24	93	13.3:1
11	$[Au(PPh_3)Cl]/AgSbF_6$, 2	Toluene	rt	24	86	21:1
12	$[Au(PPh_3)]$OTf, 2	Toluene	rt	24	93	13.3:1
13	$[Au(PPh_3)Cl]$/AgOTf, 2	$CHCl_3$	rt	24	83	7:1
14	$[(AuCl_2)$BINAP]/AgOTf, 2	Toluene	rt	24	99	7:1
15	$[Au(PPh_3)(NTf_2)]$, 2	Toluene	rt	24	–	–
16	[Au(IPr)(Cl)]/AgOTf, 5	Toluene	80	48	61	7:1[a]
17	$[Au(IPr)(Cl)]/AgSbF_6$, 5	Toluene	80	48	85	4:1
18	$AuCl_3$, 2	Toluene	rt	1.5	99	12.3:1
19	$AuCl_3$, 2	Toluene	0	18	96	13.3:1
20	$PtCl_2$, 2	Toluene	rt	24	–	–

Reaction conditions: entries 1,2 and 4-20: to a solution of the catalyst in the appropriate solvent (2 mL), **23a** and **14a** were added and the mixture was stirred at the stated temperatures for 1.5-48 h. Entry 3: to a solution of **23a** and **14a** in toluene (6 mL) at -20 °C, $BF_3{\cdot}OEt_2$ was added and the mixture was stirred for 1.5 h. **24a** and **24'a** were separated by column chromatography.
[a] Isolated yields. [b] Determined by ^{1}H NMR analysis of the crude mixture.

In all the experiments, tetrahydrocarbazoles (±)**24a/24'a** were the main reaction product, and the Michael-type adduct was neither isolated nor observed by ^{1}H-NMR analysis of the crude reaction

mixture. Entry 1 covers our previously reported results with $Mg(ClO_4)_2$[10] and entries 2-3 the evaluation of $Sc(OTf)_3$ and $BF_3{\cdot}OEt_2$ which we selected as best catalysts for the DA reactions of 2-vinylindoles with cyclic dienophiles.[33] Almost quantitative yields were obtained with both the latter two Lewis acids, however, reasonable level of diastereoselectivity resulted when the reaction was performed in toluene at a less practical temperature of -20 °C with $BF_3{\cdot}OEt_2$.

Subsequently, we tested the activity of coinage metals. CuOTf and $Cu(OTf)_2$ were active catalysts when dichloromethane was used as the solvent, whereas in toluene only copper(II) triflate was effective (entries 4-7). The reactions could be performed at room temperature with a catalyst loading of 15 mol%, and excellent yields and moderate diastereomeric excess values were achieved under these conditions. However, no reaction occurred with more convenient catalyst loadings such as 5.0 mol%, under otherwise identical conditions. Ag(OTf) gave similar results, although with a more advantageous catalyst loading of 2 mol% (entry 8). A prototypical neutral gold catalyst as $[Au(PPh_3)]Cl$ was ineffective to promote the cycloaddition (entry 9), whereas the corresponding *in-situ* genterated cationic gold(I) complex, provided **24a** in an excellent yield, comparable to common Lewis acids, (entries 10-11), but more importantly, with the highest diastereoisomeric ratio (up to 21:1, entry 11). Notably, these reactions took place at low catalyst loadings as well. The effective catalyst was a cationic gold(I) species as indicated by the experiment performed with isolated $[PPh_3AuOTf]$[115] (Entry 12).[116] Toluene seemed to be the solvent of choice, as the reaction that was performed in chloroform (Entry 13) resulted in a reduced yield and diasteroisomers ratio.

Furthermore, we briefly explored other cationic gold species. Hence, the reaction performed in the presence of a bidentate phosphane ligand resulted in a marked decrease of diastereoselectivity (entry 14), whereas the reaction carried out with a gold catalyst bearing a more coordinating counterion (NTf_2) was unsuccessful (entry 15). Cationic gold catalysts derived from an *N*-heterocyclic carbene (NHC) were ineffective at room temperature, although proved active when the temperature was rised up to 80 °C, affording **24a** in moderate yields and diastereoselectivities (entries 16-17). In addition, $AuCl_3$ was tested at room temperature in toluene and gave similar results with respect to gold(I) catalysts. However, there was a tangible reduction in the reaction time. A decrease of the reaction temperature to 0 °C did not affect the yield and barely influenced the diastereomeric ratio (entry 19). Finally, a comparison between platinum and gold-based catalysts was performed (Entry 20), however, $PtCl_2$ was totally ineffective catalyst.

[115] The catalyst was prepared by mixing equimolar amounts of $[Au(PPh_3)(Cl)]$ and AgOTf in dry toluene. The obtained suspension was filtered through a syringe that was fitted with a Whatman Anotop 10 IC filter to remove the AgCl precipitate. The obtained solution was charged with the reactants and treated as reported in Table 2.3.

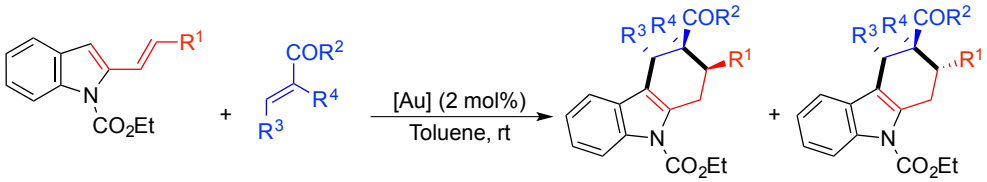
[116]

In most cases, the coinage metal catalysts gave better diastereomeric ratios than those obtained with magnesium perchlorate and scandium triflate, and these reactions proceeded faster or under milder conditions (Entries 1 and 2 *vs*. 7 and 8, 10-14, and 16-19). On the other hand, these results were comparable to those obtained under boron trifluoride catalysis. Although under coinage metal catalysis, the reactions could be performed at room temperature (Entries 3 *vs*. 10 and 18) and with lower catalyst loadings.

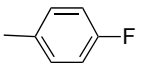
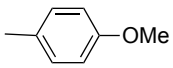
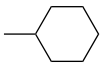
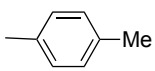
2.3.3.2 Scope of gold-catalyzed [4+2] cycloaddition reaction

After the screening of the reaction conditions, the scope of this transformation was evaluated as catalyst a cationic gold(I) species generated *in situ* from [Au(PPh_3)(Cl)]/AgOTf or gold(III) in toluene at room temperature (Table 2.4).

Table 2.4: Scope of the gold-catalyzed cycloaddition reaction between 23a-f and 14a-d or 56a

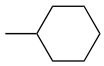
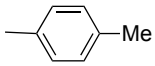
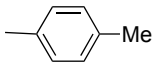
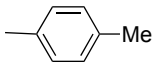


23a-f **14a-d; 56a** **(±)-24** **(±)-24'**

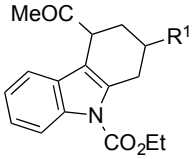
Entry	23	R^1	24	R^2	R^3	R^4	24-24'	[Au]	Time, h	Yield,[a] %	24/24'[b]
1	**23b**		**14a**	Me	H	H	**24b-'b**	[Au(PPh_3)Cl]/AgOTf	24	89	9:1
								$AuCl_3$	1.5	91	14.4:1
2	**23c**		**14a**	Me	H	H	**24c-'c**	[Au(PPh_3)Cl]/AgOTf	24	94	7:1
								$AuCl_3$	18	62	49:1
3	**23d**	Me	**14a**	Me	H	H	**24d-'d**	[Au(PPh_3)Cl]/AgOTf	24	93[c]	49:1
								$AuCl_3$	2	97[d]	> 99:1
4	**23e**		**14a**	Me	H	H	**24e-'e**	[Au(PPh_3)Cl]/AgOTf	28	80[c]	> 99:1
								$AuCl_3$	3	95[d]	> 99:1
5	**23f**	*n*-Bu	**14a**	Me	H	H	**24f-'f**	[Au(PPh_3)Cl]/AgOTf	24	82[c]	> 99:1
								$AuCl_3$	5	62[d]	> 99:1
6	**23a**		**14b**	Me	Ph	H	**24g-'g**	[Au(PPh_3)Cl]/AgOTf	24	84	1:1
								$AuCl_3$	1.5	86	1:1

continues on the next page

Table 2.4: Scope of the gold-catalyzed cycloaddition reaction between 23a-f and 14a-d or 56a

Entry	23	R^1	14	R^2	R^3	R^4	24-24'	[Au]	Time, h	Yield,[a] %	24/24'
7	**23e**		**14b**	Me	Ph	H	**24h-'h**	$[Au(PPh_3)Cl]/AgOTf$	65[e]	53	0
								$AuCl_3$	65[e]	38	1.4:1
8	**23a**		**14c**	H	H	H	**24i-'i**	$[Au(PPh_3)Cl]/AgOTf$	24	89	2.7:1
								$AuCl_3$	1.5	96	49:1
9	**23a**		**14d**	H	Ph	H	**24j-'j**	$[Au(PPh_3)Cl]/AgOTf$	24	70	1.2:1
								$AuCl_3$	48	96	2:1
10	**23a**		**56a**	H	$-(CH_2)_3-$		**57a-'a**	$[Au(PPh_3)Cl]/AgOTf$	24[f]	81	1.3:1
								$AuCl_3$	24	24	1:3

Reaction conditions: To a solution of the gold catalyst in Toluene (2 mL) **23a-f** and **14a-d** or **56a** (1.2 equiv.) and the mixture was stirred at rt for the stated time.
[a] Isolated yields. [b] Determined by ^1H NMR analysis of the crude reactio mixture. [c] Given yields include 5, 6 and 10%, respectively, of regioisomeric **24a"**, **24b"** and **24c".** [d] Given yields include 3, 8 and 7%, respectively, of regioisomeric **24a"**-**24c"**. [e] At rt for 48 h then at 80 °C for 17 h. [f] At rt for 12 h then at 110 °C for 12 h.

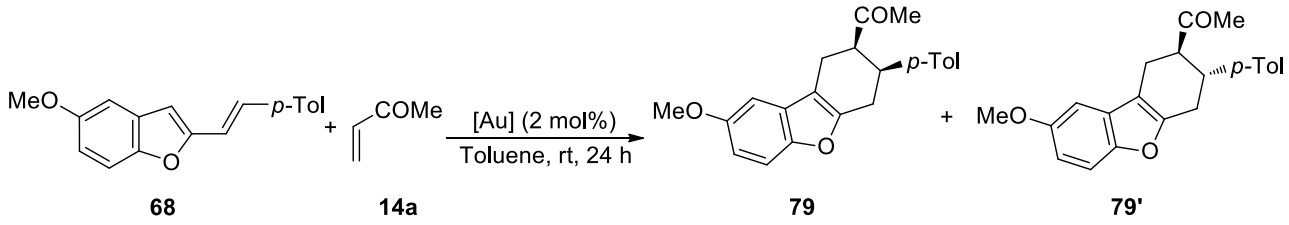


24"a: R^1 = Me
24"b: R^1 = Cy
24"c: R^1 = *n*-Bu

In almost all reported experiments, tetrahydrocarbazoles (±)-**24** and (±)-**24**' were obtained in good to excellent yields. Once again, the Michael-type addition compounds were neither isolated nor detected. The diastereoselectivity for the *endo* product remained high with 2-vinylindoles bearing arenes with different electronic properties at the β-position (entries 1 and 2). Moreover, nearly *endo* diastereospecific reactions were attained with β-alkyl-substituted vinylindoles **23d**-**23f** (entries 3-5). In these reactions, a small percentage of the corresponding regioisomeric 1,3-disubstituted tetrahydrocarbazoles **24''** was also isolated as diastereomeric mixtures. Modification of the dienophile by the introduction of a phenyl group at the β-position resulted in an almost complete loss of diastereoselectivity with both aryl and alkyl vinyl indoles (entries 6-7), and a higher reaction temperature was required when cyclohexyl-substituted vinylindole **23e** was the substrate (entry 7). A decrease of diastereoselectivity was also observed when crotonaldehyde and cinnamaldehyde were used as dienophiles (entries 8-9). In particular, the use of cynnamaldehyde (**14d**) led to the isolation of almost equimolar amounts of *endo*/*exo* cycloadducts (entry 9). Finally, cyclic dienophile **56a** proved less reactive (entry 10). The reaction with cationic gold(I) at room temperature for 12 h followed by treatment at 110 °C for 12 h gave rise to **57a/57'a** in good yield but with a poor diastereoselectivity. Besides, the reaction with $AuCl_3$ afforded **57a**/**57'a** in a poorer yield but with preference for the *exo* adduct.

In most of the cases, $AuCl_3$ appeared to be superior to the cationic gold(I) as catalyst and provided better yields and diastereomeric ratios.

Not only 2-vinylindoles but also other heterocyclic compounds such as 2-vinylbenzofuran derivative **68** were tested, as reported in Scheme 2.28.



68 **14a** **79** **79'**

[Au] = [Au(PPh$_3$)Cl]/AgOTf Yield, 61%; **79**/**79'** = 3.4:1

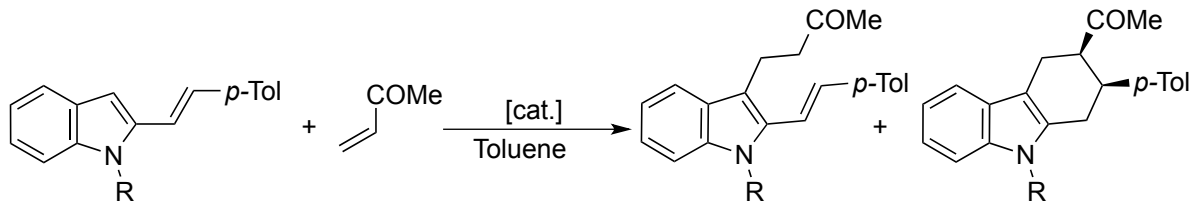
$AuCl_3$ Yield, 61%; **79**/**79'** = 21:1

Scheme 2.28

The behavior of **68** towards cationic gold(I) or gold(III) catalysts was similar to that of *N*-ethoxycarbonyl protected vinylindoles. Thus, under the same reaction conditions, the corresponding tetrahydrodibenzo[*b*,*d*]furan derivative **79/79'** was obtained in moderate yield. Again, the use of $AuCl_3$ provided the better diastereomeric ratio, leading to *cis* isomer with high selectivity.

In addition to these results, the reactivity of *N*-unsubstituted and *N*-methyl-2-vinylindoles **23g** and **23h** with ketone **14a** was also explored (Table 2.5).

Table 2.5: Reactions between 23g, h and 14a



23g, R = H
23h, R = Me

14a

80a, R = H
80b, R = Me

(±)-**24l,** R = H
(±)-**24m,** R = Me

Entry	23	Catalyst, mol%	Time, h	Overall Yield,[a] %	80/24[a]
1	**23g**	$BF_3{\cdot}OEt_2$, 15	2.5	28	1:1.6
2	**23g**	[Au(PPh_3)Cl]/AgOTf, 2 mol	24	62	2.4:1
3	**23g**	$AuCl_3$, 2	24	76	3.2:1
4	**23h**	$BF_3{\cdot}OEt_2$, 15	4	80	>1:99
5	**23h**	[Au(PPh_3)Cl]/AgOTf, 2 mol	24	72	>1:99
6	**23h**	$AuCl_3$, 2	24	77	2.9:1

Reaction conditions: To a solution of the catalyst in toluene, **23g-h** and **14a** were added at rt (entries 2,3 and 5,6) or at -20 °C (entries 1 and 4) and stirred for 2.5-24 h. [a] Yields and ratio refer to pure isolated compounds.

Unprotected 2-vinylindoles are reported to react thermally with electrophilic acyclic alkenes or in the presence of silica gel or molecular sieves to yield the single *endo* diastereomer, although in low yield.[5] Using **23g** and $BF_3{\cdot}OEt_2$ or gold as catalysts the reaction gave poor results and the Michael-type addition product **80a** was always isolated along with [4+2] cycloadduct **24l**, which was obtained as a single diastereomer (entries 1–3). On the other side, **23h** in the presence of boron trifluoride or cationic gold(I) afforded the cycloadduct **24m** in high yields and with complete diastereoselectivity (entries 4 and 5). Conversely, the reaction of **23h** with gold(III) furnished a mixture of **80b** and **24m** (as a single diastereomer, Entry 6). Therefore, the Michael-type addition and the Diels-Alder reaction were in competition when the more electron-rich 2-vinyl-1*H*-indole **23g** was employed.

The structures of the diastereomeric cycloadducts **24** and **24'** were assigned on the basis of analytical and spectroscopic data.[34] Representative ^{1}H- and ^{13}C-NMR for products **24a** and **24'a** are reported in Figures 2.6a,b and 2.7a,b.

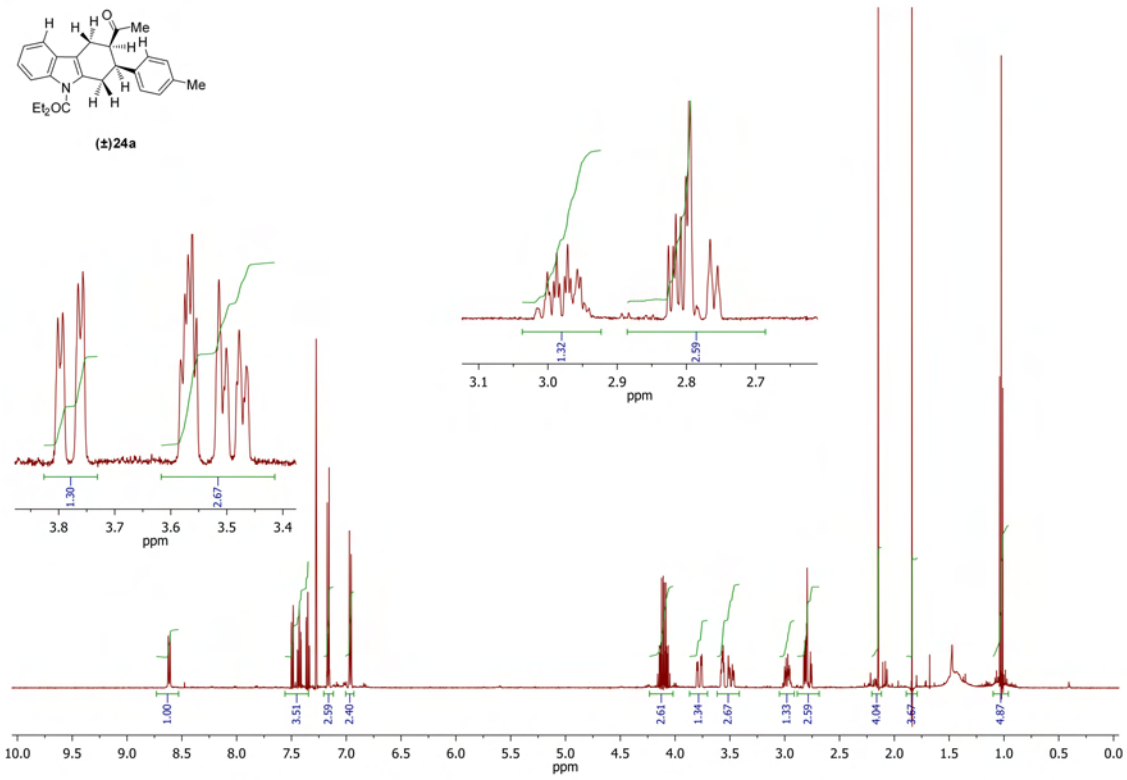


Figure 2.6a

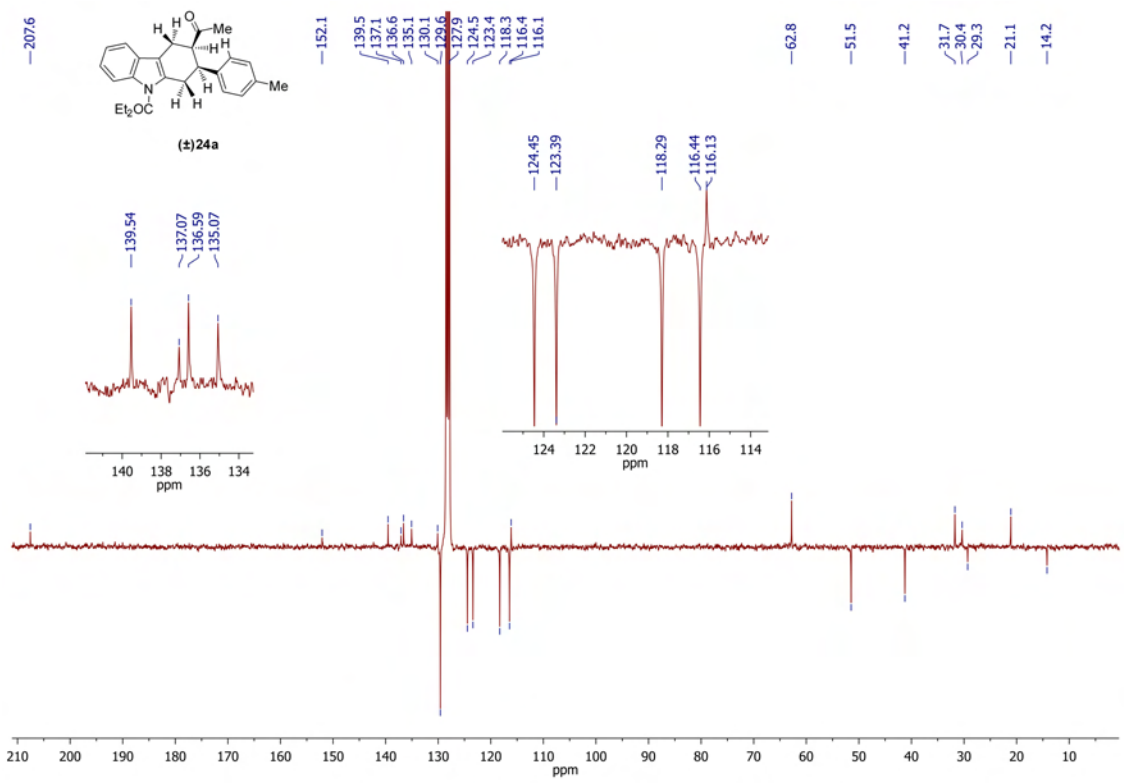


Figure 2.6b

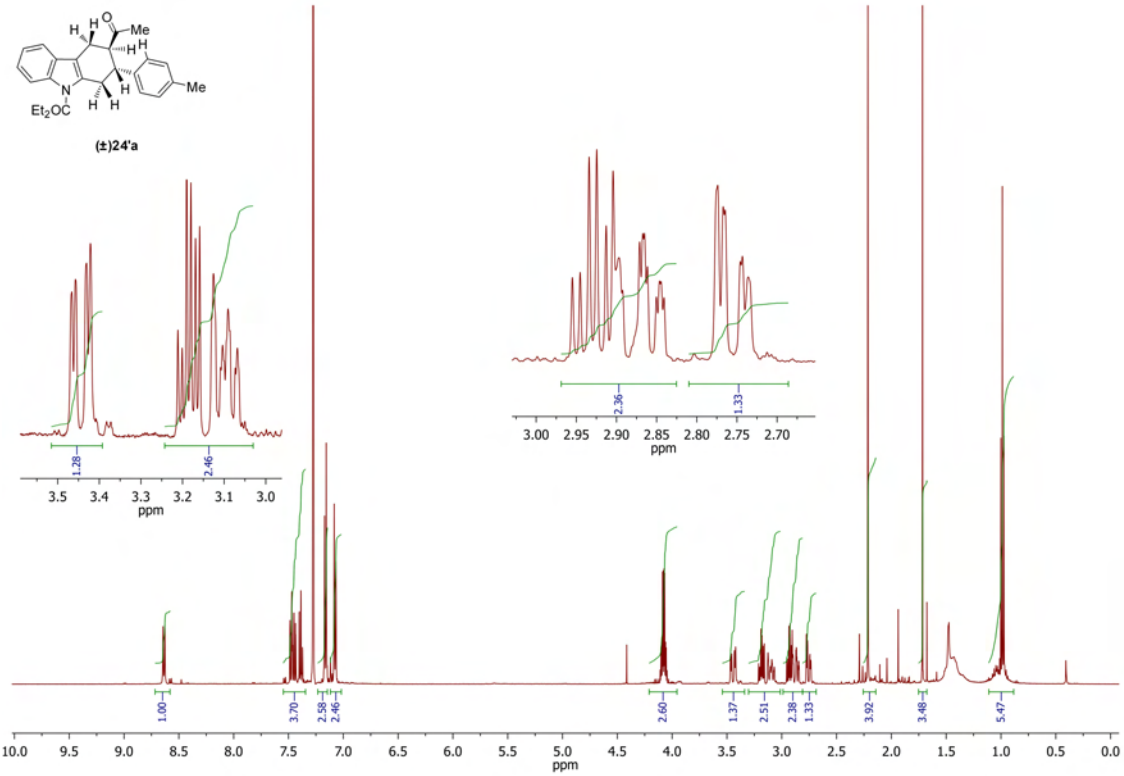


Figure 2.7a

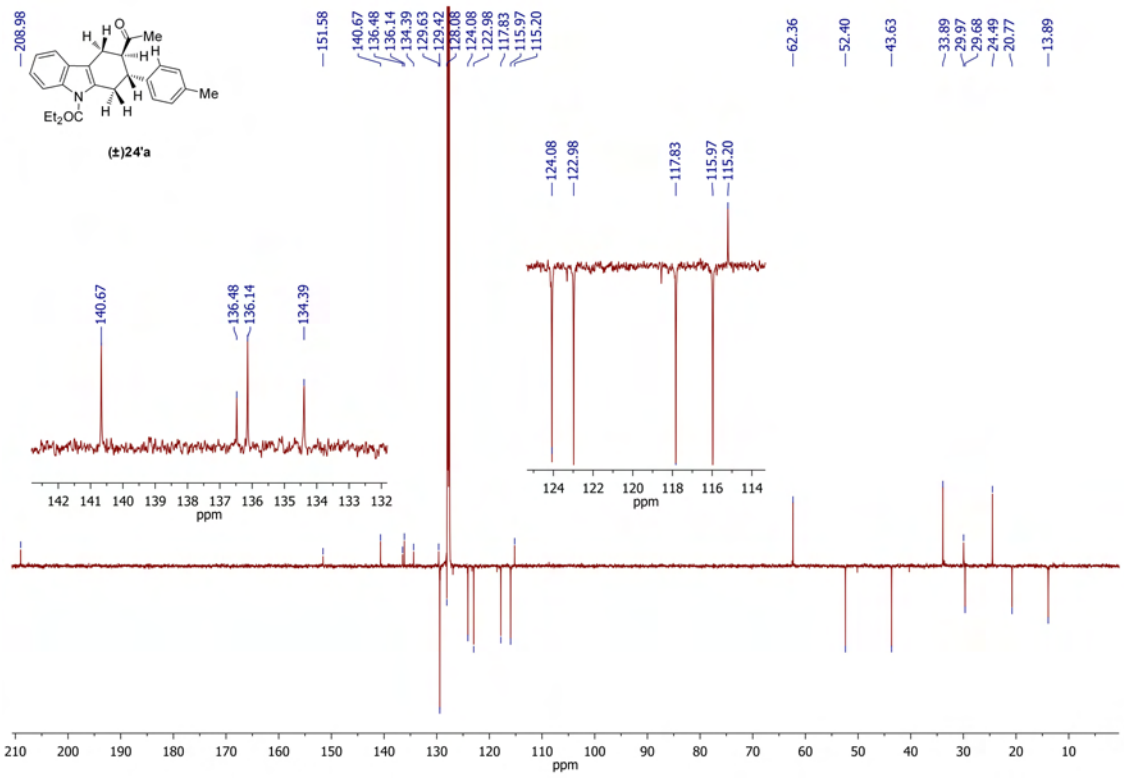
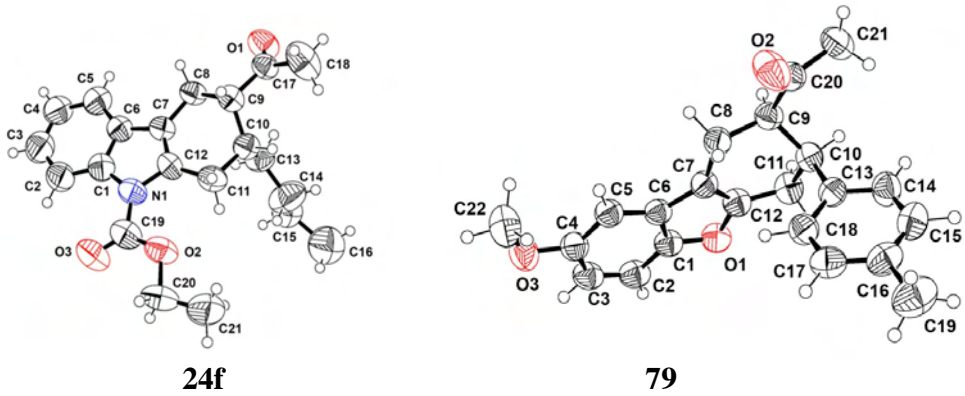


Figure 2.7b

Moreover, the structures and the *endo* stereochemistry of compounds **24f** and **79** were assigned on the same basis and unambiguously confirmed by X-ray diffraction analysis of a single crystal (Figure 2.8).

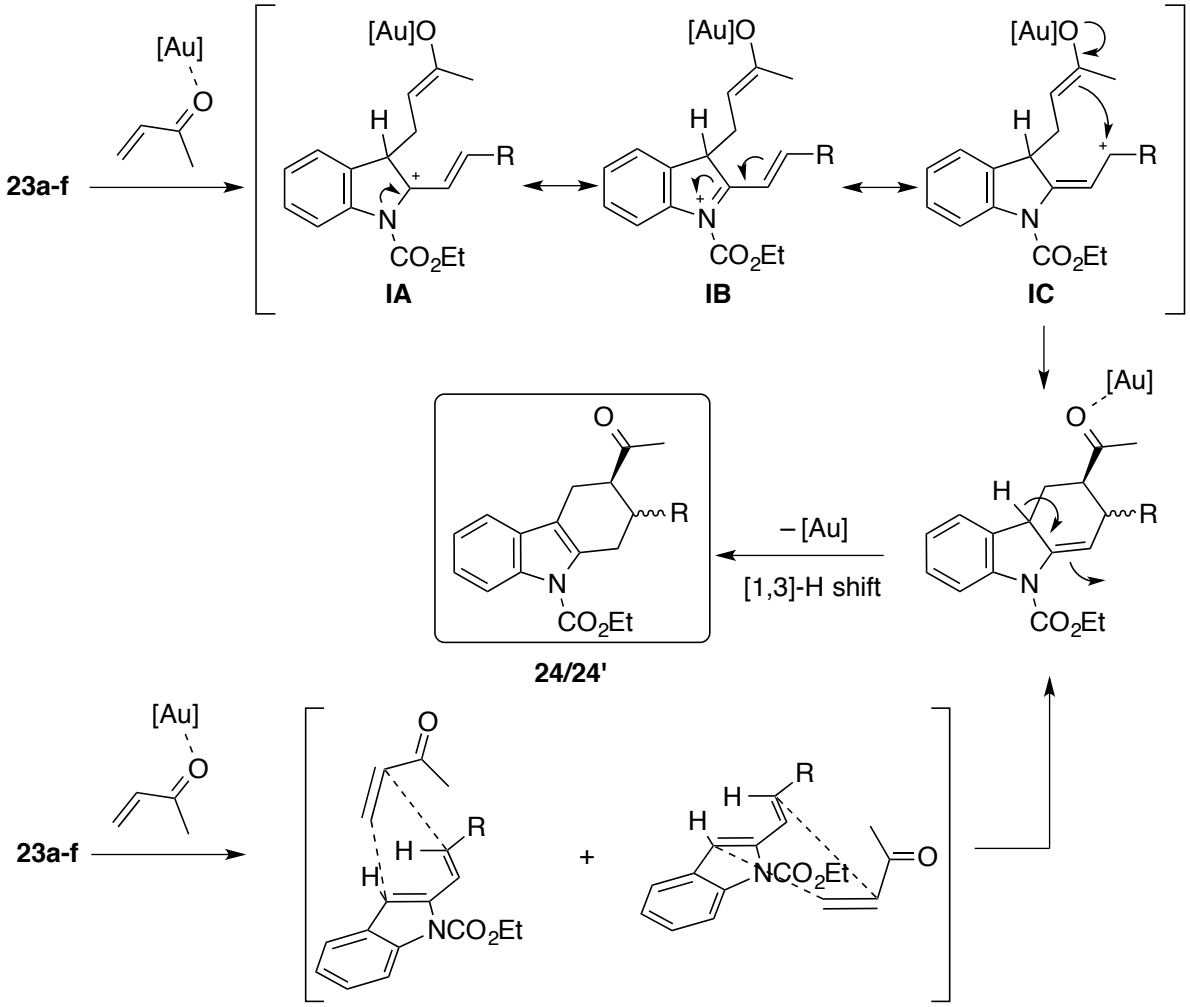


24f **79**

Figure 2.8

2.3.3.3 Proposed mechanism

The reaction mechanism probably involves σ-activation of the dienophile by the metal. The formation of the Diels-Alder adduct would probably take place through a pseudoconcerted or a fast stepwise mechanism, as the results in terms of selectivity pointed out (Scheme 2.29).

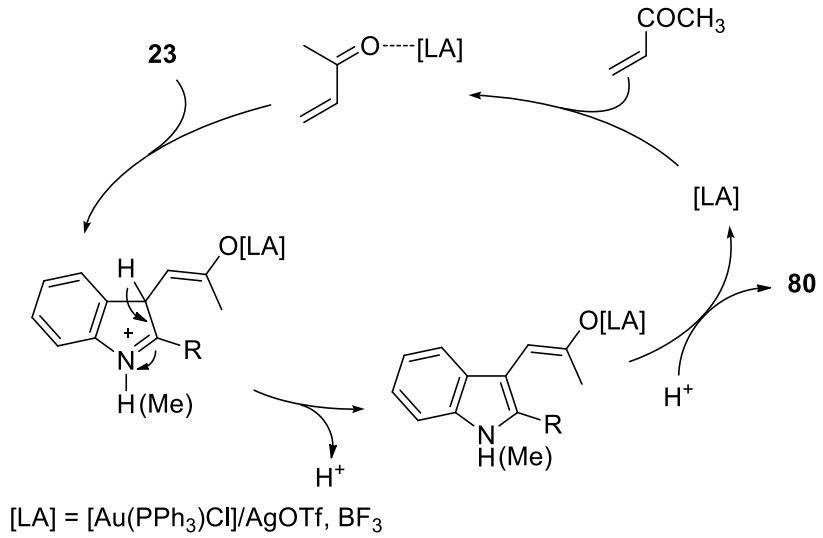


Scheme 2.29

In the fast stepwise path, the driving force to the exclusive formation of the cycloaddition products, which avoids the formation of the Michael-type adducts, could be related to the presence of the carbamate substituent on the indole. This can lower the nucleophilic character of the indole nitrogen, and thus the relative contribution of intermediate **IB** with respect to **IC** results in the enhanced electrophilic character of the outer carbon atom of the vinyl system. Similar concerns account for the results obtained with compound **68**. Additionally, the observed *endo*/*exo* ratios could be rationalized as reported for common Lewis acid-catalyzed Diels-Alder reactions. Thus, LA-catalysed cycloadditions proceed faster than their thermal counterparts and are often more

regio- and stereoselective, depending on the LA employed.[117] In our experience, the *endo* diastereoselectivity for the reactions of indole-*N*-carbamates **23a**-**f** with β-unsubstituted dienophiles **14a** and **14c** remains consistently high or specific, which is a result best explained through FMO theory. The loss of diastereoselectivity that is observed in the reactions with dienophiles **14b** and **14d** is probably due to secondary orbital interactions (SOI) between the β-phenyl substituent of the dienophile and the π-system of the diene, with a consequent decrease in the energy difference between the *endo* and *exo* transition states.[1] When the double bond of the dienophile is secured as part of a cycle, as in **56a**, the obtained results are erratically distributed and difficult to rationalize, which suggests that additional factors such as steric and electrostatic effects, closed-shell repulsions, and secondary orbital interactions could be operative.

In the reaction with *N*-unsubstituted 2-vinylindoles, a competitive mechanism takes place enabling the formation of the Micheal addition product. Thus, compounds **80a-b** could arise from a Friedel-Crafts-type reaction (Scheme 2.30).



Scheme 2.30

Considering the well-known σ-acidity of boron trifluoride, this mechanism (Scheme 2.30) likely operates when this Lewis acid is employed. Therefore, behaviors of **23g** and **23h** reflect the relative reaction rate of the Micheal addition with respect to the Diels-Alder reaction of *N*-unsubstituted and *N*-alkyl-substituted indoles, with the latter being less reactive than the former. On the other hand, a mechanism involving C–H activation of the heteroaromatic system accounts in the case of gold(III) catalysis, as suggested by several authors (Scheme 2.31).[118]

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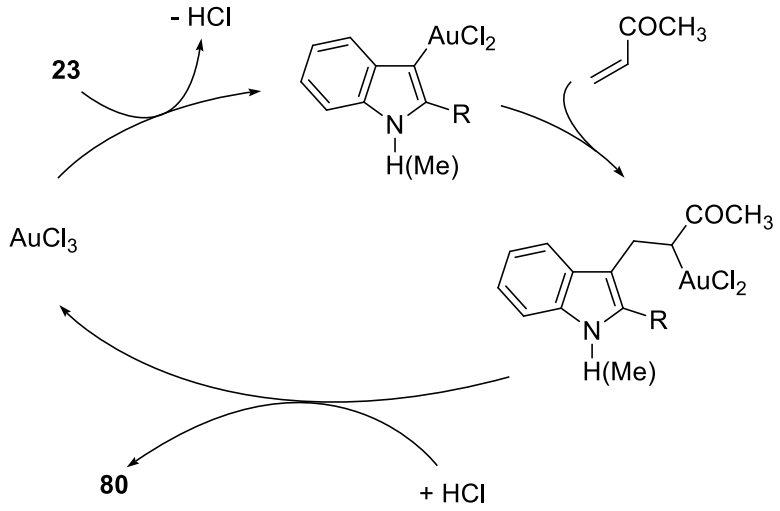
[117] F. Fringuelli, A. Taticchi, *Diels-Alder Reaction: Selected Pratical Methods*, John-Wiley&Sons, New York, **2002**.

[118] a) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382-2385; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285-2288; b) G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *Adv. Synth. Catal.* **2003**, *345*, 1247-1252; c)



Scheme 2.31

Nevertheless, under gold(I) catalysis, the Csp_2–H bond activation has been demonstrated to be consistent only for electron-deficient substrates.[119] Moreover, 3-benzofuranyl- and 3-indolyl-gold(I) derivatives have been isolated and characterized by Hashmi as stable intermediates of gold(I)-catalyzed hydroxylation and hydroamination reactions of *ortho*-alkynylphenols and anilines. However, they easily undergo deauration reactions and cannot be prepared from the corresponding benzofuran or indole derivatives and gold(I).[120] On the contrary, the oxophilic character of gold(I) species has been highlighted by several authors, in particular by Toste with regard to gold(I)-catalyzed Mannich reactions of azalactones[121] and by Youn with regard to the gold(I)-catalyzed intramolecular cyclizations of 2-alkenyl carbonyl compounds.[122] Thus, considering these works, we could reasonably disregard, a mechanism involving a Csp_2–H activation step under gold(I) catalysis, and because of the well-known σ-acidity of cationic gold(I) species, a Friedel–Crafts-type mechanism could more realistically explain the formation of the observed Micheal addition products.

A. Arcadi, G. Bianchi, M. Chiarini, G. D'Anniballe, F. Marinelli, *Synlett* **2004**, 944-950; d) Z. Li, Z. Shi, C. He, *J. Organomet. Chem.* **2005**, *690*, 5049-5054; e) V. Nair, N. Vidya, K. G. Abhilash, *Synthesis* **2006**, 3647-3653; f) M. Alfonsi, A. Arcadi, G. Bianchi, F. Marinelli, A. Nardini, *Eur. J. Org. Chem.* **2006**, 2393-2402; g) D. Aguilar, M. Contel, R. Navarro, E. P. Urriolabeitia, *Organometallics* **2007**, *26*, 4604-4611; h) D. Aguilar, M. Contel, R. Navarro, T. Soler, E. P. Urriolabeitia, *J. Organomet. Chem.* **2009**, *694*, 486-493.

[119]) T. de Haro, C. Nevado, *Synthesis* **2011**, 2530-2539; b) P. Lu, T. C. Boorman, A. M. Slawin, I. Larrosa, *J. Am. Chem. Soc.* **2010**, *132*, 5580-5581; c) S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 2742-2744; d) I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* **2010**, *132*, 8858-8859.

[120] A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 971-975.

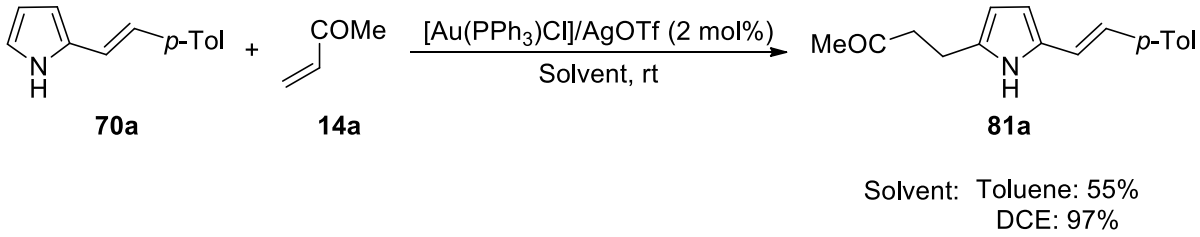
[121] A. D. Melhado, G. W. Amarante, Z. J. Wang, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 3517-3527

[122] a) A. R. Jagdale, S. W. Youn, *Eur. J. Org. Chem.* **2011**, 3904-3910; b) A. R. Jagdale, J. H. Park, S. W. Youn, *J. Org. Chem.* **2011**, *76*, 7204-7215.

2.3.4 Preliminary experiments using 2-vinylpyrroles

In the last part of our investigation, we got interested in testing the reactivity of 2-vinylpyrroles in gold-catalyzed cycloadditions with open-chain dienophiles. 2-Vinylpyrroles encompass two types of diene systems, namely, the cyclic diene and the internal-external cyclic diene and, as a consequence, two alternative mode of participation in Diels-Alder cycloadditions. Moreover, Michael additions are possibly competitive reaction pathways as well as [2+2] cycloadditions and polymerization reactions.[1c] Direct functionalization of pyrrole by Michael addition-type reactions has been achieved under $InCl_3$ catalysis whereas reactions between the exocyclic diene system and activated acyclic alkenes have been seldomly reported in the literature.[123]

We started our investigation using (*E*)-*N*-unsubstituted-2-(4-methylstyryl)pyrrole (**70a**) which was reacted with a slight excess of **14a** (1.2 equivalents) in the presence of [Au(PPh_3)Cl]/AgOTf (2 mol%) and, as expected, hydroarylated pyrrole **81a** was the main reaction product (Scheme 2.32).



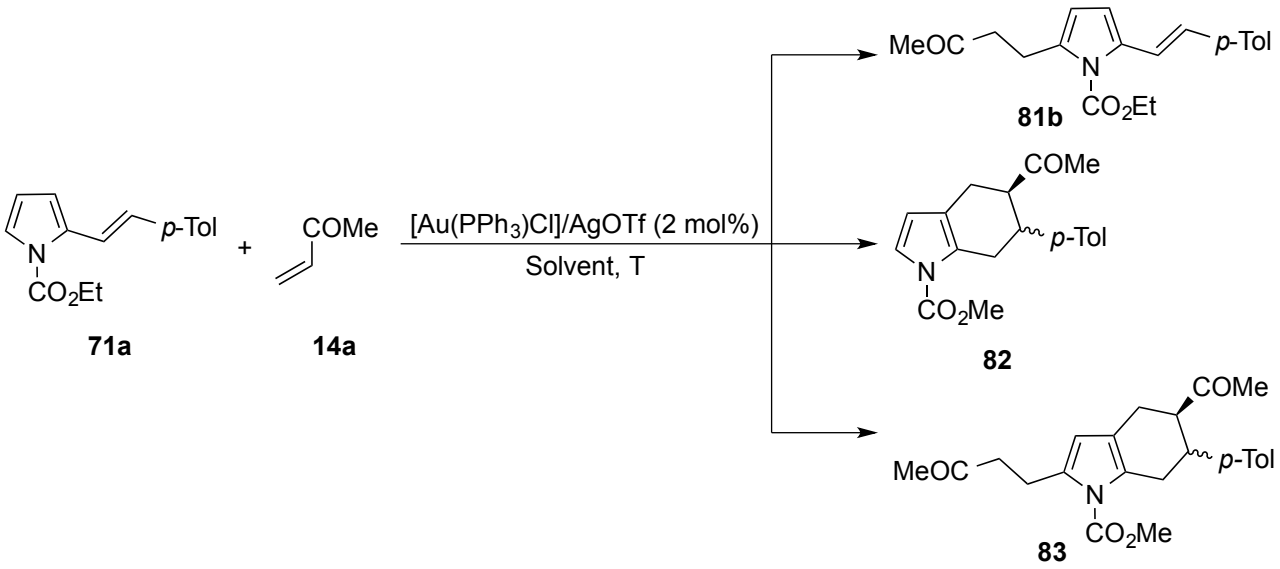
Scheme 2.32

Better yields were obtained in 1,2-dichloroethane at room temperature probably because of the increased solubility of **70a** in this solvent with respect to toluene. Any product arising from cycloaddition process was either isolated or detected in the crude reaction mixture.

As already observed in the cycloadditions of 2-vinylindoles, deactivation of the heterocyclic nucleus towards electrophilic substitutions can be achieved by adding an electronwithdrawing substituent at *N*-1. Therefore, we considered the behavior of pyrrole derivative bearing an alkoxycarbonyl substituent such as **71a** in the cationic gold(I)-catalyzed reaction with **14a**. The obtained results are summarized in Table 2.6.

[123] a) J. S. Yadav, S. Abraham, B. V. Subba Reddy, G. Sabitha *Tetrahedron Lett*. **2001**, *42*, 8063-8065; b) 2-Vinylpyrroles and activated open chain dienophiles: see ref. 1c, p. 372-374; c) 2-Vinylfurans and activated open chain dienophiles: see ref. 1c, p. 370-371.

Table 2.6: Reaction between 2-vinyl pyrrole 71a and 14a



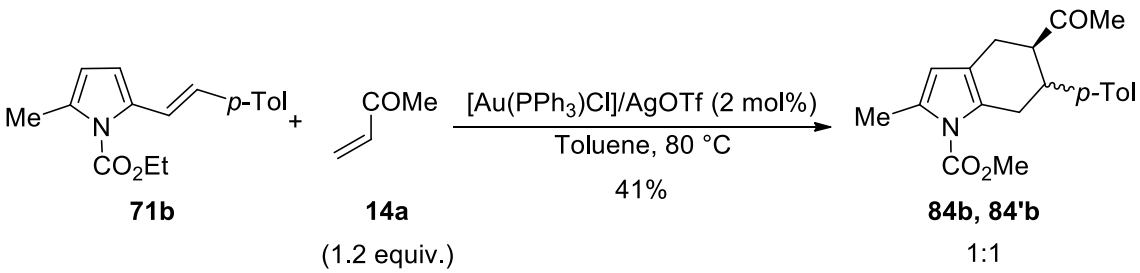
Entry	Equiv. of 14a	T, ¡C	Solvent	81b, %[a]	82, %[a]	83, %[a]
1	1.2	80	Toluene	10	18	24
2	5	80	Toluene	D	D	39
3	2.2	rt	Toluene	D	D	56
4	2.2	rt	DCE	D	22	26

Reaction conditions: to a mixture of [Au(PPh$_3$)Cl]/AgOTf in the appropriate solvent (4 mL), **71a** and **14a** were added and the mixture stirred at the stated temperature.
[a] Isolated yields.

Using a slight excess of methyl vinyl ketone **14a** in toluene at 80 °C, a mixture of products arising from Michael addition (**81b**), Diels-Alder cycloaddition (**82**) and from concomitant MA and DA processes (**83**) were obtained (entry 1). Diels-Alder adducts **82** and **83** were in this case formed as inseparable mixture of diasteroisomers. Thus, taking into account the formation of addition products in position 5 of the heterocyclic nucleus a flexible amount **14a** was used. A strong excess of **14a** gave rise to **83** as the only reaction product but only in modest yields and besides a mixture of unidentified side-products (entry 2). Better results were achieved by the use of 2.2 equivalents of **14a**, in toluene at room temperature. Under these conditions **83** was isolated in 56% yield (entry 3). The change of solvent to 1,2-dichloroethane was not beneficial to the reaction since gave rise to a mixture of **82** and **83** in poor yields (entry 4).

Next, we tested the reactivity of 5-methyl derivative **71b** in order to verify the possibility to avoid concomitant alkylation side-reactions. Thus, reaction between **71b** and 1.2 equivalents of **14a**, in toluene at 80 °C and in the presence of cationic gold(I) catalyst afforded a 1.1 mixture of separable

diasteroisomers **84'/84** in 41% yield (Scheme 2.33). The same transformation conducted at room temperature gave poorer yield of the product.



71b **14a** (1.2 equiv.) **84b, 84'b** 1:1

Scheme 2.33

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2.3.5 Spectroscopic characterization of tetrahydrocarbazole derivatives

The structures of all synthesized carbazole derivatives were assigned on the basis of analytical and spectral data. In particular, combined 1D-NMR (^{1}H, APT) and 2D-NMR (COSY, HETCOR) experiments allowed the complete assignment of proton and carbon chemical shifts and H-H coupling constants. Figure 2.9 shows the chemical shifts attributed to each hydrogen *via* 1D experiments, appropriate for subsequent spectroscopic investigations, for compounds **24a** and **24'a**. The spectra were performed using C_6D_6 as solvent at 300 and 500 MHz, respectively.

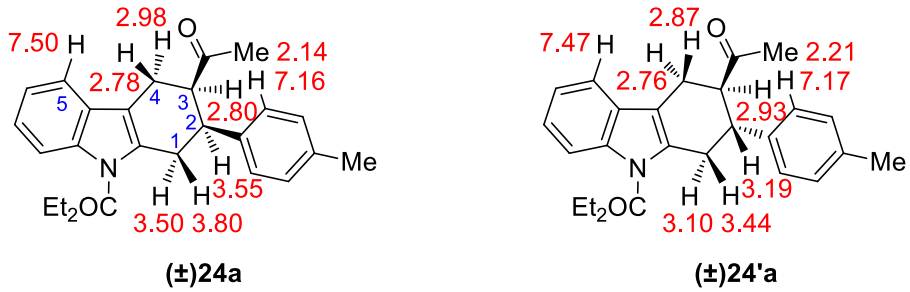


Figure 2.9

The regiochemistry and stereochemistry around C1–C4 moiety were assigned on the basis of spatial coupling interactions detected by 2D-NOESY experiments and by a computational investigation on both conceivable conformers ascribable to each isomer as exemplified in figure 2.10. Chemical shifts are represented in red colour while NOE interactions in blue.

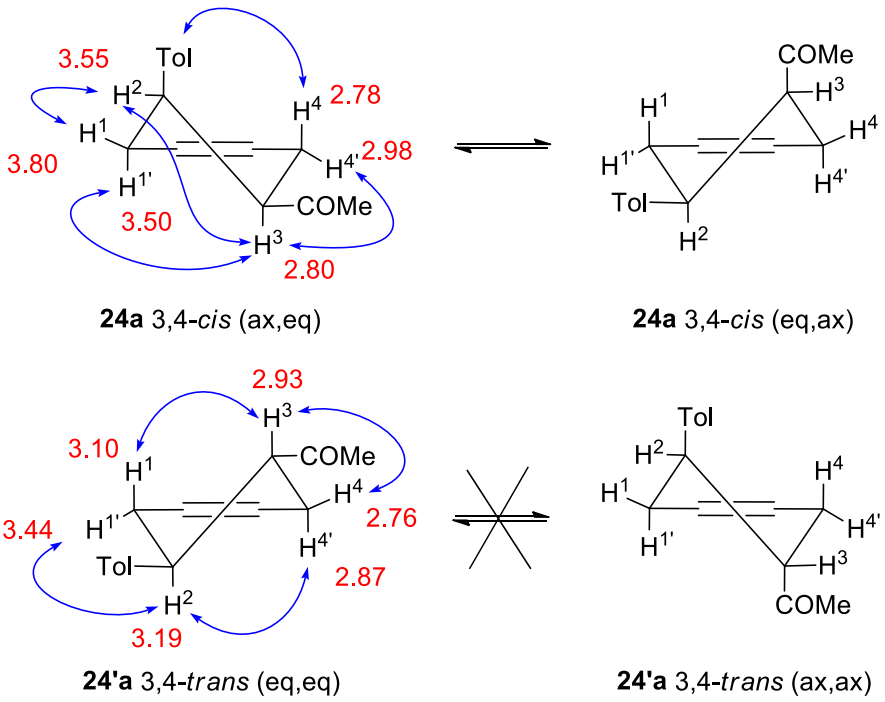
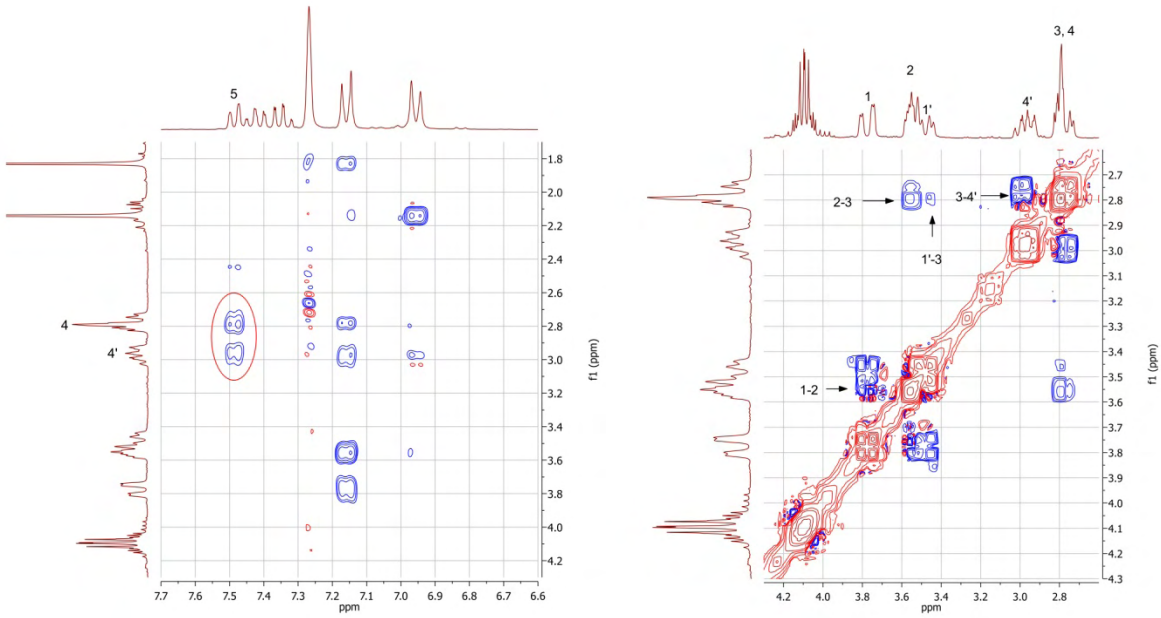


Figure 2.10

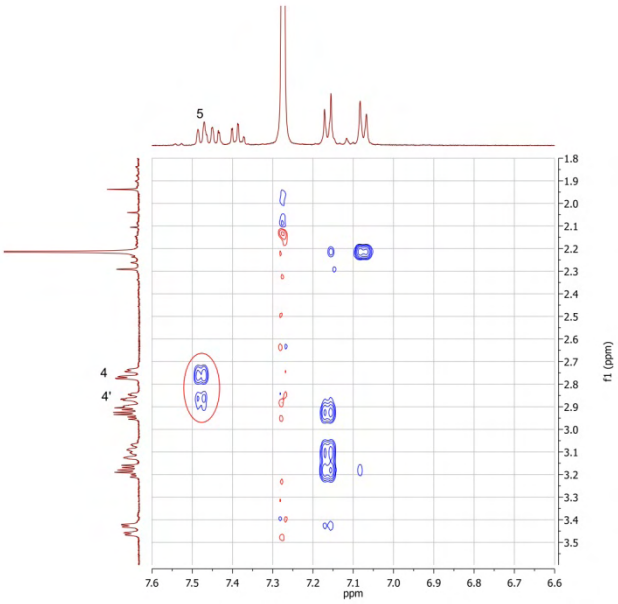
The regiochemistry of Diels-Alder adduct **24a** was usefully assigned on the basis of NOE interactions between H–5 and H4/H4' as shown in Figure 2.11, spectrum A. Furthermore it was possible to observe diagnostic NOE interactions between hydrogens 1-2, 2-3, 1'-3, 3-4', H*p*-tol-4 (Figure 2.11, spectrum B) which are in agreement with the proposed geometry.



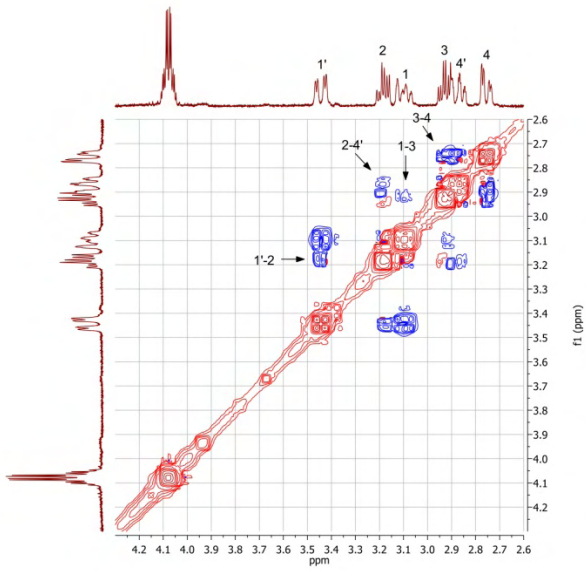
2D-NOESY, compound **24a**, spectrum A 2D-NOESY, compound **24a**, spectrum B

Figure 2.11

Similarly, in Figure 2.12 are illustrated NOE interactions between H–5 and the hydrogens at C–4 (spectrum A) as well as diagnostic NOE signals between 1-3, 1'-2, 2-4', 3-4 (spectrum B) for compound **24'a**.



2D-NOESY, compound **24'a**, spectrum A



2D-NOESY, compound **24'a**, spectrum B

Figure 2.12

Moreover, the four hypothetical structures **24a** (3,4 *cis* ax,eq), **24a** (3,4 *cis* eq,ax), **24'a** (3,4 *trans* eq,eq) and **24'a** (3,4 *trans* ax,ax) were subjected to a preliminary conformational analysis[10] at molecular mechanics level using the MM+ force field, (an implemented version of Allinger MM2[124] force field included in the Hyperchem® molecular modeling program[125]), specifically developed for small and middle sized organic molecules. The minima were re-optimized at ab-initio level using DFT (B3LYP/6-31G*). Ab-initio calculations were performed with Gaussian03® molecular modeling program[126] using default options. The character of minima of the optimized geometries were confirmed by the absence of imaginary frequencies. The results are reported in Table 2.7.

[124] N. L. Allinger, *J. Am. Chem. Soc*. **1977**, *99*, 8127-8134.
[125] Hypercube, 1115 NW 4th Street, Gainesville, FL 32601, USA; http://www.hyper.com.
[126] M. J. Frisch, G. W. Trucks, H. B. Schlegel, M. A. Robb, J. R.; Montgomery Jr., J. A.Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pom- elli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Foresman, J. B. Raghavachari, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. González, J. A. Pople, *Gaussian 03*, *Revision B.04*, Gaussian, Inc., Pittsburgh, PA, **2003**.

Table 2.7: Measured ^{1}H–^{1}H coupling constant and NOE interaction *versus* calculated ^{1}H–^{1}H coupling constant range (derived from dihedral angles) and interatomic distances

	24a exp. data	**24a 3,4-*cis* (ax, eq) calc. data**	**24a 3,4-*cis* (eq, ax) calc. data**	**24'a exp. data**	**24'a 3,4-*trans* (eq, eq) calc. data**	**24'a 3,4-*trans* (ax, ax) calc. data**
E rel[a] (Kcal/mol)	-	3.0	2.7	-	0.0	3.4
^3J H^1-H^2	4.0 Hz	82 ° (0.0-1.0 Hz)	167 ° (8.9-13.9 Hz)	10.5 Hz	164 ° (**8.6-13.4** Hz)	80 ° (0.0-1.0 Hz)
^3J H$^{1'}$-H^2	6.6 Hz	32 ° (5.5-9.5 Hz)	51 ° (3.0-5.5 Hz)	5.0 Hz	49 ° (**3.2-6.1** Hz)	35 ° (5.4-9.4 Hz)
^3J H^2-H^3	4.0 Hz	58 ° (2.0-4.0 Hz)	61 ° (1.8-3.8 Hz)	10.5 Hz	175 ° (**9.4-14.4** Hz)	65 ° (1.5-2.8 Hz)
^3J H^3-H^4	5.5 Hz	170 ° (9.1-14.2 Hz)	76 ° (0.2-1.3 Hz)	4.0 Hz	49 ° (**3.2-6.0** Hz)	42 ° (4.2-7.8 Hz)
^3J H^3-H$^{4'}$	7.3 Hz	55 ° (2.5-5.0 Hz)	39 ° (4.5-8.5 Hz)	10.5 Hz	165 ° (**8.7-13.6** Hz)	74 ° (0.2-1.3 Hz)
NOE H$^{1'}$-H^3	yes	**2.7** Å	4.3 Å	no	**3.8** Å	**3.9** Å
NOE H$^{1'}$-H^2	indet[b].	2.3 Å	2.4 Å	yes	**2.4** Å	**2.3** Å
NOE H^1-H^2	yes	**2.6** Å	3.1 Å	no	**3.1** Å	2.6 Å
NOE H^1-H^3	no	**3.8** Å	**4.0** Å	yes	**2.8** Å	4.3 Å
NOE H^2-H^3	yes	**2.4** Å	**2.4** Å	no	**3.0** Å	2.4 Å
NOE H^3-H^4	indet.[b]	3.1 Å	2.6 Å	yes	**2.4** Å	**2.4** Å
NOE[c] Tol-H^4	yes	**2.7** Å	5.2 Å (I)	no	**5.0** Å (I)	3.0 Å (P)
NOE[c] Tol-Me	yes	**2.8** Å	3.8 Å (P)	no	**3.1** Å (P)	**3.4** Å (**I**)

a: DFT (B3LYP/6-31G*) ZPE corrected.
b: This NOE was experimentally indeterminable because the proton signals have the same chemical shift.
c: Tolyl and Methyl groups have some degree of freedom; the reported interatomic distances are referred to the most vicinal proton of each group in the minima conformation. P (possible) and I (impossible) means that can exist at least one alternative conformation resulting from the simple rotation of Tolyl and/or Metyl groups around the C-C single bond, in which the interatomic distance drop-off under 3 Å.

The experimental results and structure assignments are in agreement with computational analyses. In particular, it is interesting to note that the energetic difference between the two conformers of **24a** is quite small (0.3 Kcal/mol), suggesting a rapid equilibrium between the two *cis* isomers. This hypothesis is confirmed by the observation that measured coupling constants of **24a** show average values with respect to the computed coupling constants ranges of conformers **24a** (3,4 *cis* ax,eq), and **24a** (3,4 *cis* eq,ax). Moreover, the measured NOE interactions and calculated interatomic distances, are also in agreement with this suggestion; in fact, although isomer **24a** (3,4 *cis* ax,eq) shows best fitting among measured and calculated data, the potential critical data (NOE H$^{2'}$-H^3, H^2-H^4, and H^4-H^5 *vs* calculated interatomic distances) cannot rule out the conformer **24a** (3,4 *cis* eq,ax).

On the contrary, the conformer **24'a** (3,4-*trans* eq,eq) is 3.4 kcal/mole more stable than **24'a** (3,4-*trans* ax,ax) and on the basis of Boltzman factors this energetic difference is consistent with a ratio between **24'a** (3,4-*trans* eq,eq) and **24'a** (3,4-*trans* ax,ax), at room temperature, totally shifted toward the former. This statement is supported by the experimental data that prove to be in agreement only with the calculated data for the conformer **24'a** (3,4-*trans* eq,eq).

2.4 Experimental data

2.4.1 Preface

2.4.1.1 General methods

All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere.

2.4.1.2 Reagents

This study was carried out using 2-vinylindoles **23a-h**, 2-vinylbenzofuran **68** and 2-vinylpyrroles **71a,b**, which were prepared following the procedures described in sections 2.4.2.1-2.4.2.4.
2-Trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester (**61**) and the corresponding precursors **58**-**60** were synthetize according to literature procedures.[8]
Enones **14a**-**d** and **56c** are commercially available products, while cyclopent-1-ene-1-carboxaldehyde (**56a**) and cyclohex-1-ene-1-carbaldehyde (**56b**) were prepared according to known procedure.[23,24] 2,5-Dihydrofuran-3-carbaldehyde **56d** is a known compound while **57f,g** were synthetized following the same experimental steps.[25]
$Mg(ClO_4)_2$, $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$, AgOTf, $AgSbF_6$, $Cu(OTf)_2$, $AuCl_3$, $[Au(PPh_3)Cl]$ and $PtCl_2$ were purchased from commercial suppliers and used as received, the rest of the gold catalysts were prepared according to literature procedures.[127]

2.4.1.3 Solvents

Solvents, used for reactions sensitive to oxygen and hydrolysis, were distilled and stored in a protected atmosphere of nitrogen, according to the following standard operations:
Dichloromethane: distilled on $CaCl_2$ and placed on 4Å sieves into a recycling appliance.
Toluene: distilled on metallic sodium and placed on 4Å sieves into a recycling appliance.
The other anhydrous solvents employed are available commercially.

[127] a) N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133-4136; b) L. Ricard, F. Gagosz, *Organometallics*, **2007**, *26*, 4704-4707.

2.4.1.4 Chromatography/purification of compounds

The chromatographic column separations were conducted by flash technique, using silica gel *Merck Grade 9385 60Å* (230-400 mesh).
For thin-layer chromatography (TLC), silica gel 60778-25EA *FLUKA* thin-layer plates were employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 365 nm), by basic solution of $KMnO_4$ (3.0 g $KMnO_4$, 20.0 g K_2CO_3 and 0.3 g KOH in 300 mL of H_2O) or with iodine vapours.

2.4.1.5 NMR spectroscopy

^{1}H NMR analyses were performed with a Varian-Gemini 200 or with Bruker 300, 500 Avance spectrometers at room temperature, respectively at 200, 300, or 500 MHz. The coupling constants (*J*) are expressed in Hertz (Hz), the chemical shifts (δ) in ppm. The multiplicities of the proton spectra were described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), dq (double quartet), dt (double triplet), td (triple doublet), ddd (double double doublet).

^{13}C NMR analyses were performed with the same instruments at 50.3, 75.45 and 125.75 MHz; APT sequences were used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms.

^{19}F NMR analyses were carried out with Bruker 300 Avance spectrometer at 282.4 MHz.

Two-dimensional NMR techniques (COSY, NOESY, HSQC, HMBC) were performed, where appropriate, to aid the correct assignment of structures.

2.4.1.6 IR spectroscopy

Infrared spectra were recorded with *Perkin Elmer FT-IR 16 PC* spectrometer, using discs of NaCl for liquid samples and KBr tablets for solid samples. The absorbance is expressed in wavenumbers (cm^{-1}) with values between 4000 and 400 cm^{-1}.

2.4.1.7 Mass spectrometry

Low resolution MS spectra were recorded with a Fisons MD 800 spectrometer with electron impact source and a Thermo-Finnigan LCQ-advantage AP electrospray/ion trap equipped instrument, using a syringe pump device to directly inject sample solutions. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown in brackets.

2.4.1.8 Melting points

The melting points of the solid products were measured in capillary tube with the device *Stuart Scientific SMP3*.

2.4.1.9 X-ray diffraction

Single crystals suitable for X-ray diffraction were obtained by slow evaporation of a DCM solution of **24f** and a THF solution of **79** at low temperature. Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

2.4.2 Experimental data

2.4.2.1 Representative procedure for the synthesis of 2-vinyl indoles **23a-f**

To a solution of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)-1*H*-indole-1-carboxylate (**61**) (1.00 g, 2.96 mmol) in anhydrous toluene (50 mL), $Pd(PPh_3)_4$ (0.17 g, 0.14 mmol) was added. The reaction was stirred for 30 minutes at room temperature, then a solution of (*E*)-(4-methylstyryl)boronic acid (**62a**) (0.72 g, 4.45 mmol) in EtOH-$NaHCO_3$ (sat.) (3:2, 50 mL) was added dropwise at room temperature. The mixture was then heated at reflux for 2 h, cooled at room temperature and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent evaporated under vacuum. The crude was purified by flash chromatography (SiO_2, hexane/ethyl acetate 50:1) to yield **23a** (0.87 g, 96%), as a light yellow solid (m.p.: 79.2-80.5 °C). **^{1}H-NMR** (200 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.3 Hz, 1H), 7.74 (d, *J* = 16.1 Hz, 1H), 7.54-7.16 (m, 7H), 7.06 (d, *J* = 16.1 Hz, 1H), 6.87 (s, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 152.6 (C), 140.1 (C), 138.2 (C), 137.1 (C), 134.8 (C), 131.4 (CH), 130.0 (C), 129.9 (2 x CH), 127.0 (2 x CH), 124.6 (CH), 123.6 (CH), 120.7 (CH), 119.7 (CH), 116.2 (CH), 107.2 (CH), 63.7 (CH_2), 21.7 (CH_3), 14.8 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3080, 2982-2953, 1736 cm^{-1}. **APCI(+)-MS**: *m/z* (%) = 306.0 (100) $[M + 1]^+$; $C_{20}H_{19}NO_2$ [305.37].

(*E*)-Ethyl 2-(4-fluorostyryl)-1*H*-indole-1-carboxylate (23b)

Representative procedure was followed using **61** (0.50 g, 1.48 mmol), $Pd(PPh_3)_4$ (85.5 mg, 0.07 mmol) and (*E*)-(4-fluorostyryl)boronic acid (**62b**) (0.37 g, 2.22 mmol). Purification by flash chromatography (SiO_2, hexane/ethyl acetate = 98:2) yielded **23b** (0.45 g, 98%), as a white solid (m.p.: 77.2-78.0 °C). **^{1}H-NMR** (200 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 16.3 Hz, 1H), 7.58-7.41 (m, 3H), 7.36-7.16 (m, 2H), 7.13-6.96 (m, 3H), 6.87 (s, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 162.7 (d, $^1J_{C\text{-}F}$ = 247 Hz, C), 152.4 (C), 139.6 (C), 136.9 (C), 133.6 (d, $^4J_{C\text{-}F}$ = 3.4 Hz, C), 129.9 (CH), 129.8 (C), 128.4 (d, $^3J_{C\text{-}F}$ = 8 Hz, 2 x CH), 124.6 (CH), 123.5 (CH), 120.6 (CH), 120.4 (d, $^5J_{C\text{-}F}$ = 2.2 Hz, 2 x CH), 116.1 (CH), 115.9 (d, $^2J_{C\text{-}F}$ = 21 Hz, CH), 107.2 (CH), 63.6 (CH_2), 14.6 (CH_3) ppm. **^{19}F NMR** (282.4 MHz, $CDCl_3$): -114.1 (m) ppm. **IR** (KBr): $\tilde{\nu}$ =3443, 1738, 1325, 1221, 1087 cm^{-1}. **ESI(+)-MS**: m/z (%) = 310.0 (100) $[M + 1]^+$; $C_{19}H_{16}FNO_2$ [309.33].

(*E*)-Ethyl 2-(4-methoxystyryl)-1*H*-indole-1-carboxylate (23c)

Representative procedure was followed using **61** (0.50 g, 1.48 mmol), $Pd(PPh_3)_4$ (85.5 mg, 0.07 mmol) and (*E*)-(4-methoxystyryl)boronic acid (**62c**) (0.39 g, 2.22 mmol). Purification by flash chromatography (SiO_2, hexane/ethyl acetate = 98:2) yielded **23c** (0.48 g, 98%) as a white solid (m.p.: 110.5-111.2 °C). **^{1}H-NMR** (200 MHz, $CDCl_3$): δ = 8.09 (m, 1H), 7.65 (d, *J* = 16.2 Hz, 1H), 7.54-7.40 (m, 3H), 7.29-7.21 (m, 2H), 7.03 (d, *J* = 16.2 Hz, 1H), 6.94-6.81 (m, 3H), 4.54 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.55 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 159.8 (C), 152.4 (C), 140.1 (C), 136.9 (C), 130.9 (CH), 130.3 (C), 129.9 (C), 128.2 (2 x CH), 124.3 (CH), 123.5 (CH), 120.5 (CH), 118.5 (CH), 116.0 (CH), 114.4 (2 x CH), 106.7 (CH), 63.5 (CH_2), 55.6 (CH_3), 14.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3444, 2910, 1735, 1602, 1509, 1300, 1248, 1120 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 322.0 (100) $[M + 1]^+$; $C_{20}H_{19}NO_3$ [321.37].

(*E*)-Ethyl 2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate (23d)

Representative procedure was followed using **61** (0.30 g, 0.89 mmol), $Pd(PPh_3)_4$ (51 mg, 0.05 mmol) and (*E*)-1-propenylboronic acid pinacol ester (**62d**) (0.22 g, 1.3 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate = 95:5) yielded **23d** (0.167 g, 82%) as yellow wax. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 8.07 (m, 1H), 7.48 (m, 1H), 7.23 (m, 2H), 6.97 (ddd, *J* = 15.6, 1.8, 0.9 Hz, 1H), 6.63 (s, 1H), 6.20 (dq, *J* = 15.6, 6.7 Hz, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 1.93 (m, 3H), 1.50 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$) δ = 152.3 (C), 140.1 (C), 136.6 (C), 129.8 (C), 128.9 (CH), 124.0 (CH), 123.4 (CH), 123.2 (CH), 120.3 (CH), 115.9 (CH), 106.6 (CH), 63.3 (CH_2), 18.9 (CH_3), 14.6 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3442.30, 2985.01, 2908.78, 1731.45, 1325.64, 1231.67, 741.96 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 230.2 (100) $[M + 1]^+$, $C_{14}H_{15}NO_2$ [229.27]: calcd.

(*E*)-Ethyl 2-(hex-1-en-1-yl)-1*H*-indole-1-carboxylate (23e)

Representative procedure was followed using **61** (0.30 g, 0.89 mmol), $Pd(PPh_3)_4$ (0.051 g, 0.05 mmol) and (*E*)-1-hexen-1-ylboronic acid (**62e**) (0.28 g, 1.3 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate = 95:5) yielded **23e** (0.241 g, 99%) as yellow oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 8.09 (m, 1H), 7.48 (m, 1H), 7.23 (m, 2H), 6.95 (dd, *J* = 15.7, 0.7 Hz, 1H), 6.64 (s, 1H), 6.39 (dt, *J* = 15.6, 6.9 Hz, 1H), 4.51 (q, *J* = 7.3 Hz, 2H), 2.25 (q, *J* = 6.6 Hz, 2H), 1.41 (m, 7H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$) δ = 152.3 (C), 140.2 (C), 136.7 (C), 134.4 (CH), 129.9 (C), 124.0 (CH), 123.2 (CH), 122.1 (CH), 120.3 (CH),

115.9 (CH), 106.6 (CH), 63.33 (CH_2), 32.90 (CH_2), 31.50 (CH_2), 22.50 (CH_2), 14.60 (CH_3), 14.20 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3053.42, 2958.11, 2872.55, 1738.45, 1608.55 cm^{-1}. **APCI(+)-MS**: *m/z* (%) = 272.3 (100) $[M + 1]^+$, $C_{17}H_{21}NO_2$ [271.35]: calcd.

(*E*)-Ethyl 2-(2-cyclohexylvinyl)-1*H*-indole-1-carboxylate (23f)

Representative procedure was followed using **61** (0.30 g, 0.89 mmol), $Pd(PPh_3)_4$ (0.051 g, 0.05 mmol) and (*E*)-(2-cyclohexylvinyl)boronic acid (**62f**) (0.21 g, 1.3 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate = 98:2) yielded **23f** (0.262 g, 99%) as light yellow oil. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ = 8.08 (m, 1H), 7.46 (m, 1H), 7.23 (m, 2H), 6.97 (d, *J* = 15.8 Hz, 1H), 6.64 (s, 1H), 6.16 (dd, *J* = 15.8, 6.7 Hz, 1H), 4.50 (q, *J* = 7.3 Hz, 2H), 2.16 (m, 1H), 1.7 - 1.92 (m, 4H), 1.50 (t, *J* = 7.3 Hz, 3H), 1.38-1.10 (m, 6H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 152.5 (C), 140.6 (C), 140.0 (CH), 136.8 (C), 130.0 (C), 124.2 (CH), 123.6 (CH), 120.4 (CH), 120.0 (CH), 116.1 (CH), 106.6 (CH), 63.8 (2 x CH_2), 41.3 (2 x CH_2), 33.1 (CH_2), 26.6 (CH_2), 26.4 (CH), 14.8 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3449, 2922, 1739, 1454, 1373, 1323, 1210, 1122, 1088 cm^{-1}. **MS** ESI(+): *m/z* (%) = 298 (100) $[M + 1]^+$, $C_{19}H_{23}NO_2$ [297.39]: calcd.

2.4.2.2 Synthesis of 2-vinylindoles **23g** and **23h**

(*E*)-2-(4-Methylstyryl)-1*H*-indole (23g)

To a solution of (*E*)-ethyl 2-(4-methylstyryl)-1*H*-indole-1-carboxylate (**23a**) (0.50 g, 1.64 mmol) in dry methanol (16 mL), K_2CO_3 (0.23 g, 1.64 mmol) was added and the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the crude taken up with water/ethyl acetate (15 mL each). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to yield **23g** (0.386 g, 99%) as a yellow solid (m.p.: 216.8-218.2 °C). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.45-7.03 (m, 8H), 6.88 (d, *J* = 16.5 Hz, 1H), 6.59 (s, 1H), 2.37 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 138.0 (C), 137.1 (C), 136.8 (C), 134.3 (C), 129.7 (2 x CH), 129.6 (C), 127.4 (CH), 126.5 (2 x CH), 123.0 (CH), 120.8 (CH), 120.4 (CH), 118.3 (CH), 110.8 (CH), 103.7 (CH), 21.5 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{17}H_{15}N]^+$ 233.1204, found 233.1206.

(*E*)-1-Methyl-2-(4-methylstyryl)-1*H*-indole (23h)

To a suspension of NaH (27.1 mg, 1.13 mmol-60% in mineral oil) in DMF (5 mL), (*E*)-2-(4-methylstyryl)-1*H*-indole (**23g**) (0.240 g, 1.03 mmol) was added at 0 °C and stirred for 30 minutes, then CH_3I (0.071 mL, 1.13 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 4 h. After that time water (5 mL) was added slowly and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with water (20 mL) and with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vaccum. After column chromatography (SiO_2, hexane/EtOAc 40:1), **23h** (0.238 g, 93%) was obtained as a yellow solid (m.p.: 147.2-148.9 °C). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.59 (m, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.34-7.02 (m, 7 H), 6.79 (s, 1H), 3.80 (s, 3H), 2.38 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 138.9 (C), 138.3 (C), 138.1 (C), 134.6 (C), 131.2 (CH), 129.7 (2 x CH), 128.3 (C), 126.6 (2 x CH), 121.8 (CH), 120.6 (CH), 120.1 (CH), 116.3 (CH), 109.3 (CH), 98.9 (CH), 30.1 (CH_3), 21.5 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{18}H_{17}N]^+$ 247.1361, found: 247.1366.

2.4.2.3 Synthesis of 5-methoxy-2-(4-methylstyryl)benzofuran (**68**)

To suspension of *p*-tolyltriphenylphosphonium bromide **67** (5.1 g, 11.4 mmol) in THF (40 mL) KHMDS (11.4 mL) was added and stirred at room temperature for 0.5 h. The reaction mixture was then cooled to -78 °C and 5-methoxy-benzofuran-2-carbaldehyde (**66**)[128] (2.0 g, 11.4 mmol) was injected after solubilization in the minimun amount of THF. The resulting mixture was allowed to warm slowly to room temperature and stirred for 24 h. Water (50 mL) and ether (50 mL) were added to the flask and the organic layer was separated from the aqueous layer. The aqueous layer was extracted once with ether (50 mL) and once with dichloromethane (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum and the crude was purified by column chromatography (SiO_2, hexane/ethyl acetate 99:1) to yield a separable mixture of ***Z*-68** (0.891 g, 30%, clear oil) and ***E*-68** (0.438 g, 15%, white solid; (m.p.: 145.7-147.0 °C). Spectroscopic Data for ***Z*-68: ^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.1 Hz, 3H), 7.30-7.14 (m, 2H), 6.95-6.80 (m, 2H), 6.69-6.52 (m, 2H), 6.42 (m, 1H), 3.82 (s, 3H), 2.39 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 156.2 (C), 155.1 (C), 149.5 (C), 137.9 (C), 134.2 (C), 131.8 (CH), 129.5 (C), 129.1 (2 x CH), 129.0 (2 x CH), 117.8 (CH), 113.6 (CH), 111.7 (CH), 106.3 (CH), 103.3 (CH), 55.1 (CH_3), 21.6 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{18}H_{16}O_2]^+$ 264.3184, found 2643185.

[128] J. Maillard, M. Langlois, V. V. Tri, C. Guillonneau, J. Legeai, M. Benharkate, M. Blozovski, *Eur. J. Med. Chem.* **1983**, *18*, 353-358.

Spectroscopic Data for ***E*-68:** **^{1}H NMR** (300 MHz, $CDCl_3$): 7.47-7.29 (m, 3H), 7.27-7.13 (m, 3H), 7.00 (m, 2H), 6.87 (m, 1H), 6.60 (s, 1H), 3.85 (s, 3H), 2.37 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): 156.4 (C), 156.3 (C), 150.1 (C), 138.4 (C), 134.1 (C), 130.4 (CH), 130.0 (C), 129.7 (2 x CH), 126.9 (2 x CH), 115.8 (CH), 113.3 (CH), 111.4 (CH), 105.1 (CH), 103.5 (CH), 56.1 (CH_3), 21.5 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{18}H_{16}O_2]^+$ 264.1150, found 264.1155.

2.4.2.4 Synthesis of 2-vinyl pyrroles **71a,b**

A flask was charged with tBuOK (0.184 g, 1.6 mmol) in anhydrous THF. The suspension was stirred for a few minutes and cooled to 0 °C before of adding 2-(4-methylstyryl)-1*H*-pyrrole (**70a**) (0.300 g, 1.6 mmol). The mixture was allowed to warm to room temperature and stirred for 2 hours. After that time, ethyl chloroformate (0.24 mL, 2.5 mmol) was added dropwise at 0 °C, the reaction mixture was stirred at room temperature for 24 hours and then washed with water (10 mL). The organic layer was removed and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The crude was purified by flash column chromatography to yield **71a** (0.22 g, 52%) as a brown solid (m.p.: 43.2-44.1 °C). **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 16.3 Hz, 1H), 7.42-7.23 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 16.3 Hz, 1H), 6.55 (m, 1H), 6.20 (m, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 151.2 (C), 137.5 (C), 135.1 (C), 135.0 (C), 129.5 (2 x CH), 128.7 (CH), 126.5 (2 x CH), 122.0 (CH), 118.6 (CH), 111.9 (CH), 110.8 (CH), 63.5 (CH_2), 21.4 (CH_3), 14.5 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3436, 1745, 1309, 1067 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 256 (80) $[M + 1]^+$, $C_{16}H_{17}NO_2$ [255.31]: calcd.

(*E*)-ethyl 2-methyl-5-(4-methylstyryl)-1*H*-pyrrole-1-carboxylate (71b)

Representative procedure was followed using *t*BuOK (0.170 g, 1.5 mmol), 2-methyl-5-(4-methylstyryl)-1*H*-pyrrole (**70b**) (0.30 g, 1.5 mmol) in anhydrous THF (8 mL) and ethyl chloroformate (0.22 mL, 2.3 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate = 98:2) yielded **71b** (0.210 g, 51%) as white solid (m.p.: 72.0-72.2 °C). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 16.4 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 16.3 Hz, 1H), 6.43 (d, *J* = 3.4 Hz, 1H), 5.97 (d, *J* = 3.4 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.46 (s, 3H), 2.36 (s, 3H), 1.44 (t, *J* = 7.6 Hz, 3H) ppm. **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ = 152.1 (C), 137.1 (C), 135.3 (C), 134.5 (C), 133.3 (C), 129.5 (2 x CH), 127.3 (2 x CH), 126.4 (CH), 119.8 (CH), 112.3 (CH), 109.9 (CH), 63.4 (CH_2), 21.4 (CH_3), 16.7 (CH_3), 14.5 (CH_3) ppm.

IR (KBr): $\tilde{\nu}$ = 3436.02, 2917.12, 2087.97, 1735.84, 1132.76, 1031.35 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 270.2 (100) $[M + 1]^+$; $C_{17}H_{19}NO_2$ [269.34]: calcd.

2.4.2.5 Synthesis of 1-(5-phenyl-2,5-dihydrofuran-3-yl)ethan-1-one (**56e**)

1-(5-phenyl-2,5-dihydrofuran-3-yl)ethanol (78)

To a solution of **56d** (0.72 g, 4.13 mmol) in anhydrous THF (23 mL) at 0° C, MeMgCl (1.38 mL, 3M in THF) is added dropwise. The mixture is stirred for 12 h at room temperature before of cooling to 0 °C and adding NH_4Cl sat. (10 mL). The aqueous layer is extracted with ethyl acetate (3 x 20 mL). Combined organic phases are washed with water (50 mL) and crine (50 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **78** as a yellow oil (0.52 g, 66%). **^{1}H-NMR** (200 MHz, $CDCl_3$): δ = 7.39-7.23 (m, 5H), 5.82 (m, 1H), 5.76 (m, 1H), 4.84 (m, 2H), 4.56 (m, 1H), 4.33 (s, 1H), 1.40 (dd, *J* = 6.2, 1.5 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 145.3 (C), 142.2 (C), 128.7 (2 x CH), 128.1 (CH), 126.5 (2 x CH), 123.7 (CH), 88.5 (CH), 75.2 (CH_2), 64.8 (CH), 22.8 (CH_3) ppm. **IR** (NaCl): $\tilde{\nu}$ = 3401, 3064, 3031, 2852, 1659 ,1455, 1176, 1058, 910, 859, 760, 700 cm^{-1}. **ESI(–)-MS**: *m/z* (%) = 189.1 (100) $[M - 1]^-$, $C_{12}H_{14}O_2$ (190.24).

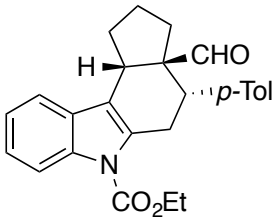
1-(5-phenyl-2,5-dihydrofuran-3-yl)ethan-1-one (56e)

To a solution of oxalyl chloride (0.20 g, 0.14 mmol) in anhydrous CH_2Cl_2 (2 mL) at -78 °C are added sequentially DMSO (0.25 g, 3.36 mmol), **78** (0.20 g, 1.05 mmol) and after 15 minutes triethylamine (0.68 g, 6.72 mmol). The mixture is stirred for 20 minutes at -78 °C and at room temperature for further 3 h. The reaction is then quenched with brine (5 mL) and extracted with ethyl acetate (3 x 5 mL). Combined organic phases are dried over Na_2SO_4, filtered and concentrated under vacuum. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **56e** (0.11 g, 58%) as a yellow oil. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ = 7.43-7.26 (m, 5H), 6.67 (m, 1H), 6.00 (m, 1H), 5.00 (m, 2H), 2.37 (s, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 194.7 (C), 141.4 (C), 140.5 (CH), 140.3 (C), 129.0 (CH), 128.6 (2 xCH), 126.5 (2 x CH), 89.0 (CH), 74.9 (CH_2), 27.4 (CH_3) ppm. **IR** (NaCl): $\tilde{\nu}$ = 2918, 2860, 1672, 1632, 1379, 1265, 1096-1045, 700 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 189.0 (100) $[M + 1]^+$, $C_{12}H_{12}O_2$ (188.22).

2.4.2.6 General procedure for $Sc(OTf)_3$ catalyzed [4+2] cycloaddition reactions.

To a nitrogen-flushed solution of $Sc(OTf)_3$ (13 mol%) in CH_2Cl_2 (1 mL) a solution of **23a** (1.00 mmol) and **56** (1.00 mmol) in CH_2Cl_2 (3 mL) was added via syringe and the mixture refluxed for 24 h. The solvent was then removed in vacuo and the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2 to 80:20) to yield progressively the corresponding diasteromeric tetrahydrocarbazoles **57'** and **57** (for yields see Table 2.2).

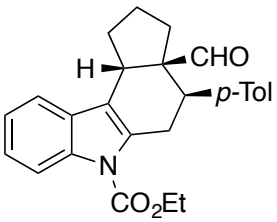
(±)-(3a,4-*trans*)-Ethyl 3a-formyl-4-(*p*-tolyl)-1,3,3a,4,5,10c-hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57'a)



Yellow oil.

^{1}H-NMR (300 MHz, C_6D_6): δ = 9.46 (s, 1H), 8.59 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.42 (m, 1H), 7.34 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.56 (m, 1H), 3.39 (m, 2H), 3.22 (m, 1H), 2.21 (s, 3H), 2.17 (m, 1H), 1.92 (m, 2H), 1.84 (m, 1H), 1.60 (m, 1H), 1.47 (m, 1H), 1.01 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6): δ = 203.8 (CH), 152.0 (C), 138.6 (C), 137.2 (C), 136.9 (C), 134.3 (C), 129.7 (2 x CH), 129.5 (C), 128.8 (2 x CH), 124.4 (CH), 123.3 (CH), 119.2 (CH), 118.7 (C), 116.4 (CH), 62.9 (CH_2), 62.4 (C), 44.4 (CH), 39.1 (CH), 30.1 (CH_2), 29.4 (CH_2), 24.5 (CH_2), 24.3 (CH_2), 21.1 (CH_3), 14.3 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3047, 2934, 2871, 2693, 1728, 1612, 1513, 1458 cm^{-1} **ESI(+)-MS**: *m/z* (%) = 402 (100) $[M + 1]^+$. $C_{26}H_{27}NO_3$ (401.50): calcd. for C 77.78, H 6.78, N 3.49; found C 77.75, H 6.69, N 3.43.

(±)-(3a,4-*cis*)-Ethyl 3a-formyl-4-(*p*-tolyl)-1,3,3a,4,5,10c-hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57a)

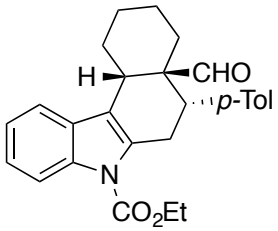


Yellow solid; m.p.: 130-131 °C.

^{1}H-NMR (300 MHz, C_6D_6): δ = 9.68 (s, 1H), 8.60 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.43 (m, 1H), 7.36 (m, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.81 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.53 (dd, *J* = 18.4, 5.5 Hz, 1H), 3.43 (m, 1H), 3.08 (dd, *J* = 9.6, 5.5 Hz, 1H), 2.35 (m, 1H), 2.18 (s, 3H), 1.96 (m, 1H), 1.75 (m, 3H), 1.58 (m, 1H), 0.97 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6): δ = 203.0 (CH), 152.0 (C), 139.1 (C), 137.2 (C), 136.8 (C), 134.5 (C), 129.9 (C), 129.6 (2 x CH), 129.5 (2 x CH), 124.5 (CH), 123.3 (CH), 119.0 (CH), 118.9 (C), 116.5 (CH), 62.8 (CH_2), 60.0 (C), 44.8 (CH), 39.3 (CH), 32.3 (CH_2), 31.0 (CH_2), 30.3

(CH_2), 24.0 (CH_2), 21.1 (CH_3), 14.2 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3052, 2942, 2871, 2699, 1735, 1615, 1514, 1475 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 402 (100) $[M + 1]^+$. $C_{26}H_{27}NO_3$ (401.50): calcd. for C 77.78, H 6.78, N 3.49; found C 77.62, H 6.83, N 3.47.

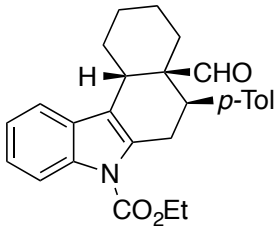
(±)-(3a,4-*trans*)-Ethyl 4a-formyl-5-(*p*-tolyl)-2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]carbazole-7(11c*H*)-carboxylate (57'b)



Yellow solid; m.p.: 161.8-162.5 °C.

^{1}H-NMR (300 MHz, C_6D_6): δ = 9.33 (s, 1H), 8.66 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.42 (m, 1H), 7.33 (m, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.74 (m, 1H), 3.48 (m, 1H), 3.16 (m, 1H), 3.01 (dd, *J* = 12.2, 5.2 Hz, 1H), 2.69 (m, 1H), 2.22 (s, 3H), 2.02 (m, 1H), 1.68 (m, 1H), 1.60 (m, 1H), 1.48 (m, 1H), 1.28 (m, 1H), 1.22 (m, 1H), 1.04 (m, 1H), 1.03 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6): δ = 206.9 (CH), 151.9 (C), 137.2 (C), 137.0 (C), 136.8 (C), 135.2 (C), 129.9 (C), 129.6 (2 x CH), 129.5 (2 x CH), 124.1 (CH), 123.2 (CH), 120.2 (CH), 117.2 (C), 116.4 (CH), 62.9 (CH_2), 52.8 (C), 47.9 (CH), 36.1 (CH), 29.6 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 22.1 (CH_2), 21.1 (CH_2), 21.1 (CH_3), 14.3 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3050, 2924, 2853, 2702, 1731, 1668, 1514 cm^{-1}. **ESI(+)-MS**: m/z (%) = 438 (100) $[M + Na]^+$.

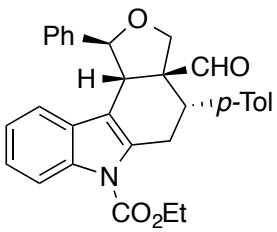
(±)-(3a,4-*cis*)-Ethyl 4a-formyl-5-(*p*-tolyl)-2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]carbazole-7(11c*H*)-carboxylate (57b)



Yellow solid; m.p.: 146.2-147 °C.

^{1}H NMR (300 MHz, C_2D_6CO): δ = 9.83 (s, 1H), 8.18 (m, 1H), 7.60 (m, 1H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.27 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.80 (dd, *J* = 10.4, 6.9 Hz, 1H), 3.57 (m, 2H), 3.17 (dd, *J* = 11.2, 4.3 Hz, 1H), 2.33 (s, 3H), 2.29 (m, 1H), 1.77 (m, 1H), 1.60-1.46 (m, 6H), 1.43 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_2D_6CO): δ = 205.6 (CH), 151.9 (C), 138.9 (C), 136.7 (C), 136.6 (C), 134.3 (C), 129.6 (2 x CH), 129.4 (2 x CH), 129.0 (C), 124.0 (CH), 123.0 (CH), 120.0 (C), 118.4 (CH), 115.9 (CH), 63.2 (CH_2), 51.0 (C), 41.0 (CH), 35.2 (CH), 31.8 (CH_2), 28.1 (CH_2), 27.0 (CH_2), 25.3 (CH_2), 20.7 (CH_2), 20.5 (CH_3), 14.1 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3020, 2929, 2855, 2733, 1734, 1709, 1609, 1513 cm^{-1}. **ESI(+)-MS**: m/z (%) = 438 (100) $[M + Na]^+$.

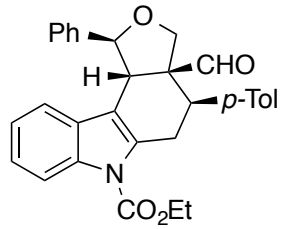
(±)-(3a,4-*trans*)-Ethyl 3a-formyl-1-phenyl-4-(*p*-tolyl)-3,3a,4,5-tetrahydro-1*H*-furo[3,4-*c*]carbazole-6(10c*H*)-carboxylate (57'd)



Yellow solid; m.p.: 167-168 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.62 (s, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.35 (m, 5H), 7.28 (m, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.07 (m, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 4.62 (d, *J* = 5.8 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 4.48 (d, *J* = 9.5 Hz, 1H), 4.31 (d, *J* = 9.5 Hz, 1H), 4.06 (d, *J* = 5.8 Hz, 1H), 3.61 (m, 1H), 3.48 (m, 2H), 2.38 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, $CDCl_3$): δ = 204.6 (CH), 152.3 (C), 140.6 (C), 137.8 (C), 136.7 (C), 136.5 (C), 134.4 (C), 130.0 (CH), 129.0 (2 x CH), 128.9 (2 x CH), 128.8 (C), 128.6 (CH), 128.1 (CH), 124.6 (CH), 123.2 (CH), 119.5 (CH), 117.5 (C), 115.9 (CH), 90.3 (CH), 69.1 (CH_2), 63.6 (CH_2), 62.8 (C), 47.3 (CH), 44.6 (CH), 29.1 (CH_2), 21.4 (CH_3), 14.8 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3027, 2925, 2854, 2747, 1733, 1722, 1612, 1512, 1492 cm^{-1}. *ESI(+)-MS*: *m/z* (%) = 502 (100) $[M + Na]^+$. $C_{31}H_{29}NO_4$ (479.31): calcd. for C 77.64, H 6.10, N 2.92; found C 77.56, H 5.97, N 3.07.

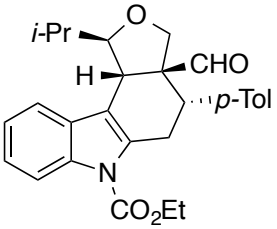
(±)-(3a,4-*cis*)-Ethyl 3a-formyl-1-phenyl-4-(*p*-tolyl)-3,3a,4,5-tetrahydro-1*H*-furo[3,4-*c*]carbazole-6(10c*H*)-carboxylate (57d)



Yellow solid; m.p.: 186-187 °C.

^{1}**H-NMR** (300 MHz, $CDCl_3$): δ = 9.85 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.42 (m, 5H), 7.23 (m, 5H), 6.85 (m, 1H), 5.98 (d, *J* = 7.8 Hz, 1H), 4.95 (d, *J* = 8.7 Hz, 1H), 4.52 (d, *J* = 9.7 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 4.15 (d, *J* = 9.7 Hz, 1H), 3.75 (d, *J* = 8.7 Hz, 1H), 3.72 (m, 3H), 2.36 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, $CDCl_3$): δ = 201.1 (CH), 152.2 (C), 140.9 (C), 137.7 (C), 137.2 (C), 136.4 (C), 135.6 (C), 129.9 (2 x CH), 129.7 (2 x CH), 129.1 (CH), 129.1 (CH), 128.9 (C) 127.9 (CH), 124.4 (CH), 122.9 (CH), 119.7 (CH), 113.7 (CH), 115.7 (C), 87.9 (CH), 72.0 (CH_2), 63.5 (CH_2), 60.9 (C), 49.6 (CH), 43.8 (CH), 31.1 (CH_2), 21.4 (CH_3), 14.8 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3031, 2918, 2852, 2737, 1733, 1513, 1492 cm^{-1}. **ESI(+)-MS:** *m/z* (%) = 502 (100) $[M + Na]^+$. $C_{31}H_{29}NO_4$ (479.31): calcd. for C 77.64, H 6.10, N 2.92; found C 77.49, H 6.03, N 3.12.

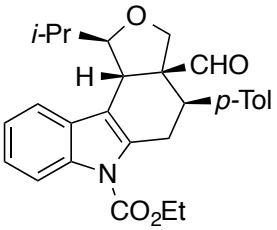
(±)-(3a,4-*trans*)-Ethyl 3a-formyl-1-isopropyl-4-(*p*-tolyl)-3,3a,4,5-tetrahydro-1*H*-furo[3,4-*c*]carbazole-6(10c*H*)-carboxylate (57'f)



Yellow solid; m.p.: 135-136 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.56 (s, 1H), 8.19 (m, 1H), 7.47 (m, 1H), 7.30 (m, 2H), 7.16-7.09 (m, 4H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.36 (d, *J* = 9.5 Hz, 1H), 4.20 (d, *J* = 9.5 Hz, 1H), 3.80 (d, *J* = 4.6 Hz, 1H), 3.60 (t, *J* = 4.6 Hz, 1H), 3.52-3.40 (m, 2H), 3.42 (m, 1H), 2.36 (s, 3H), 1.97 (m, 1H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, $CDCl_3$): = 205.4 (CH), 152.2 (C), 137.6 (C), 136.9 (C), 136.6 (C), 134.9 (C), 129.9 (2 x CH), 129.0 (C), 128.6 (2 x CH), 124.5 (CH), 123.4 (CH), 118.6 (CH), 117.6 (C), 116.2 (CH), 91.8 (CH), 67.7 (CH_2), 63.5 (CH_2), 62.4 (C), 44.7 (CH), 42.5 (CH), 31.8 (CH), 29.2 (CH_2), 21.4 (CH_3), 21.2 (CH_3), 16.9 (CH_3), 14.8 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3049, 2926, 2869, 2721, 1729, 1615, 1515 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 468 (100) $[M + Na]^+$.

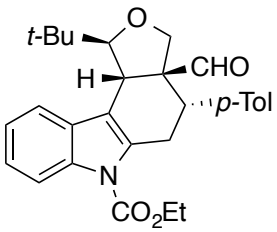
(±)-(3a,4-*cis*)-Ethyl 3a-formyl-1-isopropyl-4-(*p*-tolyl)-3,3a,4,5-tetrahydro-1*H*-furo[3,4-*c*]carbazole-6(10c*H*)-carboxylate (57f)



White solid; m.p.: 129-130 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.74 (s, 1H), 8.21 (m, 1H), 7.48 (m, 1H), 7.34 (m, 1H), 7.29 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.14 (d, *J* = 9.4 Hz, 1H), 4.03 (d, *J* = 9.4 Hz, 1H), 4.00 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.74-3.64 (m, 3H), 3.61-3.57 (m, 1H), 2.35 (s, 3H), 2.20 (m, 1H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, $CDCl_3$): δ = 201.4 (CH), 152.0 (C), 137.3 (C), 137.2 (C), 136.5 (C), 135.3 (C), 129.6 (2 x CH), 129.5 (2 x CH), 129.2 (C), 124.4 (CH), 123.2 (CH), 118.4 (CH), 116.1 (CH), 114.7 (C), 90.0 (CH), 71.4 (CH_2), 63.3 (CH_2), 60.7 (C), 42.7 (CH), 41.5 (CH), 31.2 (CH), 30.6 (CH_2), 21.7 (CH_3), 21.2 (CH_3), 15.2 (CH_3), 14.6 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3054, 2926, 2869, 2723, 1738, 1724, 1612, 1514 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 468 (30) $[M + 23]^+$.

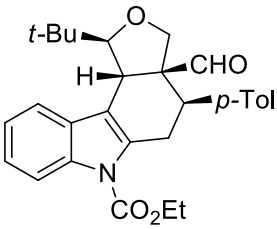
(±)-(3a,4-*trans*)-Ethyl 3a-formyl-1-*terz*-butyl-4-(*p*-tolyl)-3,3a,4,5-tetrahydro-1*H*-furo[3,4-*c*]carbazole-6(10c*H*)-carboxylate (57'g)



White solid; m.p.: 175-176 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.56 (s, 1H), 8.19 (m, 1H), 7.62 (m, 1H), 7.30 (m, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 4.51 (q, *J* = 7.1 Hz, 2H), 4.17 (s, 2H), 3.71 (d, *J* = 6.4 Hz, 1H), 3.62 (dd, *J* = 16.7, 4.2 Hz, 1H), 3.46 (d, *J* = 6.4 Hz, 1H), 3.46 (dd, *J* = 16.7, 12.4 Hz, 1H), 3.30 (dd, *J* = 12.4, 4.2 Hz, 1H), 2.35 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.01 (s, 9H) ppm. **^{13}C-NMR** (75.45 MHz, $CDCl_3$): δ = 203.7 (CH), 152.2 (C), 137.7 (C), 137.4 (C), 136.7 (C), 136.5 (C), 129.7 (2 x CH), 129.2 (C), 128.7 (2 x CH), 124.3 (CH), 123.1 (CH), 119.2 (CH), 118.0 (C), 116.1 (CH), 95.5 (CH), 67.9 (CH_2), 63.6 (C), 63.5 (CH_2), 45.6 (CH), 41.3 (CH), 34.7 (C), 28.9 (CH_2), 27.3 (CH_3), 21.4 (CH_3), 14.8 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3050, 2955, 2871, 2715, 1737, 1721, 1606, 1512 cm^{-1}. ESI(+)-MS: *m/z* (%) = 482 (100) $[M + Na]^+$.

(±)-(3a,4-*cis*)-Ethyl 3a-formyl-1-*terz*-butyl-4-(*p*-tolyl)-3,3a,4,5-tetrahydro-1*H*-furo[3,4-*c*]carbazole-6(10c*H*)-carboxylate (57g)



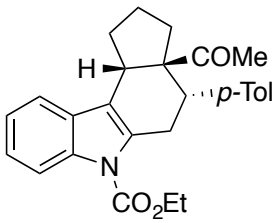
Yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.55 (s, 1H), 8.19 (m, 1H), 7.60 (m, 1H), 7.32 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.13 (d, *J* = 9.2 Hz, 1H), 3.99 (d, *J* = 9.2 Hz, 1H), 3.87 (d, *J* = 8.7 Hz, 1H), 3.75 (dd, *J* = 16.1, 5.9 Hz, 1H), 3.73 (dd, *J* = 7.9, 5.9 Hz, 1H), 3.71 (d, *J* = 8.7 Hz, 1H), 3.66 (dd, *J* = 16.1, 7.9 Hz, 1H), 2.34 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 9H) ppm. **^{13}C- NMR** (75.45 MHz, $CDCl_3$): δ = 200.3 (CH), 151.1 (C), 136.4 (C), 136.3 (C), 135.7 (C), 135.5 (C), 128.8 (2 x CH), 128.6 (2 x CH), 128.5 (C), 123.3 (CH), 121.9 (CH), 118.6 (CH), 115.1 (CH), 114.2 (C), 92.9 (CH), 69.4 (CH_2), 62.6 (C), 62.4 (CH_2), 60.8 (C), 41.5 (CH), 39.8 (CH), 30.7 (CH_2), 26.1 (CH_3), 20.3 (CH_3), 13.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3051, 2925, 2870, 2721, 1734, 1638, 1514 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 460 (100) $[M + 1]^+$.

2.4.2.7 General procedure for $BF_3{\cdot}OEt_2$ catalyzed [4+2] cycloaddition reactions

To a nitrogen-flushed solution of **23** (1.00 mmol) and **56** (1.5 mmol) in toluene (6 mL) was added $BF_3{\cdot}OEt_2$ (15 mol%) at -20 °C, unless otherwise stated, and the mixture was stirred at the same temperature for the stated time. The solvent was then removed in vacuo and the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2 to 80:20) to yield progressively the corresponding diasteromeric tetrahydrocarbazole **57'** and **57** (for yields see Table 2.2).

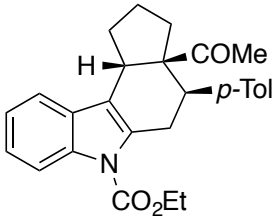
(±)-(3a,4-*trans*)-Ethyl 3a-acetyl-4-(*p*-tolyl)-1,3,3a,4,5,10c-hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57'c)



White solid; m.p.. 142-143 °C.

^{1}H-NMR (300 MHz, C_6D_6): δ = 8.63 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.45 (m, 1H), 7.37 (m, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.74 (d, *J* = 7.0 Hz, 1H), 3.37 (m, 3H), 2.54 (m, 1H), 2.20 (s, 3H), 2.09 (m, 1H), 1.90 (m, 2H), 1.82 (s, 3H), 1.72 (m, 1H), 1.53 (m, 1H), 1.00 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6): δ = 210.1 (C), 151.7 (C), 139.4 (C), 136.9 (C), 136.4 (C), 133.8 (C), 129.4 (2 x CH), 129.3 (C), 128.2 (CH), 124.1 (CH), 122.9 (CH), 119.2 (C), 119.0 (CH), 116.1 (CH), 65.5 (C), 62.5 (CH_2), 46.0 (CH), 41.8 (CH), 30.6 (CH_2), 29.1 (CH_2), 26.0 (CH_3), 25.1 (CH_2), 23.3 (CH_2), 20.8 (CH_3), 14.0 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3033, 2915, 1740, 1701, 1634, 1612, 1514 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 416 (100) $[M + 1]^+$.

(±)-(3a,4-*cis*)-Ethyl 3a-acetyl-4-(*p*-tolyl)-1,3,3a,4,5,10c- hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57c)

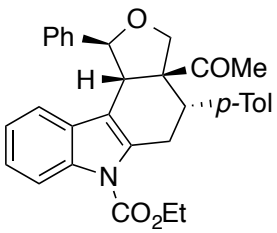


White solid, m.p.: 185-186 °C.

^{1}H-NMR (300 MHz, C_6D_6): δ = 8.53 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.37 (m, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.91 (d, *J* = 7.8 Hz, 2H), 4.08 (m, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.77 (dd, *J* = 18.2, 5.8 Hz, 1H), 3.56 (dd, *J* = 18.2, 5.8 Hz, 1H), 3.25 (t, *J* = 5.8 Hz, 1H), 2.42 (m, 1H), 2.10 (s, 3H), 1.98-1.81 (m, 2H), 1.86 (s, 3H), 1.45-1.70 (m, 3H), 0.97 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C- NMR** (75.45 MHz, C_6D_6): δ = 208.8 (C), 152.0 (C), 140.1 (C), 137.0 (C), 136.3 (C), 133.3 (C), 129.5 (C), 129.3 (2 x CH), 128.7 (2 x CH), 124.0 (CH), 123.0 (CH), 120.3 (C), 118.8 (CH), 116.2 (CH), 62.4

(CH_2), 62.3 (C), 45.5 (CH), 37.7 (CH), 34.6 (CH_2), 32.1 (CH_2), 30.8 (CH_2), 26.6 (CH_3), 23.6 (CH_2), 20.7 (CH_3), 13.9 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3045, 2919, 1731, 1697, 1616, 1513 cm^{-1}. ESI(+)-MS: *m/z* (%) = 416 (100) $[M + 1]^+$.

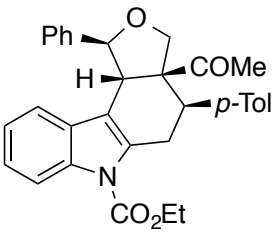
(±)-(3a,4-*trans*)-Ethyl 3a-acetyl-1-phenyl-4-(*p*-tolyl)-3,3a,4,5-tetrahydro-1*H*-furo[3,4-*c*]carbazole-6(10c*H*)-carboxylate (57'e)



Yellow solid, m.p.: 182-183 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.1 Hz, 1H), 7.33 (m, 5H), 7.10 (m, 6H), 6.83 (d, *J* = 7.7 Hz, 1H), 4.61 (m, 2H), 4.48 (q, *J* = 7.0 Hz, 2H), 4.21 (d, *J* = 9.9 Hz, 1H), 4.11 (d, *J* = 5.1 Hz, 1H), 3.45 (m, 3H), 2.35 (s, 3H), 1.92 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 212.6 (C), 152.1 (C), 140.8 (C), 137.5 (C), 137.4 (C), 136.4 (C), 134.0 (C), 129.8 (2 x CH), 128.8 (2 x CH), 128.8 (C), 128.6 (CH), 128.2 (2 x CH), 127.7 (2 x CH), 124.3 (CH), 123.0 (CH), 119.3 (CH), 118.0 (C), 115.8 (CH), 89.3 (CH), 69.3 (CH_2), 65.3 (CH_2), 63.3 (C), 49.2 (CH), 46.3 (CH), 29.2 (CH_2), 27.7 (CH_3), 21.2 (CH_3), 14.6 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3023, 2925, 1723, 1701, 1515 cm^{-1}. **ESI(+)-MS:** *m/z* (%) = 494 (100) $[M + 1]^+$. $C_{32}H_{31}NO_4$ (493.59): calcd. for C 77.87, H 6.33, N 2.84; found C 77.93, H 6.42, N 2.76.

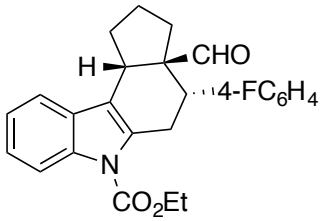
(±)-(3a,4-*cis*)-Ethyl 3a-acetyl-1-phenyl-4-(*p*-tolyl)-3,3a,4,5-tetrahydro-1*H*-furo[3,4-*c*]carbazole-6(10c*H*)-carboxylate (57e)



Yellow solid; m.p.: 209-210 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.4 Hz, 1H), 7.43 (m, 5H), 7.14 (m, 5H), 6.88 (m, 1H), 6.19 (d, *J* = 7.7 Hz, 1H), 4.86 (d, *J* = 8.1 Hz, 1H), 4.53 (d, *J* = 9.5 Hz, 1H), 4.46 (q, *J* = 7.3 Hz, 2H), 4.25 (d, *J* = 9.5 Hz, 1H), 3.96 (d, *J* = 8.1 Hz, 1H), 3.63 (m, 3H), 2.32 (s, 3H), 2.04 (s, 3H), 1.45 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 208.0 (C), 152.1 (C), 141.3 (C), 137.7 (C), 137.3 (C), 136.4 (C), 134.8 (C), 129.5 (2 x CH), 129.3 (2 x CH), 128.9 (CH), 128.8 (2 x CH), 128.5 (C) 128.0 (2 x CH), 124.1 (CH), 122.7 (CH), 119.5 (CH), 115.6 (CH), 115.5 (C), 88.8 (CH), 72.0 (CH_2), 63.3 (CH_2), 63.0 (C), 48.6 (CH), 44.3 (CH), 31.2 (CH_2), 28.9 (CH_3), 21.2 (CH_3), 14.6 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3036, 2925, 2872, 1724, 1615, 1514 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 494 (100) $[M + 1]^+$; $C_{32}H_{31}NO_4$ (493.59): calcd. for C 77.87, H 6.33, N 2.84; found C 77.84, H 6.35, N 2.72.

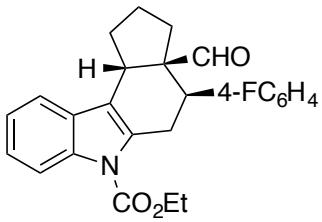
(±)-(3a,4-*trans*)-Ethyl 4-(4-fluorophenyl)-3a-formyl-1,3,3a,4,5,10c-hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57'h)



White solid; m.p. 139-142 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 9.49 (s, 1H), 8.15 (m, 1H), 7.49 (m, 1H), 7.36-7.19 (m, 4H), 7.04 (m, 2H), 4.47 (q, *J* = 7.3 Hz, 2H), 3.67 (m, 1H), 3.53-3.28 (m, 3H), 2.15-1.88 (m, 4H), 1.72-1.53 (m, 2H), 1.46 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 205.0 (CH), 162.2 (d, $J_{C\text{-}F}$ = 246 Hz, C), 152.1 (C), 136.7 (d, $J_{C\text{-}F}$ = 3 Hz, C), 136.5 (C), 133.9 (C), 130.1 (d, $J_{C\text{-}F}$ = 8 Hz, 2 x CH), 128.8 (C), 124.3 (CH), 123.1 (CH), 118.9 (CH), 118.5 (C), 115.9 (CH), 115.7 (d, $J_{C\text{-}F}$ = 22 Hz, 2 x CH), 63.3 (C), 62.4 (CH_2), 44.1 (CH), 39.1 (CH), 29.8 (CH_2), 29.2 (CH_2), 24.3 (CH_2), 24.0 (CH_2), 14.6 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3045, 2963, 2865, 2703, 1722, 1607, 1510 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 406 (100) $[M + 1]^+$; $C_{25}H_{24}FNO_3$ (405.46): calcd. for C 74.06, H 5.97, N 3.45; found C 73.92, H 5.95, N 3.48.

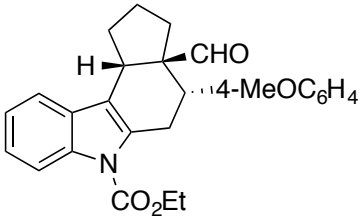
(±)-(3a,4-*cis*)-Ethyl 4-(4-fluorophenyl)-3a-formyl-1,3,3a,4,5,10c-hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57h)



Yellow solid; m.p.: 97-98 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 9.65 (s, 1H), 8.15 (m, 1H), 7.50 (m, 1H), 7.36-7.16 (m, 4H), 6.98 (m, 2H), 4.48 (q, *J* = 7.0 Hz, 2H), 3.51 (m, 3H), 3.30 (dd, *J* = 8.0, 5.8 Hz, 1H) 2.56-1.53 (m, 6H), 1.45 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 204.0 (CH), 162.1 (d, $J_{C\text{-}F}$ = 246 Hz, C), 152.2 (C), 137.3 (d, $J_{C\text{-}F}$ = 3 Hz, C), 136.5 (C), 133.9 (C), 130.7 (d, $J_{C\text{-}F}$ = 8 Hz, 2 x CH), 129.2 (C), 124.3 (CH), 123.1 (CH), 118.7 (CH), 118.6 (C), 116.0 (CH), 115.6 (d, $J_{C\text{-}F}$ = 21 Hz, 2 x CH), 63.2 (C), 60.1 (CH_2), 44.0 (CH), 38.5 (CH), 32.1 (CH_2), 31.1 (CH_2), 30.5 (CH_2), 23.8 (CH_2), 14.6 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3043, 2923, 2853, 1735, 1618, 1509 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 406 (100) $[M + 1]^+$. $C_{25}H_{24}FNO_3$ (405.46): calcd. for C 74.06, H 5.97, N 3.45; found C 73.96, H 5.92, N 3.55.

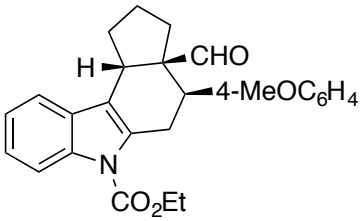
(±)-(3a,4-*trans*)-Ethyl 3a-formyl-4-(4-methoxyphenyl)-1,3,3a,4,5,10c-hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57'i)



Yellow solid, m.p.: 129-131 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 9.49 (s, 1H), 8.16 (m, 1H), 7.49 (m, 1H), 7.35-7.16 (m, 4H), 6.84 (d, *J* = 8.9 Hz, 2H), 4.46 (q, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 3.66 (m, 1H), 3.49-3.29 (m, 3H), 2.08 (m, 1H), 2.00-1.80 (m, 3H), 1.70-1.52 (m, 2H), 1.45 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 204.3 (CH), 158.9 (C), 152.1 (C), 136.6 (C), 134.1 (C), 133.6 (C), 130.2 (2 x CH), 129.3 (C), 124.1 (CH), 123.0 (CH), 118.8 (C), 118.7 (CH), 115.9 (CH), 114.2 (2 x CH), 63.1 (C), 60.1 (CH_2), 55.4 (CH_3), 44.1 (CH), 38.5 (CH), 32.1 (CH_2), 31.1 (CH_2), 30.6 (CH_2), 23.7 (CH_2), 14.6 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3044, 2959, 2870, 2718, 1730, 1611, 1513 cm^{-1}. ESI(+)-MS: *m/z* (%) = 418 (100) $[M + 1]^+$.

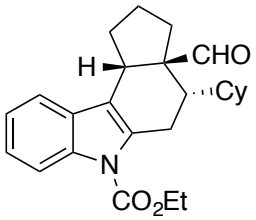
(±)-(3a,4-*cis*)-Ethyl 3a-formyl-4-(4-methoxyphenyl)-1,3,3a,4,5,10c-hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57i)



Yellow solid; m.p.: 116-117 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 9.69 (s, 1H), 8.16 (m, 1H), 7.50 (m, 1H), 7.34-7.11 (m, 4H), 6.82 (m, 2H), 4.45 (q, *J* = 7.3 Hz, 2H), 3.77 (s, 3H), 3.45 (m, 3H), 3.27 (m, 1H), 2.45 (m, 1H), 2.17-1.70 (m, 5H), 1.47 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 205.4 (CH), 158.9 (C), 152.1 (C), 136.5 (C), 134.2 (C), 132.9 (C), 129.6 (2 x CH), 128.9 (C), 124.2 (CH), 123.0 (CH), 118.9 (CH), 118.4 (C), 115.9 (CH), 114.2 (2 x CH), 63.2 (C), 62.5 (CH_2), 55.5 (CH_3), 44.1 (CH), 39.0 (CH), 29.8 (CH_2), 29.2 (CH_2), 24.3 (CH_2), 24.0 (CH_2), 14.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3037, 2961, 2832, 2694, 1738, 1611, 1513 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 418 (100) $[M + 1]^+$.

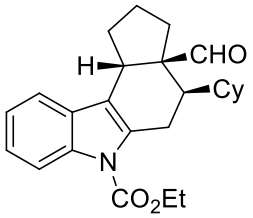
(±)-(3a,4-*trans*)-Ethyl 4-cyclohexyl-3a-formyl-1,3,3a,4,5,10c-hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57'j)



Yellow solid; m.p.: 81-82 °C.

^{1}H-NMR (300 MHz, C_6D_6): δ = 9.54 (s, 1H), 8.51 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.40 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.32 (dt, *J* = 7.3, 1.1 Hz, 1H), 4.16 (m, 2 H), 3.39 (ddd, *J* = 17.9, 4.8, 1.2 Hz, 1H), 3.22 (dd, *J* = 4.8, 2.6, 1H), 2.82 (ddd, *J* = 17.9, 12.0, 2.6 Hz, 1H), 2.41 (m, 1H), 1.99 (dt, *J* = 12.0, 4.8 Hz, 1H), 1.92 (m, 1 H), 1.86-1.63 (m, 6H), 1.58-1.33 (m, 5H), 1.30-1.17 (m, 2H), 1.09 (m, 2H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C-NMR (75.45 MHz, C_6D_6): δ = 203.6 (CH), 152.0 (C), 137.1 (C), 135.5 (C), 129.4 (C), 124.2 (CH), 123.2 (CH), 119.1 (CH), 117.6 (C), 116.4 (CH), 62.8 (CH_2), 62.4 (C), 43.1 (CH), 41.0 (CH), 39.8 (CH), 33.7 (CH_2), 30.0 (CH_2), 28.9 (CH_2), 27.4 (CH_2), 27.1 (CH_2), 26.7 (CH_2), 24.8 (CH_2), 23.8 (CH_2), 23.8 (CH_2), 14.3 (CH_3) ppm. IR (NaCl): $\tilde{\nu}$ = 3051, 2920, 2855, 2695, 1732, 1616 cm^{-1}. ESI(+)-MS: *m*/*z* (%) = 394 (90) $[M + 1]^+$.

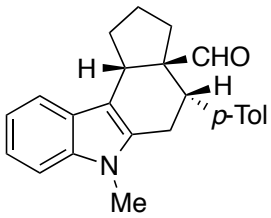
(±)-(3a,4-*cis*)-Ethyl 4-cyclohexyl-3a-formyl-1,3,3a,4,5,10c- hexahydrocyclopenta[*c*]carbazole-6(2*H*)-carboxylate (57j)



Yellow solid; m.p.: 116-119 °C.

^{1}H-NMR (200 MHz, C_6D_6): δ = 9.51 (s, 1H), 8.37 (d, *J* = 7.3 Hz, 1H), 7.35-7.11 (m, 3H), 3.99 (q, *J* = 6.9 Hz, 2H), 3.17 (m, 2H), 2.16 (m, 2H), 1.76-1.03 (m, 17H), 0.92 (t, *J* = 6.9 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6): δ = 202.9 (CH), 151.8 (C), 136.8 (C), 134.8 (C), 129.6 (C), 123.9 (CH), 123.0 (CH), 118.8 (CH), 118.4 (C), 116.1 (CH), 62.4 (CH_2), 59.7 (C), 44.0 (CH), 39.2 (CH), 39.0 (CH), 34.4 (CH_2), 32.2 (CH_2), 31.0 (CH_2), 29.5 (CH_2), 27.3 (CH_2), 26.9 (CH_2), 26.4 (CH_2), 24.1 (CH_2), 23.9 (CH_2), 14.0 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3049, 2923, 2852, 1732, 1702, 1620 cm^{-1}. **ESI(+)-MS**: *m*/*z* (%) = 394 (100) $[M + 1]^+$.

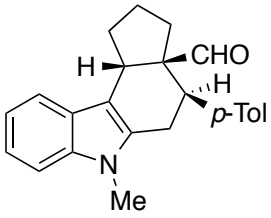
(±)-(3a,4-*trans*)-6-Methyl-4-(*p*-tolyl)-1,2,3,3a,4,5,6,10c-octahydrocyclopenta[*c*]carbazole-3a-carbaldehyde (57'k)



Yellow solid; m.p.: 161-163 °C.

^{1}H-NMR (200 MHz, C_6D_6): δ = 9.39 (s, 1H), 7.59 (m, 1H), 7.30-7.17 (m, 2H), 7.16-7.03 (m, 5H), 3.50 (m, 1H), 3.15 (m, 1H), 2.85 (s, 3H), 2.65 (ddd, *J* = 16.1, 11.7, 2.2 Hz, 1H), 2.38 (ddd, *J* = 16.1, 5.1, 1.5 Hz, 1H), 2.19-1.96 (m, 2H), 2.08 (s, 3H), 1.86-1.28 (m, 4H) ppm. **^{13}C-NMR** (50.3 MHz, C_6D_6): δ = 203.3 (CH), 138.7 (C), 137.9 (C), 136.6 (C), 133.9 (C), 129.4 (2 x CH), 128.5 (C), 128.2 (CH), 121.2 (CH), 119.2 (2 x CH), 119.0 (CH), 110.1 (C), 118.9 (CH), 62.9 (C), 43.6 (CH), 39.7 (CH), 30.1 (CH_2), 28.3 (CH_3), 25.6 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 20.8 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3023, 2920, 2868, 2701, 1723, 1614, 1513 cm^{-1}. ESI(+)-MS: m/z (%) = 344 (100) $[M + 1]^+$.

(±)-(3a,4-*cis*)-6-Methyl-4-(*p*-tolyl)-1,2,3,3a,4,5,6,10c-octahydrocyclopenta[*c*]carbazole-3a-carbaldehyde (57k)



White solid; m.p.: 181-183 °C.

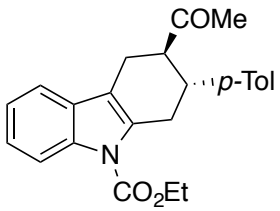
^{1}H-NMR (300 MHz, C_6D_6): δ = 9.61 (s, 1H), 7.73 (m, 1H), 7.38 (m, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.19 (dd, *J* = 6.1, 1.8 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 2H), 3.53 (t, *J* = 7.8 Hz, 1H), 3.31 (dd, *J* = 16.2, 9.6 Hz, 1H), 3.14 (dd, *J* = 9.6, 5.3 Hz, 1H), 2.96 (s, 3H), 2.72 (dd, *J* = 16.2, 5.3 Hz, 1H), 2.39 (m, 1H), 2.22 (s, 3 H), 1.85 (m, 1H), 1.79-1.58 (m, 4H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6): δ = 203.0 (CH), 139.5 (C), 138.2 (C), 136.8 (C), 134.6 (C), 129.7 (2 x CH), 129.6 (2 x CH), 127.7 (C), 121.5 (CH), 119.5 (CH), 119.1 (CH), 108.8 (C), 109.3 (CH), 60.7 (C), 44.9 (CH), 40.2 (CH), 33.1 (CH_2), 31.2 (CH_2), 28.7 (CH_3), 27.6 (CH_2), 24.4 (CH_2), 21.1 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3046, 2926, 2820, 2721, 1706, 1616, 1513 cm^{-1}. **ESI(+)-MS**: m/z (%) = 344 (100) $[M + 1]^+$.

2.4.2.8 General procedure for gold-catalyzed [4+2] cycloaddition reactions

To a solution of [Au(PPh_3)Cl] (2.0 mol%) and AgOTf (2.0 mol%) or $AuCl_3$ (2.0 mol%) in the indicated solvent (1 mL/0.2 mmol), dienes **23, 24a-f, 68, 70a, 71a,b** (1.0 equiv.) and dienophiles **14a-d, 56a** (1.2 or 2.4 equiv.) were added, and the solution was stirred at the appropriate temperature for the stated time The solvent was then removed *in vacuo* and the residue purified by flash column chromatography (SiO_2, hexane/ethyl acetate 98:2 to 80:20) to yield the corresponding

compounds **24, 24', 24'', 79, 79', 80, 81, 82, 83**. (See Tables 2.4, 2.5, 2.6 and Schemes 2.28, 2.32, 2.33 for details).

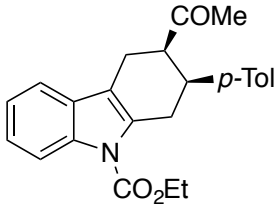
(±)-(trans)-Ethyl 3-acetyl-2-(p-tolyl)-3,4-dihydro-1H-carbazole-9(2H)-carboxylate (24'a)10



White solid; m.p.: 165.9-166.2 °C.

^{1}H-NMR (500 MHz, C_6D_6): δ = 8.63 (d, J = 8.2 Hz, 1H), 7.47 (m, 2H), 7.38 (m, 1H), 7.08 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 4.23 (m, 2H), 3.44 (dd, J = 5.0, 17.5 Hz, 1H), 3.19 (ddd, J = 5.0, 10.5, 10.5 Hz, 1H), 3.10 (dd, J = 10.5, 17.5 Hz, 1H), 2.93 (ddd, J = 4.0, 10.5, 10.5 Hz, 1H), 2.87 (dd, J = 10.5, 15.6 Hz, 1H), 2.76 (dd, J = 4.0, 15.6 Hz, 1H), 2.21 (s, 3H), 1.72 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, C_6D_6): δ = 209.0 (C), 151.6 (C), 140.7 (C), 136.5 (C), 136.2 (C), 134.4 (C), 129.6 (C), 129.4 (2 x CH), 128.0 (2 x CH), 124.1 (CH), 123.0 (CH), 117.8 (CH), 115.2 (CH), 115.2 (C_q), 62.4 (CH_2), 52.4 (CH), 43.6 (CH), 33.9 (CH_2), 29.7 (CH_3), 24.5 (CH_2), 20.8 (CH_3), 19.3 (CH_3) ppm; **IR** (KBr): $\tilde{\nu}$ = 3052, 2916, 2849, 1723 cm^{-1} **ESI(+)-MS**: m/z (%) = 376 (40) [M + 1]$^+$, 304 (100).

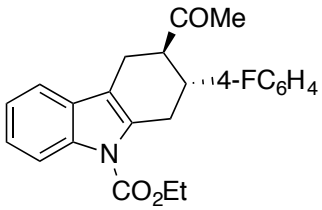
(±)-(*cis*)-Ethyl 3-acetyl-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24a)[10]



White solid; m.p.: 141.6-142.7 °C.

^{1}H-NMR (300 MHz, C_6D_6): δ = 8.61 (d, J = 8.3 Hz, 1H), 7.32-7.50 (m, 3H), 6.96 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 4.1 (q, J = 7.1 Hz, 2H), 3.80 (dd, J = 4.0, 17.6 Hz, 1H), 3.55 (ddd, J = 4.0, 4.0, 6.6 Hz, 1H), 3.50 (dd, J = 6.6, 17.6 Hz, 1H), 2.98 (dd, J = 7.3, 18.1 Hz, 1H), 2.80 (m, 1H), 2.78 (dd, J = 5.5, 18.1 Hz, 1H), 2.14 (s, 3H), 1.83 (s, 3H), 1.02 (t, J = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6): δ = 209.0 (C), 152.4 (C), 139.6 (C), 137.1 (C), 136.6 (C), 135.1 (C), 130.1 (C), 129.6 (2 x CH), 127.9 (2 x CH), 124.5 (CH), 123.4 (CH), 118.3 (CH), 116.5 (CH), 116.1 (C), 62.8 (CH_2), 51.5 (CH), 41.2 (CH), 31.7 (CH_2), 30.4 (CH_3), 29.3 (CH_3), 21.1 (CH_2), 14.2 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3054, 2921, 1722, 1701 cm^{-1}. **ESI(+)-MS**: m/z (%) = 376 (25) [M + 1]$^+$, 304 (100), 100 (70).

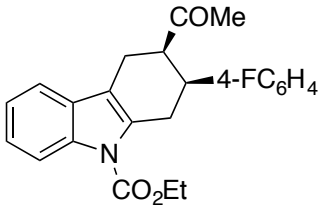
(±)-(*trans*)-Ethyl 3-acetyl-2-(4-fluorophenyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24'b)



White solid; m.p.: 161.7-161.9 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 7.1 Hz, 1H), 7.35-7.26 (m, 4H), 7.06-7.03 (m, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.52 (dd, *J* = 4.9, 18.2 Hz, 1H), 3.35 (ddd, *J* = 5.5, 10.5, 21.0 Hz, 1H), 3.23 (ddd, *J* = 5.5, 10.5, 21.0 Hz, 1H), 3.14 (m, 1H), 2.99 (m, 1H), 2.93 (m, 1H), 1.97 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, $CDCl_3$): δ = 210.4 (C), 161.0 (d, $J_{C\text{-}F}$ = 245 Hz, C), 151.2 (C), 138.1 (d, $J_{C\text{-}F}$ = 4 Hz, C), 135.2 (C), 133.4 (C), 128.4 (d, $J_{C\text{-}F}$ = 8 Hz, 2 x CH), 128.3 (C), 123.4 (CH), 122.3 (CH), 117.0 (CH), 115.0 (CH), 114.9 (d, $J_{C\text{-}F}$ = 21 Hz, 2 x CH), 114.3 (C), 62.3 (CH_2), 52.2 (CH), 42.4 (CH), 32.7 (CH_2), 29.5 (CH_3), 23.6 (CH_2), 13.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3447, 2917, 2849, 1735, 1212 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 380 (100) $[M + 1]^+$; anal. calcd, for $C_{23}H_{22}FNO_3$ (379.42): C 72.81, H 5.84, N, 3.69; found C 72.78, H 5.81, N, 3.72.

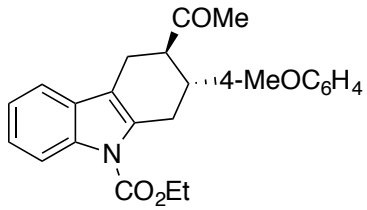
(±)-(*cis*)-Ethyl 3-acetyl-2-(4-fluorophenyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24b)



White solid; m.p.: 151.7-152.2 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.33 (m, 2 H), 7.10 (m, 2H), 6.93 (m, 2H), 4.52 (m, 2H), 3.82 (m, 1H), 3.61 (m, 1H), 3.54 (m, 1H), 3.17 (m, 1H), 2.95 (dd, *J* = 5.3, 16.6 Hz, 1H), 2.84 (m, 1H), 2.17 (s, 3H), 1.51 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, $CDCl_3$): δ = 208.7 (C), 161.1 (d, $J_{C\text{-}F}$ = 245 Hz, C), 151.3 (C), 136.5 (d, $J_{C\text{-}F}$ = 3 Hz, C), 135.5 (C), 133.5 (C), 128.7 (d, $J_{C\text{-}F}$ = 8 Hz, 2 x CH), 128.5 (C), 123.4 (CH), 122.3 (CH), 117.1 (CH), 115.0 (CH), 114.9 (C), 114.6 (d, $J_{C\text{-}F}$ = 21 Hz, 2 x CH), 62.3 (CH_2), 50.6 (CH), 39.6 (CH), 30.7 (CH_2), 28.8 (CH_3), 19.5 (CH_2), 13.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3424, 2920, 2849, 1721, 1702, 1209 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 380 (100) $[M + 1]^+$, 355 (40), 279 (30); anal. calcd, for $C_{23}H_{22}FNO_3$ (379.42): C 72.81, H 5.84, N, 3.69; found C 72.73, H 5.76, N, 3.62.

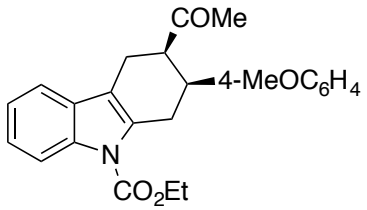
(±)-(*trans*)-Ethyl 3-acetyl-2-(4-methoxyphenyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24'c)



Yellow solid; m.p.: 161.2-162.8 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.34-7.26 (m, 2H), 7.23 (m, 2H), 6.90 (m, 2H), 4.47 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.50 (dd, J = 5.2, 18.1 Hz, 1H), 3.28 (ddd, J = 5.2, 10.5, 21.0 Hz, 1H), 3.21 (m, 1H), 3.16 (m, 1H), 2.94 (m, 2H), 1.94 (s, 3 H), 1.45 (t, J = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, $CDCl_3$): δ = 210.9 (C), 157.8 (C), 151.2 (C), 135.3 (C), 134.3 (C), 133.7 (C), 128.4 (C), 128.0 (2 x CH), 123.3 (CH), 122.2 (CH), 117.0 (CH), 114.9 (CH), 114.4 (C), 113.4 (2 x CH), 62.2 (CH_2), 54.6 (CH), 52.4 (CH_3), 42.5 (CH), 32.8 (CH_2), 29.5 (CH_3), 23.6 (CH_2), 13.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3436, 2918, 1724, 1703, 1513, 1211, 1031 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 392 (20) $[M + 1]^+$, 414 (25) $[M + Na]^+$; anal. calcd, for $C_{24}H_{25}NO_4$ (391.46): C 73.64, H 6.44, N 3.58; found C 73.61, H 6.40, N 3.62.

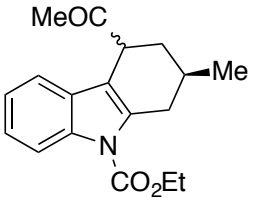
(±)-(*cis*)-Ethyl 3-acetyl-2-(4-methoxyphenyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24c)



Yellow solid; m.p.: 167.8-168.8 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.35-7.28 (m, 2H), 7.05 (d, J = 8.7 Hz, 2H), 6.78 (m, 2H), 4.51 (m, 2H), 3.81 (m, 1H), 3.77 (s, 3H), 3.60 (m, 1H), 3.52 (m, 1H), 3.16 (m, 1H), 2.93 (dd, J = 5.2, 16.6 Hz, 1H), 2.85 (m, 1H), 2.17 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, $CDCl_3$): δ = 209.1 (C), 157.8 (C), 151.3 (C), 135.5 (C_q), 133.7 (C), 132.8 (C), 128.6 (C), 128.1 (2 x CH), 123.3 (CH), 122.2 (CH), 117.1 (CH), 115.0 (C), 114.9 (CH) 113.1 (2 x CH), 62.2 (CH_2), 54.5 (CH), 50.8 (CH_3), 39.6 (CH), 30.8 (CH_2), 28.8 (CH_3), 19.4 (CH_2), 13.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3430, 2909, 1724, 1699, 1611, 1512, 1339, 1251 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 392 (10) $[M + 1]^+$, 414 (100) $[M + Na]^+$; anal. calcd, for $C_{24}H_{25}NO_4$ (391.46): C 73.64, H 6.44, N 3.58; found C 73.60, H 6.42, N 3.60.

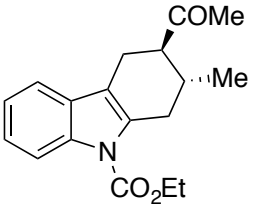
Ethyl 4-acetyl-2-methyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24"a)[10,37]



Yellow oil.

^{1}H-NMR (300 MHz, C_6D_6) (major diastereoisomer): δ = 8.50 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.32 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.83 (m, 1H), 3.17 (m, 1H), 2.50 (ddd, J = 3.0, 10.8, 17.9 Hz, 1H), 1.88 (s, 3H), 1.80 (m, 1H), 1.57 (m, 1H), 1.27 (t, J = 12.2 Hz, 1H), 1.06 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6) (major diastereoisomer): δ = 208.7 (C), 151.9 (C), 137.4 (C), 136.8 (C), 129.3 (C), 124.4 (CH), 123.6 (CH), 118.8 (CH), 116.3 (CH), 115.1 (C), 62.8 (CH_2), 50.4 (CH), 34.8 (CH_2), 34.2 (CH_2), 29.7 (CH), 25.6 (CH_3), 21.9 (CH_3), 14.3 (CH_3) ppm. **IR** (neat): $\tilde{\nu}$ = 3076, 2953, 2917, 2884, 1735, 1703 cm^{-1}. **ESI(+)-MS**: m/z (%) = 300 (100) $[M + 1]^+$.

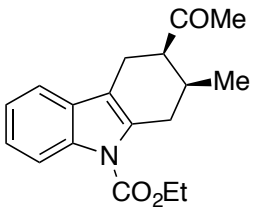
(±)-(*trans*)-Ethyl 3-acetyl-2-methyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24'd)



Yellow oil.

^{1}H-NMR (500 MHz, C_6D_6): δ = 8.56 (d, J = 8.2 Hz, 1H), 7.43-7.34 (m, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.22 (dd, J = 4.9, 17.9 Hz, 1H), 2.67 (m, 2H), 2.57 (m, 1H), 2.27 (ddd, J = 5.4, 9.9, 19.8 Hz, 1H), 2.15 (m, 1H), 1.92 (s, 3H), 1.07 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, C_6D_6): δ = 208.8 (C), 150.9 (C), 135.6 (C), 133.7 (C), 129.0 (C), 123.2 (CH), 122.2 (CH), 117.0 (CH), 115.2 (CH), 114.3 (C), 61.6 (CH_2), 52.4 (CH), 32.5 (C), 30.7 (CH), 28.6 (CH_3), 23.1 (CH_2), 18.8 (CH_3), 13.2 (CH_3) ppm. **IR** (neat): $\tilde{\nu}$ = 3074, 2952, 2934, 2874, 1734, 1702 cm^{-1}. **ESI(+)-MS**: m/z (%) = 300 (100) $[M + 1]^+$.

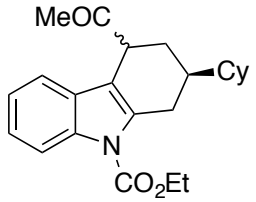
(±)-(*cis*)-Ethyl 3-acetyl-2-methyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24d)[10,37]



Pink solid; m.p.: 81.8-82.1 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 6.9 Hz, 1H), 7.32 (m, 2H), 4.51 (q, J = 7.1 Hz, 2H), 3.28 (m, 1H), 3.07 (m, 1H), 2.90 (m, 2H), 2.79 (m, 2H), 2.29 (s, 3H), 1.51 (t, J = 7.1 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, $CDCl_3$): 210.0 (C), 152.0 (C), 136.1 (C), 133.6 (C), 129.5 (C), 123.7 (CH), 122.8 (CH), 117.7 (CH), 115.5 (CH), 114.7 (C), 62.8 (CH_2), 50.7 (CH), 33.3 (CH_2), 29.3 (CH_3), 28.5 (CH), 18.3 (CH_2), 14.6 (CH_3), 14.4 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3034, 2914, 2873, 1727, 1706 cm^{-1}. **APCI(+)-MS**: m/z (%) = 300 (100) $[M + 1]^+$.

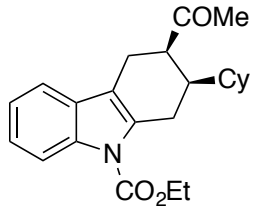
Ethyl 4-acetyl-2-cyclohexyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24"b)



White solid; m.p.: 87.5-88.6 °C.

^{1}H-NMR (500 MHz, C_6D_6) (major diastereoisomer): δ = 8.51 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.37 (td, J = 1.1, 7.2 Hz, 1H), 7.26 (m, 1H), 4.15 (m, 2H), 3.85 (m, 1H), 3.18 (m, 1H), 2.68 (m, 1H), 2.02 (m, 1H), 1.94 (s, 3H), 1.85-1.67 (m, 5H), 1.47-1.10 (m, 8H), 1.07 (t, J = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, C_6D_6) (major diastereoisomer): δ = 208.0 (C), 150.9 (C), 136.9 (C), 135.8 (C), 128.2 (C), 123.3 (CH), 122.6 (CH), 117.7 (CH), 115.3 (CH), 114.3 (C), 61.7 (CH_2), 49.6 (CH), 41.8 (CH), 39.0 (CH), 29.7 (CH_2), 29.5 (CH_2), 29.3(CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 26.0 (CH_2), 24.5 (CH_3), 13.2 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3583, 3293, 2922, 1731, 1457, 1376, 1268, 1218, 1117, 746 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 368 (100) $[M + 1]^+$, 390 (90) $[M + Na]^+$.

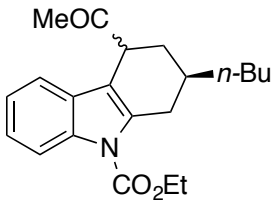
(±)-(cis)-Ethyl 3-acetyl-2-cyclohexyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24e)



White solid; m.p.: 100.6-101.7 °C.

^{1}H-NMR (500 MHz, C_6D_6): δ = 8.57 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.42 (td, J = 1.2, 7.2 Hz, 1H), 7.36 (td, J = 1.0 Hz, 7.2, 1H), 4.11 (m, 2H), 3.52 (dd, J = 8.2, 18.0 Hz, 1H), 3.28 (dd, J = 5.3, 18.0 Hz, 1H), 2.97 (dd, J = 4.1, 16.6 Hz, 1H), 2.85 (m, 1H), 2.70 (dd, J = 6.2, 16.6 Hz, 1H), 2.09 (d, J = 12.6 Hz, 1H), 1.88 (m, 4H), 1.82-1.68 (m, 5H), 1.31-1.21 (m, 3H), 1.04 (t, J = 7.7 Hz, 3H), 0.97 (m, 2H) ppm. **^{13}C NMR** (125.75 MHz, C_6D_6): δ = 207.1 (C), 151.0 (C), 135.9 (C), 135.4 (C), 129.0 (C), 123.1 (CH), 122.1 (CH), 116.8 (CH), 115.4 (CH), 113.5 (C), 61.6 (CH_2), 48.8 (CH), 41.9 (CH), 40.7 (CH), 38.5 (CH_3), 31.5 (CH_2), 31.0 (CH_2), 27.5 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.7 (CH_2), 13.1 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3400, 2924, 1730, 1456, 1347, 1327, 1210, 1144, 1042, 745 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 368 (48) $[M + 1]^+$, 390 (100) $[M + Na]^+$; anal. calcd, for $C_{23}H_{29}NO_3$ (367.48): C 75.17, H 7.95, N 3.81; found C 75.08, H 7.91, N 3.82.

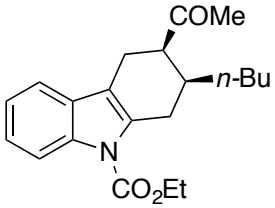
Ethyl 4-acetyl-2-n-butyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24"c)[10,37]



Yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) (major diastereoisomer): δ = 8.14 (d, J = 7.9 Hz, 1H), 7.25 (m, 3H), 4.51 (m, 2H), 3.84 (m, 1H), 3.32 (m, 1H), 2.61 (m, 1H), 2.21 (m, 1H), 2.09 (s, 3H), 1.81 (m, 1H), 1.52 (t, J = 7.1 Hz, 3H), 1.36-1.30 (m, 7H), 0.95 (t, J = 6.8 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, $CDCl_3$) (major diastereoisomer): δ = 211.5 (C), 152.3 (C), 137.9 (C), 136.4 (C), 128.8 (C), 124.3 (CH), 123.5 (CH), 118.5 (CH), 116.1 (CH), 115.1 (C), 63.4 (CH_2), 50.2 (CH), 36.6 (CH_2), 34.9 (CH), 33.5 (CH_2), 32.6 (CH_2), 29.5 (CH_2), 26.5 (CH_3), 23.3 (CH_2), 14.8 (CH_3), 14.5 (CH_3) ppm. **IR** (neat): $\tilde{\nu}$ = 2957, 2928, 2859, 1736 cm^{-1}. **ESI(+)-MS**: m/z (%) = 364 (100) $[M + Na]^+$, 296 (40).

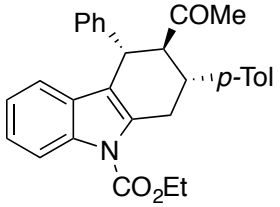
(±)-(*cis*)-Ethyl 3-acetyl-2-*n*-butyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24f)[10,37]



Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, J = 7.1 Hz, 1H), 7.38 (m, 3H), 4.52 (q, J = 7.1 Hz, 2H), 3.19 (m, 2H), 2.83 (m, 3H), 2.48 (m, 1H), 2.28 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H), 1.25 (m, 6H), 0.88 (m, 3H) ppm. **^{13}C NMR** (75.45 MHz, $CDCl_3$): δ = 210.5 (C), 152.4 (C), 136.4 (C), 134.4 (C), 129.9 (C), 124.1 (CH), 123.2 (CH), 118.1 (CH), 115.9 (CH), 115.5 (C), 63.2 (CH_2), 51.4 (CH), 35.6 (CH), 30.7 (CH_2), 30.1 (CH_2), 29.1 (CH_3), 28.8 (CH_2), 23.2 (CH_2), 19.6 (CH_2), 14.8 (CH_3), 14.4 (CH_3) ppm. **IR** (neat): $\tilde{\nu}$ = 2955, 2926, 2870, 1735, 1707 cm^{-1}. ESI(+)-MS: m/z (%) = 364 (100) $[M + Na]^+$.

(±)-(2,3-*trans*)-Ethyl 3-acetyl-4-phenyl-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24'g)

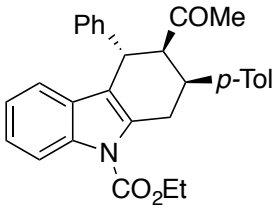


White solid; m.p.: 189.8-190.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.4 Hz, 1H), 7.35-7.10 (m, 10H), 6.95 (t, J = 7.3 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 4.60-4.38 (m, 3H), 3.55 (m, 1H), 3.36 (m, 3H), 2.35 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H), 1.35 (s, 3H) ppm. **^{13}C-NMR** (75.45 MHz, $CDCl_3$): δ = 212.6 (C), 152.3 (C), 142.6 (C), 139.6 (C), 137.1 (C), 136.6 (C), 135.8 (C), 129.8 (2 x CH), 129.2 (2 x CH), 128.9 (C), 128.7 (2 x CH), 128.2 (2 x CH), 127.5 (CH), 124.0 (CH), 122.9 (CH), 120.2 (CH), 118.5 (C), 115.7 (CH), 63.4 (CH_2), 63.3 (CH), 45.7 (CH), 45.0 (CH), 34.11 (CH), 34.08 (CH_2), 21.4 (CH_3), 14.9 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ =

3437, 2927, 1728, 1705, 1343, 1043 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 452 (20) $[M + 1]^+$, 474 (40) $[M + Na]^+$; anal. calcd, for $C_{30}H_{29}NO_3$ (451.56): C 79.80, H 6.47, N 3.10; found C 79.71, H 6.39, N 2.97.

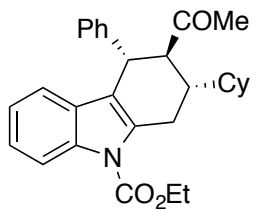
(±)-(2,3-*cis*)-Ethyl 3-acetyl-4-phenyl-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24g)



White solid; m.p.: 184.8-185.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.4 Hz, 1H), 7.27 (m, 6H), 7.05 (m, 5H), 6.85 (d, *J* = 7.8 Hz, 1H), 4.53 (m, 3H), 3.66 (d, *J* = 6.5 Hz, 2H), 3.56 (m, 1H), 3.36 (t, *J* = 4.2 Hz, 1H), 2.32 (s, 3H), 1.99 (s, 3H), 1.53 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75.45 MHz, $CDCl_3$): δ = 208.9 (C), 152.4 (C), 143.6 (C), 139.2 (C), 136.9 (C), 136.8 (C), 136.5 (C), 129.6 (2 x CH), 129.3 (C), 129.0 (2 x CH), 128.9 (2 x CH), 128.0 (2 x CH), 127.2 (CH), 124.1 (CH), 123.1 (CH), 119.5 (CH), 117.2 (C), 115.9 (CH), 63.4 (CH_2), 61.2 (CH), 39.9 (CH), 39.1 (CH), 31.6 (CH), 29.8 (CH_2), 21.4 (CH_3), 14.8 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3437, 2920, 1731, 1703, 1376, 1051 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 452 (35) $[M + 1]^+$, 474 (100) $[M + Na]^+$; anal. calcd, for $C_{30}H_{29}NO_3$ (451.56): C 79.80, H 6.47, N 3.10; found C 79.77, H 6.43, N 2.03.

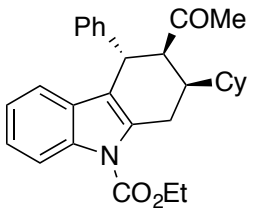
(±)-(2,3-*trans*)-Ethyl 3-acetyl-2-cyclohexyl-4-phenyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24'h)



Yellow solid; m.p.: 145.8-147.0 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 1H), 7.33-7.10 (m, 6H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.42 (d, *J* = 7.7 Hz, 1H), 4.59-4.47 (m, 2H), 4.22 (m, 1H), 3.27 (ddd, *J* = 1.5, 5.5, 8.3 Hz, 1H), 3.06-2.87 (m, 2H), 2.24 (m, 1H), 1.80-1.17 (m, 11H), 1.76 (s, 3H), 1.52 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 213.9 (C), 152.3 (C), 142.5 (C), 136.4 (C), 136.3 (C), 129.0 (2 x CH), 128.8 (C), 128.5 (2 x CH), 127.3 (CH), 123.6 (CH), 122.7 (CH), 119.9 (CH), 118.1 (C), 115.5 (CH), 63.1 (CH_2), 60.4 (CH), 46.2 (CH), 43.3 (CH), 40.0 (CH), 33.5 (CH_3), 32.3 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 25.8 (CH_2), 14.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3436, 2924, 1729, 1711, 1350, 1041 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 444 (100) $[M + 1]^+$; anal. calcd, for $C_{29}H_{33}NO_3$ (443.58): C 78.52, H 7.50, N 3.16; found C 78.48, H 7.42, N 3.05.

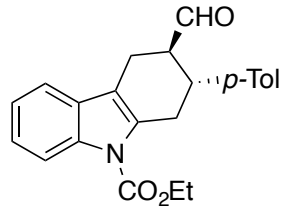
(±)-(2,3-*cis*)-Ethyl 3-acetyl-2-cyclohexyl-4-phenyl-3,4-dihydro-1H-carbazole-9(2H)-carboxylate (24h)



Yellow solid; m.p.: 157.8-159.9 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.4 Hz, 1H), 7.22 (m, 5H), 7.02 (m, 3H), 4.52 (m, 3H), 3.36 (dd, J = 18.3, 6.2 Hz, 1H), 3.16 (m, 2H), 2.28 (s, 3H), 1.94 (m, 1H), 1.80-0.70 (m, 11H), 1.51 (t, J = 7.0 Hz, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 209.3 (C), 152.3 (C), 143.5 (C), 138.2 (C), 136.6 (C), 129.3 (C), 128.7 (2 x CH), 128.3 (2 x CH), 126.8 (CH), 123.9 (CH), 122.9 (CH), 118.4 (CH), 115.8 (CH), 115.2 (C), 63.1 (CH_2), 55.7 (CH), 40.2 (CH), 39.5 (CH), 38.0 (CH), 32.0 (CH_2), 31.4 (CH_2), 30.6 (CH_3), 28.0 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 14.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3443, 2930, 1733, 1706, 1374, 1047 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 444 (90) $[M + 1]^+$, 466 (100) $[M + Na]^+$; anal. calcd, for $C_{29}H_{33}NO_3$ (443.58): C 78.52, H 7.50, N 3.16; found C 78.43, H 7.46, N 3.12.

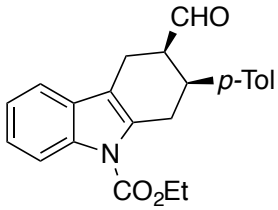
(±)-(*trans*)-Ethyl 3-formyl-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24'i)



White oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.62 (d, J = 2.0 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.1 Hz, 1H), 7.35-7.27 (m, 2H), 7.23-7.14 (m, 4H), 4.48 (q, J = 7.1 Hz, 2H), 3.52 (dd, J = 18.1, 5.92 Hz, 1H), 3.44 (m, 1H), 3.24 (m, 1H), 3.10-2.97 (m, 2H), 2.88 (m, 1H), 2.37 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, $CDCl_3$): δ = 203.2 (CH), 151.2 (C), 138.7 (C), 136.0 (C), 135.3 (C), 133.6 (C), 128.9 (2 x CH), 128.5 (C), 126.8 (2 x CH), 123.4 (CH), 122.3 (CH), 117.1 (CH), 114.9 (CH), 114.0 (C), 62.3 (CH_2), 50.5 (CH), 40.6 (CH), 31.8 (CH_2), 20.3 (CH_3), 19.9 (CH_2), 13.7 (CH_3) ppm. **IR** (neat): $\tilde{\nu}$ = 3436, 2916, 2725, 1728, 1619, 1457, 1376, 1398, 1212, 1142 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 362 (70) $[M + 1]^+$, 384.3 (75) $[M + Na]^+$; anal. calcd, for $C_{23}H_{23}NO_3$ (361.43): C 76.43, H 6.41, N 3.88; found C 76.38, H 6.37, N 3.91.

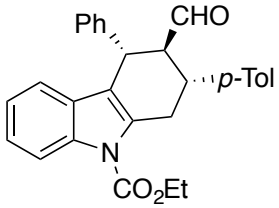
(±)-(*cis*)-Ethyl 3-formyl-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24i)



Yellow solid; m.p.: 141.7-142.4 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.85 (d, J = 0.8 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.36-7.29 (m, 2H), 7.15-7.10 (m, 4H), 4.52 (m, 2H), 3.84 (m, 1H), 3.63 (dd, J = 6.2, 18.4 Hz, 1H), 3.52 (dd, J = 6.2, 18.4 Hz, 1H), 3.10 (m, 1H), 3.01 (dd, J = 5.4, 16.5 Hz, 1H), 2.94 (dd, J = 7.2, 16.5 Hz, 1H), 2.34 (s, 3H), 1.51 (t, J = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (125.75 MHz, $CDCl_3$): δ = 202.7 (CH), 151.2 (C), 137.4 (C), 136.0 (C), 135.5 (C), 133.6 (C), 128.7 (2 x CH), 128.5 (C), 127.0 (2 x CH), 123.4 (CH), 122.3 (CH), 117.2 (CH), 114.9 (CH), 114.7 (C), 62.3 (CH_2), 49.9 (CH), 39.1 (CH), 29.5 (CH_2), 20.3 (CH_3), 18.8 (CH_2), 13.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3430, 2916, 2690, 1727, 1614, 1378, 1336, 1206, 1035 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 362 (60) $[M + 1]^+$; anal. calcd, for $C_{23}H_{23}NO_3$ (361.43): C 76.43, H 6.41, N 3.88; found C 76.41, H 6.40, N 3.90.

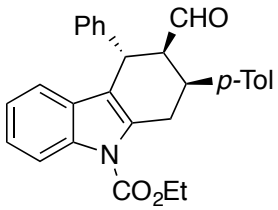
(±)-(2,3-*trans*)-Ethyl 3-formyl-4-phenyl-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24'j)[10]



Yellow oil.

^{1}H-NMR (300 MHz, C_6D_6): δ = 9.36 (d, J = 2.9 Hz, 1H), 8.56 (m, 1H), 6.94-7.33 (m, 12H), 4.61 (m, 1H), 4.10 (m, 2H), 3.52 (ddd, J = 5.0, 1.5, 17.8 Hz, 1H), 3.28 (m, 2H), 3.11 (ddd, J = 5.0, 11.3, 11.4 Hz, 1H), 2.20 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6): δ = 202.7 (CH), 152.0 (C), 142.8 (C), 139.0 (C), 137.1 (C), 137.0 (C), 135.7 (C), 130.0 (2 x CH), 129.4 (C), 129.3 (2 x CH), 129.1 (2 x CH), 128.1 (2 x CH), 127.4 (CH), 124.3 (CH), 123.3 (CH), 120.5 (CH), 118.4 (C), 116.1 (CH), 63.0 (CH_2), 61.1 (CH), 44.1 (CH), 42.3 (CH), 35.2 (CH_2), 21.2 (CH_3), 14.3 (CH_3) ppm. **IR** (neat): $\tilde{\nu}$ = 2906, 2895, 2786, 1732 cm^{-1}. **ESI(+)-MS:** m/z (%) = 460 (100) $[M + Na]^+$.

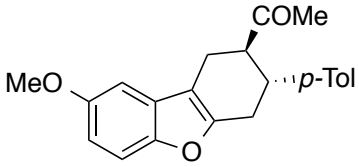
(±)-(2,3-*cis*)-Ethyl 3-formyl-4-phenyl-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (24j)[10]



Yellow oil.

^{1}H-NMR (300 MHz, C_6D_6): δ = 9.74 (d, J = 1 Hz, 1H), 8.56 (d, J = 8.3 Hz, 1H), 6.97-7.35 (m, 12H), 4.87 (d, J = 2.9 Hz, 1H), 4.14 (m, 2H), 3.67 (m, 2H), 3.56 (m, 1H), 3.07 (m, 1H), 2.17 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75.45 MHz, C_6D_6): δ = 201.5 (CH), 152.0 (C), 143.2 (C), 139.0 (C), 137.2 (C), 136.6 (C), 136.5 (C), 129.7 (2 x CH), 129.5 (C), 129.1 (2 x CH), 129.0 (2 x CH), 128.2 (2 x CH), 127.2 (CH), 124.6 (CH), 123.5 (CH), 119.7 (CH), 117.1 (C), 116.3 (CH), 63.0 (CH_2), 60.3 (CH), 38.6 (CH), 37.4 (CH), 29.3 (CH_2), 21.1 (CH_3), 14.2 (CH_3) ppm. **IR** (neat): $\tilde{\nu}$ = 3027, 2924, 2853, 1734 cm^{-1}. **ESI(+)-MS**: m/z (%) = 460 (100) $[M + Na]^+$.

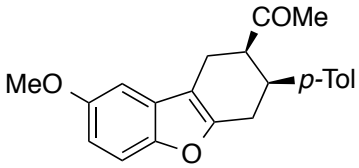
(±)-(*trans*)-8-Methoxy-2-acetyl-3-(*p*-tolyl)-1,2,3,4-tetrahydrodibenzo[*b,d*]furan (79')



Yellow solid; m.p.: 134.7-135.1 °C.

^{1}H-NMR (500 MHz, C_6D_6): δ = 7.42 (d, J = 8.8 Hz, 1H), 7.04 (m, 5H), 6.98 (dd, J = 2.5, 8.8 Hz, 1H), 3.64 (s, 3H), 3.15 (ddd, J = 5.6, 10.3, 21.3 Hz, 1H), 2.91 (dd, J = 5.6, 16.6 Hz, 1H), 2.83-2.71 (m, 3H), 2.57 (dd, J = 4.0, 14.0 Hz, 1H), 2.21 (s, 3H), 1.66 (s, 3H) ppm. **^{13}C-NMR** (125.75 MHz, C_6D_6): δ = 207.9 (C), 155.7 (C), 152.9 (C), 149.3 (C), 139.3 (C), 135.5 (C), 128.7 (2 x CH), 128.5 (C), 127.0 (2 x CH), 110.9 (CH), 110.8 (CH), 110.7 (C), 101.3 (CH), 54.6 (CH_3), 52.2 (CH), 42.1 (CH), 30.8 (CH_2), 29.0 (CH_3), 23.1 (CH_2), 20.0 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3419, 2922, 1712, 1609, 1459, 1356, 1201, 1029, 834 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 335 (100) $[M + 1]^+$, 357 (55) $[M + Na]^+$; anal. calcd, for $C_{22}H_{22}O_3$ (334.41): C 79.02, H 6.63; found C 78. 98, H 6.61.

(±)-(*cis*)-8-Methoxy-2-acetyl-3-(*p*-tolyl)-1,2,3,4-tetrahydrodibenzo[*b,d*]furan (79)

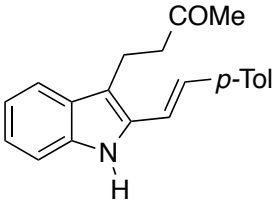


Yellow solid; m.p.: 137.1-138.4 °C.

^{1}H-NMR (500 MHz, C_6D_6): δ = 7.41 (d, J = 8.8 Hz, 1H), 7.06 (m, 3H), 6.97 (m, 3H), 3.59 (s, 3H), 3.46 (m, 1H), 3.21 (m, 1H), 3.03 (dd, J = 5.8, 16.4 Hz, 1H), 2.90 (m, 1H), 2.67 (m, 2H), 2.14 (s, 3H), 1.80 (s, 3H) ppm. **^{13}C NMR** (125.75 MHz, C_6D_6): δ = 206.1 (C), 155.7 (C), 153.3 (C), 149.6 (C), 137.7 (C), 135.6 (C), 128.5 (2 x CH), 127.0 (2 x CH), 111.4 (C), 111.1 (CH), 110.9 (CH), 101.2 (CH), 54.6 (CH_3), 50.9 (CH), 39.7 (CH), 28.3 (CH_2), 28.1 (CH_3), 20.0 (CH_3), 19.5 (CH_2) ppm (note: a C

falls under the C_6D_6 residue signal). **IR** (KBr): $\tilde{\nu}$ = 3389, 2915, 1704, 1614, 1480, 1385, 1205, 1026, 803 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 335 (100) $[M + 1]^+$, 357 (70) $[M + Na]^+$; anal. calcd, for $C_{22}H_{22}O_3$ (334.41): C 79.02, H 6.63; found C 78. 95, H 6.59.

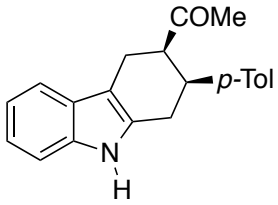
(*E*)-2-(4-methylstyryl)-3-(3'-oxo-butyl)-1*H*-indole (80a)



Yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.34-7.01 (m, 6H), 6.79 (d, *J* = 16.5 Hz, 1H), 3.14 (t, *J* = 7.5 Hz, 2H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.35 (s, 3H), 2.13 (s, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 208.7 (C), 137.9 (C), 136.8 (C), 134.5 (C), 132.8 (C), 129.7 (2 x CH), 128.9 (C), 126.5 (2 x CH), 126.4 (CH), 123.3 (CH), 119.9 (CH), 118.9 (CH), 116.2 (CH), 115.6 (C), 110.8 (CH), 44.8 (CH_2), 30.4 (CH_3), 21.5 (CH_3), 18.4 (CH_2) ppm. **IR** (neat): $\tilde{\nu}$ = 3361, 2919, 1703, 1451, 1116 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 304 (100) $[M + 1]^+$; anal. calcd, for $C_{21}H_{21}NO$ (303.40): C 83.13, H 6.98, N, 4.62; found C 83.08, H 6.95, N, 4.63.

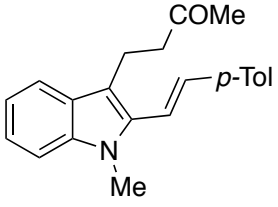
(±)-(*cis*)-3-Acetyl-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole (24l)



Yellow oil.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.75 (s, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.06-6.88 (m, 6H), 3.81 (psq, 1H), 3.36 (dd, *J* = 6.4, 16.8 Hz, 1H), 3.25 (psq, 1H), 3.00 (dd, *J* = 3.6, 16.8 Hz, 1H), 2.81 (dd, *J* = 5.3, 16.0 Hz, 1H), 2.66 (dd, *J* = 9.4, 16.0 Hz, 1H), 2.21 (s, 3H), 2.16 (s, 3H) ppm. **^{13}C-NMR** (100.4 MHz, DMSO-d_6): δ = 209.8 (C), 139.6 (C), 136.7 (C), 135.9 (C), 134.0 (C), 129.2 (2 x CH), 127.9 (2 x CH), 127.5 (C), 120.7 (CH), 118.7 (CH), 117.7 (CH), 111.2 (CH), 107.4 (C), 52.0 (CH), 39.7 (CH), 29.6 (CH_3), 29.1 (CH_2), 21.0 (CH_3), 20.0 (CH_2) ppm. **IR** (neat): $\tilde{\nu}$ = 3392, 2912, 1699, 1154 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 304 (100) $[M + 1]^+$; anal. calcd, for $C_{21}H_{21}NO$ (303.40): C 83.13, H 6.98, N, 4.62; found C 83.06, H 6.92, N, 4.67.

(*E*)-1-methyl-2-(4-methylstyryl)-3-(3'-oxo-butyl)-1*H*-indole (80b)

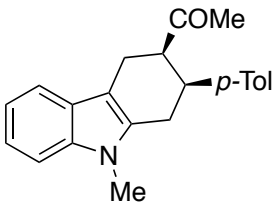


Yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.56 (m, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.32-7.03 (m, 6H), 6.88 (d, *J* = 16.6 Hz, 1H), 3.80 (s, 3H), 3.18 (m, 2H), 2.83 (m, 2H), 2.39 (s, 3H), 2.14 (s, 3H) ppm. **^{13}C-NMR** (50.3 MHz,

$CDCl_3$): δ = 208.8 (C), 138.1 (C), 138.0 (C), 134.8 (C), 134.7 (C), 132.6 (CH), 129.7 (2 x CH), 127.8 (C), 126.53 (2 x CH), 122.4 (CH), 119.5 (CH), 118.8 (CH), 116.7 (CH), 113.5 (C), 109.3 (CH), 44.7 (CH_2), 31.2 (CH_3), 30.3 (CH_3), 21.5 (CH_3), 19.4 (CH_2) ppm. **IR** (neat): $\tilde{\nu}$ = 3050, 3023, 2921, 1713, 1511, 1469, 1362, 1161 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 318 (100) $[M+1]^+$; anal. calcd, for $C_{22}H_{23}NO$ (317.42): C 83.24, H 7.30, N 4.41; found C 83.21, H 7.30, N 4.43.

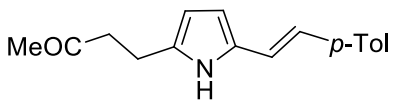
(±)-(*cis*)-3-Acetyl-9-methyl-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole (24m)



Yellow solid; m.p.: 167.3-168.1 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 7.7 Hz, 1H), 7.35-6.95 (m, 7H), 3.77 (m, 1H), 3.66 (s, 3H), 3.28-3.07 (m, 3H), 2.96 (m, 2H), 2.28 (s, 3H), 2.10 (s, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 210.5 (C), 139.0 (C), 137.6 (C), 136.8 (C), 135.0 (C), 129.3 (2 x CH), 128.0 (2 x CH), 127.0 (C), 121.1 (CH), 119.1 (CH), 118.0 (CH), 108.9 (CH), 107.8 (C), 52.5 (CH), 41.0 (CH), 29.7 (CH_3), 29.4 (CH_3), 28.1 (CH_2), 21.2 (CH_3), 21.1 (CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3048, 3023, 2908, 1698, 1514, 1472, 1349, 1161 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 318 (100) $[M+1]^+$; anal. calcd for $C_{22}H_{23}NO$ (317.42): C 83.24, H 7.30, N 4.41; found C 83.19, H 7.27, N 4.46

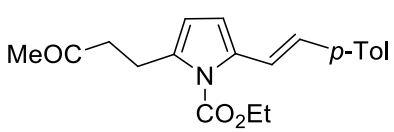
(*E*)-4-(5-(4-Methylstyryl)-1*H*-pyrrol-2-yl)butan-2-one (81a)



Yellow solid; m.p.: 138.5-139.1 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.69 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J*=16.5 Hz, 1H), 6.56 (d, *J* = 16.5 Hz, 1H), 6.15 (t, *J* = 3.0 Hz, 1H), 5.87 (t, *J* = 3.0 Hz, 1H), 2.82 (s, 4H), 2.34 (s, 3H), 2.19 (s, 3H) ppm. **^{13}C-NMR** (50.3 MHz, $CDCl_3$): δ = 209.84 (C), 136.64 (C), 135.27 (C), 133.42 (C), 130.42 (C), 129.55 (2 x CH), 125.88 (2 x CH), 122.49 (CH), 118.45 (CH), 109.15 (CH), 107.45 (CH), 44.25 (CH_2), 30.31 (CH_3), 21.75 (CH_2), 21.38 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3381, 3019, 1707, 1366, 1171 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 254 (100) $[M–CH_2CH_2COCH_3]^+$, $C_{17}H_{19}NO$ [253.37]: calcd.

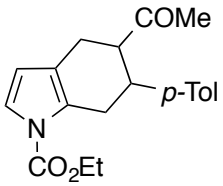
(*E*)-Ethyl 2-(4-methylstyryl)-5-(3-oxobutyl)-1*H*-pyrrole-1-carboxylate (81b)



Yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 16.1 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 16.1 Hz, 1H), 6.40 (d, *J* = 3.5 Hz, 1H), 5.97 (d, *J* = 3.5 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.17-3.05 (m, 2H), 2.85-2.72 (m, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H) ppm. **IR** (NaCl): $\tilde{\nu}$ = 3412.82, 2923.51, 1902.40, 1740.40, 1308.12, 1109.70, 803.73 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 326.1 (100) $[M + 1]^+$, $C_{20}H_{23}NO_3$ [325.40]: calcd.

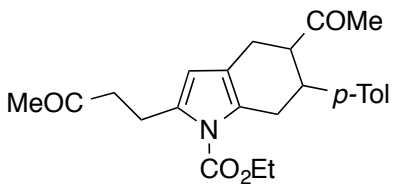
(±)-Ethyl 5-acetyl-6-(*p*-tolyl)-4,5,6,7-tetrahydro-1*H*-indole-1-carboxylate (82)



Yellow oil.

^{1}H-NMR (200 MHz, C_6D_6) (major diastereoisomer): δ = 7.30 (d, *J* = 3.3 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 5.95 (d, *J* = 3.4 Hz, 1H), 3.84 (q, *J* = 7.1 Hz, 2H), 3.64-3.17 (m, 3H), 2.76-2.35 (m, 3H), 1.99 (s, 3H), 1.63 (s, 3H), 0.80 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (50.3 MHz, C_6D_6) (major diastereoisomer): δ = 207.4 (C), 150.7 (C), 139.5 (C), 136.1 (C), 129.2 (2 x CH), 129.0 (C), 128.0 (2 x CH), 121.2 (C), 120.1 (CH), 111.4 (CH), 62.6 (CH_2), 51.8 (CH), 40.7 (CH), 30.5 (CH_2), 28.9 (CH_3), 22.8 (CH_2), 20.8 (CH_3), 13.8 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3459.98, 2087.03, 1906.98, 1738.75, 1638.03, 1334.20, 1279.49, 1035.01, 717.15 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 326.3 (100) $[M + 1]^+$, 348.2 (100) $[M + Na]^+$; $C_{20}H_{23}NO_3$ [325.40]: calcd.

(±)-Ethyl 5-acetyl-2-(3-oxobutyl)-6-(*p*-tolyl)-4,5,6,7-tetrahydro-1*H*-indole-1-carboxylate (83)

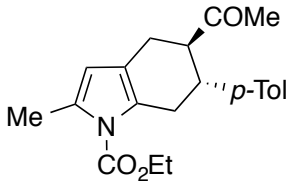


Yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereoisomers): δ = 7.16 (s, 3H), 7.00-6.80 (m, 5H), 5.80 (s, 1H), 5.76 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.81-3.68 (m, 1H), 3.59 (m, 1H), 3.29 (m, 2H), 3.11 (m, 4H), 2.43 (m, 3H), 2.76 (m, 4H), 2.59 (m, 2H), 2.34 (s, 3H), 2.28 (s, 4H), 2.17 (s, 3H), 2.16 (s, 5H), 2.03 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (50.3 MHz, $CDCl_3$) (mixture of diastereoisomers): δ = 210.3 (2 x C), 208.2 (C), 207.9 (C), 151.7 (C), 151.6 (C), 142.4 (C), 139.1 (C), 136.6 (C), 136.43 (C), 134.9 (C), 134.8 (C), 131.2 (C), 129.5 (2 x CH), 129.3 (2 x CH), 128.8 (C), 127.9 (2 x CH), 127.0 (2 x CH), 119.5 (C), 118.3 (C), 111.4 (CH), 110.3 (CH), 63.2 (CH_2), 63.1 (CH_2), 52.0 (CH), 50.4 (CH), 43.6 (CH_2),

43.5 (CH_2), 41.0 (CH), 40.9 (CH), 33.9 (CH_2), 32.1 (CH_2), 31.2 (CH_2), 30.1 (CH_3), 30.0 (CH_2), 29.8 (CH_3), 27.9 (CH_3), 27.8 (CH_3), 23.9 (CH_2), 22.8 (CH_2), 21.2 (CH_3), 21.1 (CH_3), 14.4 (CH_3), 14.3 (CH_3) ppm. **IR** (NaCl): $\tilde{\nu}$ = 3406.53, 2924.55, 2855.48, 2251.96, 1903.96, 1738.57, 1375.95, 1088.35, 805.88 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 396.2 (100) $[M + 1]^+$, 418.3 (100) $[M + Na]^+$; $C_{24}H_{29}NO_4$ [395.21]: calcd.

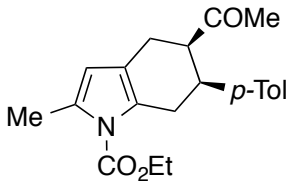
(±)-(*trans*)-Ethyl 5-acetyl-2-methyl-6-(*p*-tolyl)-4,5,6,7-tetrahydro-1*H*-indole-1-carboxylate (84')



Yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.16 (m, 4H), 5.75 (s, 1H), 4.33 (q, *J* = 7.0 Hz, 2H), 3.81-3.67 (m, 1H), 3.20 (m, 2H), 2.89 (m, 2H), 2.75-2.61 (m, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 2.16 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ = 210.5 (C), 151.9 (C), 142.6 (C), 136.4 (C), 132.0 (C), 130.7 (C), 129.6 (CH), 129.5 (2 x CH), 127.0 (2 x CH), 126.9 (CH), 118.2 (C), 110.7 (CH), 63.0 (CH_2), 50.5 (CH), 41.0 (CH), 34.1 (CH_2), 33.7 (CH_2), 27.7 (CH_3), 21.2 (CH_3), 16.4 (CH_3), 14.5 (CH_3) ppm. **IR** (NaCl): $\tilde{\nu}$ = 3391.62, 2924.64, 2250.90, 1902.89, 1738.47, 1515.49, 1347.75, 1294.54, 1093.15, 817.23 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 340.2 (100) $[M + 1]^+$, 362.3 (100) $[M + Na]^+$; $C_{21}H_{25}NO_3$ [339.43]: calcd.

(±)-(*cis*)-Ethyl 5-acetyl-2-methyl-6-(*p*-tolyl)-4,5,6,7-tetrahydro-1*H*-indole-1-carboxylate (84)



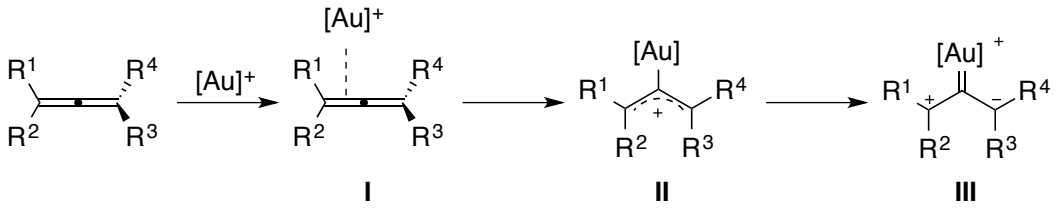
Yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 5.79 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.61 (m, 1H), 3.29 (m, 2H), 3.00 (m, 1H), 2.59 (m, 2H), 2.44 (s, 3H), 2.28 (s, 3H), 2.04 (s, 3H), 1.37 (t, *J*=7.1 Hz, 3H) ppm. **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ = 210.4 (C), 152.0 (C), 139.2 (C), 136.5 (C), 131.9 (C), 129.3 (2 x CH), 129.3 (CH), 128.3 (C), 127.9 (2 x CH), 127.0 (CH), 119.5 (C), 111.8 (CH), 62.9 (CH_2), 52.1 (CH), 41.0 (CH), 31.3 (CH_2), 29.7 (CH_3), 22.5 (CH_2), 21.2 (CH_3), 16.4 (CH_3), 14.5 (CH_3) ppm. **IR** (NaCl): $\tilde{\nu}$ = 3400.44, 2923.81, 2252.03, 1905.09, 1732.68, 1514.81, 1343.87, 1243.31, 1088.36, 816.60 cm^{-1}. **ESI(+)-MS**: *m/z* (%) = 340.2 (100) $[M + 1]^+$, 362.3 (100) $[M + Na]^+$; $C_{21}H_{25}NO_3$ [339.43]: calcd.

Chapter 3. Gold-catalyzed [4+2]-cycloaddition reactions between 2-vinylindoles and *N*-allenamides

3.1 Introduction

Allenes are interesting precursors in synthetic organic chemistry because of their ability of undergo a variety of distinctive transformations due to their particular structures.[129] Among catalysts employed to promote these reactions, the use of gold species appears particularly attractive. Because of their soft Lewis acid and carbophilic character, gold catalysts could activate allenes selectively allowing the transformations of this moiety in the presence of different functional groups.[130] Allenes are the simplest cumulenes and are characterized by a central sp-hybridized carbon linked with double bonds with other two sp^2-hybridized carbon atoms. This unique bonding situation comprising of two orthogonal π-systems allows for the formation of up to four regioisomeric η^2 complexes of type **I**, depending on the substitution pattern (Scheme 3.1). The particular sp-hybridized central carbon can also give rise to η^1 σ-complexes, such as gold-stabilized allylic cations of type **II** or carbenes of type **III** (Scheme 3.1).[131]



Scheme 3.1

The coordination of gold to allenes activate them towards the addition of oxygen-, nitrogen- or carbon nucleophiles to the external or central carbons, giving rise to the corresponding hydrofunctionalization products (Scheme 3.2, Eq. 1). With π-systems as nucleophiles (alkenes, dienes, alkynes, allenes, ketones) the formation of a bond at the external allene carbon may be followed, in a stepwise or asynchronous concerted fashion, by the creation of a second C–C bond (Scheme 3.2, Eq. 2). Thus, allene can also be activated as formal 3-carbon dipoles in [3C+*n*] cycloaddition reactions. The reaction outcome will then depend on the evolution or trapping of the resulting gold carbenoid.

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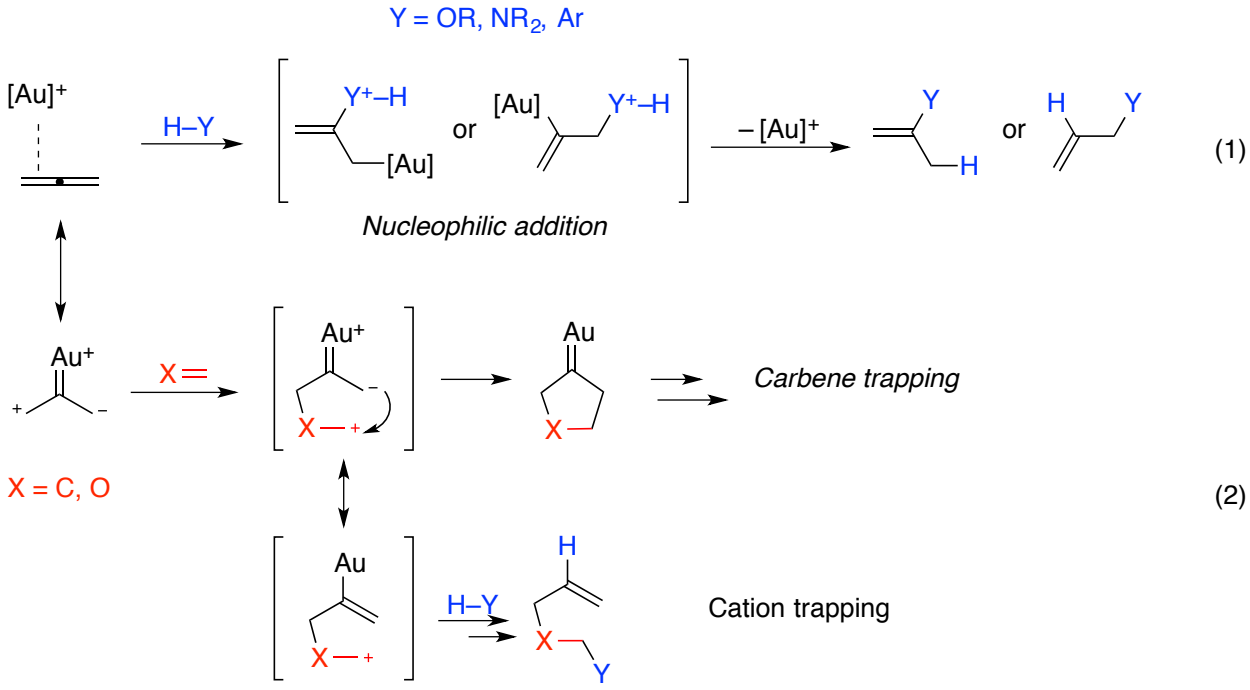
[129] a) N. Krause, A. S. K., *Modern Allene Chemistry*, Wiley-VCH, Weinheim, **2004**; b) S. Ma, *Chem. Rev.* **2005**, *105*, 2829-2871; c) N. Krause, *Cumulenes and Allenes, Science of Synthesis*, Thieme, Stuttgart, **2007**, vol. 44.

[130] M. Malacria, L. Fensterbank, V. Gandon, *Top. Curr. Chem.* **2011**, *302*, 157-182; b) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.

[131] For reviews on metal-allene complexes see: a) T. L. Jacobs, S. R. Landor, *The Chemistry of Allenes*, Academic Press., London, **1982**, vol. 2, p. 277; b) B. L. Shaw, A. J. Stringer, *Inorg. Chim. Acta Rev.* **1973**, *7*, 1-81.



Scheme 3.2

In the following section a selection of representative examples of gold-catalyzed transformations of allenes is discussed.

3.1.1.1 Gold-catalyzed nucleophilic addition to allenes

As indicate before, the activation of allene by gold catalysts can facilitate the addition of nucleophiles to these unsaturated systems. Hence, the reactions with oxygen-, nitrogen- or carbon-nucleophiles have been described generally for both inter- and intramolecular processes.[132]

A first example intramolecular hydroalkoxylation was given by Krause[133] in 2001, studying the cycloisomerization of allenyl carbinols **1** to yield 2,5-dihydrofurans **2** (Scheme 3.3). Similar approaches to **2** were also proposed more recently by Kim and Lee[134] and by Marco-Contelles.[135] Moreover enantioselective cycloisomerization reactions[136] have been reported as well.

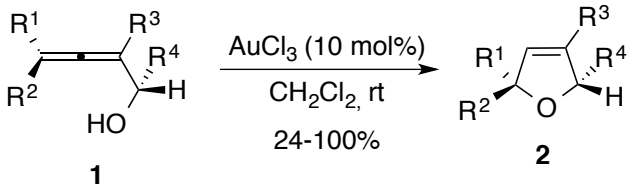
[132] For reviews on this topic see: a) C. H. Shen, *Tetrahedron* **2008**, *64*, 3885-3903; b) T. Lu, Z. Lu, Z. -X. Ma, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2013**, *113*, 4862-4904.

[133] a) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537-2538; b) N. Krause, A. Hoffmann-Röder, J. Cansius, *Synthesis* **2002**, 1759-1774.

[134] a) J. Park, S. H. Kim, P. H. Lee, *Org. Lett.* **2008**, *10*, 506-xxx; b) S. Kim,P. H. Lee, *Adv.Synth.Catal.* **2008**, *350*, 547-551;

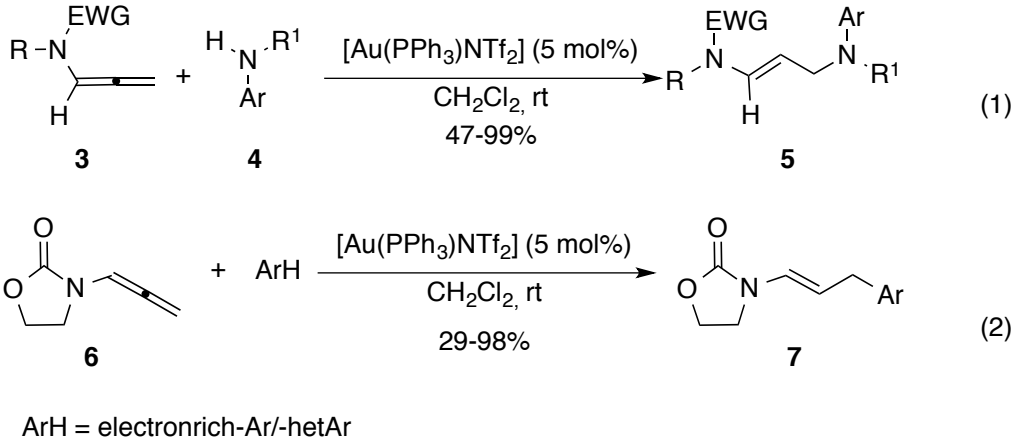
[135] B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano, J. L. Marco-Contelles, *Chem. Eur. J.* **2009**, *15*, 1901-1908.

[136] a) Z. B. Zhang, R. A. Widenhoefer, *Angew. Chem., Int. Ed.* **2007**, *46*, 283-285; b) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496-499.



Scheme 3.3

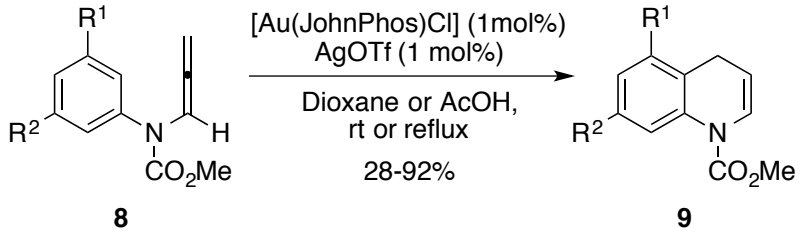
In a series of works, Kimber described the stereoselective hydroaminations of allenamides **3** with various amine derivatives as anilines **4** using cationic Au(I)-catalysis (Scheme 3.4, Eq. 1).[137] In this way, it was possible to prepare the corresponding enamides **5** with complete *E*-selectivity. Intermolecular hydroarylation of allenamides **6** were reported by Kimber as well.[138] Under very mild conditions, *E*-enamides **7** were prepared using of electron-rich arenes or heteroarenes as nucleophiles and cationic gold(I) catalysts (Scheme 3.14, Eq. 2).



Scheme 3.4

First gold-catalyzed intramolecular hydroarylation reactions of allenamides **8** were described by in Ohno in 2007.[139] These substrates in the presence of cationic gold(I) species afforded hydroquinones **9** derivatives in moderate to high yield (Scheme 3.5).

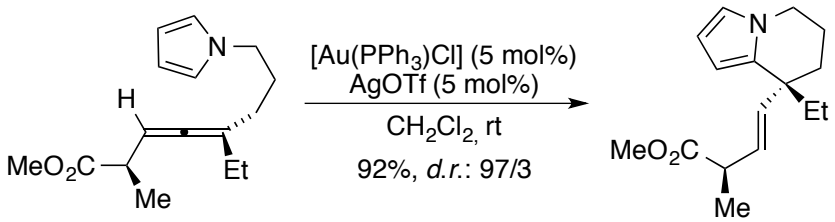
[137] A. W. Hill, M. R. J. Elsegood, M. C. Kimber, *J. Org. Chem.* **2010**, *75*, 5406-5409.
[138] C. Kimber, *Org. Lett.* **2010**, *12*, 1128-1131.
[139] T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2007**, *9*, 4821-4824.



8 **9**

Scheme 3.5

An interesting application of this reactivity was described by Nelson and coworkers in the enantioselective synthesis of (-)-Rhazinilam.[140] Thus, diastereomerically enriched allene **10** was subjected to Au-catalysis yielding the desired tetrahydroindolizine **11** in good yield, through intramolecular hydroarylation process. (Scheme 3.6). High regioselectivity was observed for all of the catalysts tested, but reactivity and chirality transfer were sensitive to the precise catalyst. In particular the use of [Au(Ph_3]Cl/AgOTf provided the best results in terms of yield and fidelity in the chirality transfer.



10

e.e: 99%
d.e.: >98%

11

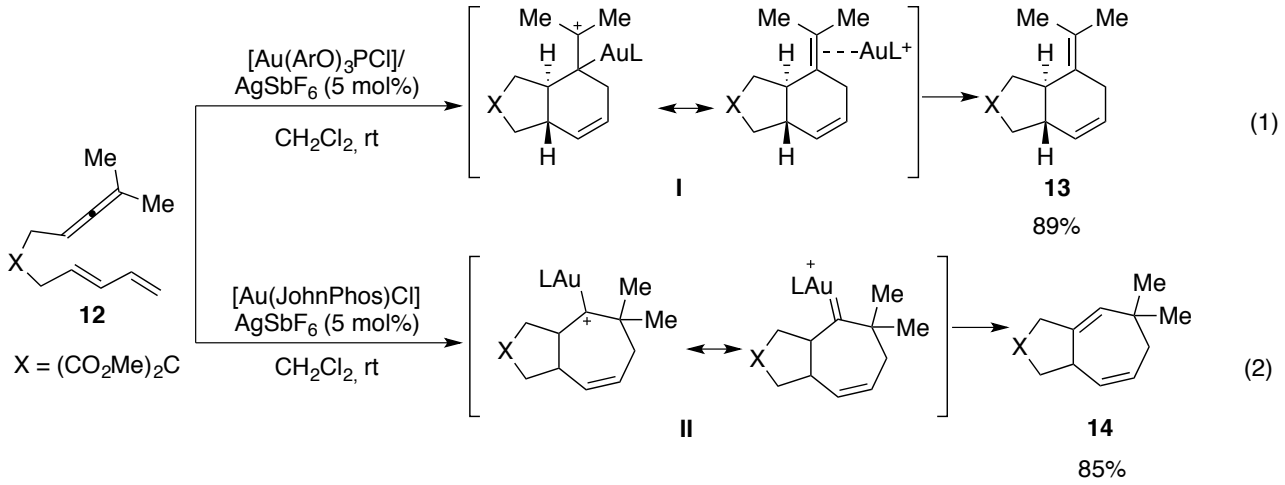
Scheme 3.6

[140] Z. S. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 10352-10353.

3.1.1.2 Gold-catalyzed cyclizations involving allenes

Gold-catalyzed cyclizations involving allenes represent a synthetic useful class of transformations and, in particular, intramolecular processes have been widely studied in the last years.[141]

An interesting example of selective [4+2] or [4+3] cycloaddition reactions of allene-diene **12** were reported by Toste in 2009 (Scheme 3.7).[142] In this work, the formation of 6- or 7-membered carbocycles could be achieved by a fine-tuning of the electronic properties of the ligand, which influence the stability of the postulated carbocations and translates into different outcomes. Thus, the use of π-acceptor-containing ligand phosphitegold(I) complex, decreased the stability of carbenoid intermediate **II**, favoring on the other side the formation of intermediate **I** and of [4+2]-cycloaddition product **13** (Scheme 3.3, Eq. 1). In contrast, cationic $[Au(JohnPhos)]^+$ catalyst, bearing electron rich σ-donor ligand, afforded the [4+3] cycloadduct **14** by stabilization of intermediate **II** (Scheme 3.3, Eq. 2). An enantioselective version of [4+3]-cyclization of substrates related to **12** has been also proposed by Mascareñas and coworkers by the use of a phosphoramidite-based gold catalyst.[143]



Scheme 3.7

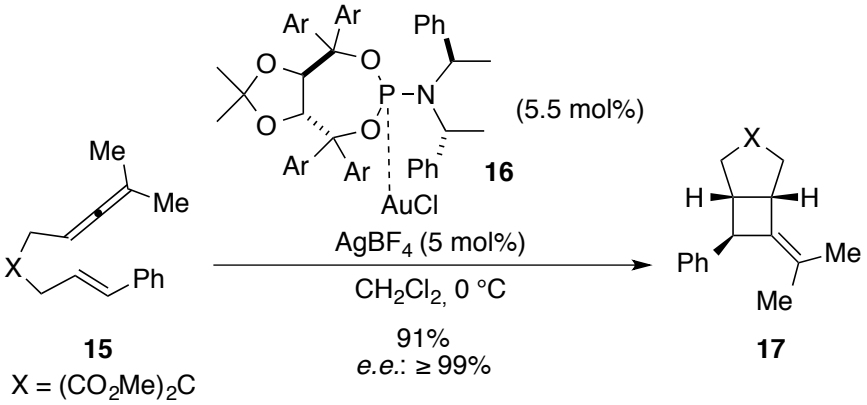
Not only [4+*n*] but also intramolecular [2+2] cycloadditions have been described when using 1,*n*-allenenes as recently reported by Fürstner. Thus, the cyclization of allenenene **15** afforded

[141] For some selected examples see: a) D. Benitez, E. Tkatchouk, A. Z. González, A. Z. Goddard, F. D. Toste, *Org. Lett.* **2009**, *11*, 4798-4801; b) B. Chen, W. Fan, G. Chai, S. Ma, *Org. Lett.* **2012**, *14*, 3616-3619, b) A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 4580-4533.

[142] P. Mauleón, R. M. Zeldin, A. Z. González, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6348-6349.

[143] I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledó, J. L. Mascareñas, *J. Am. Chem. Soc.* **2009**, *131*, 13020-13030.

cyclobutane derivative **17** was accomplished in high yield and with excellent enantioselectivity by using phosphoramide derived chiral cationic gold catalyst **16** (Scheme 3.8).



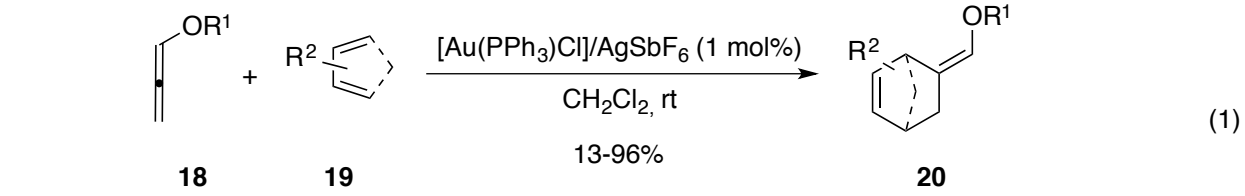
Scheme 3.8

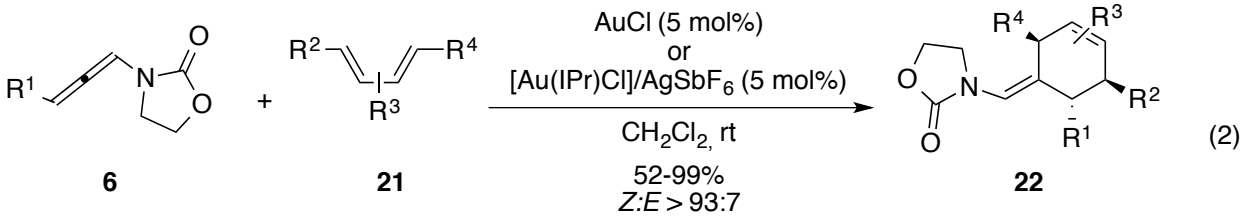
In contrast to the well established intramolecular cycloaddition of allenes, the extension of this strategy to an intermolecular process remains less explored and studies has been mainly focused on the use of allenamides. In fact, only in 2011 two examples of intermolecular [4+2] cycloaddition were described indipendently by Wang, Goeke[144] and Mascareñas[145] (Scheme 3.9).

In the first example simple allenyl ethers **18** were efficiently activated by a cationic gold(I) catalyst towards the cycloaddition with dienes **19**, leading regioselectively to the corresponding cyclohexene derivatives **20** (Scheme 3.9, Eq. 1).

On the other hand, the work of Mascareñas reported a gold-catalyzed intermolecular [4+2] cycloaddition of allenamides **6** and acyclic conjugated dienes **21**, providing regioselectively the cyclohexene derivatives **22**. In addition, the transformation showed a wide scope and generality and it can be catalyzed by simple AuCl or by *in-situ* generated the cationic gold(I) complexes (Scheme 3.9, Eq. 2).

[144]G. Wang, J. Zou, Z. Li, Q. Wang, A. Goeke, *Adv. Synth. Catal.* **2011**, *353*, 550-556.
[145] H. Faustino, F. López, L. Castedo, J. L. Mascareñas, *Chem. Sci.* **2011,** *2,* 633-637.

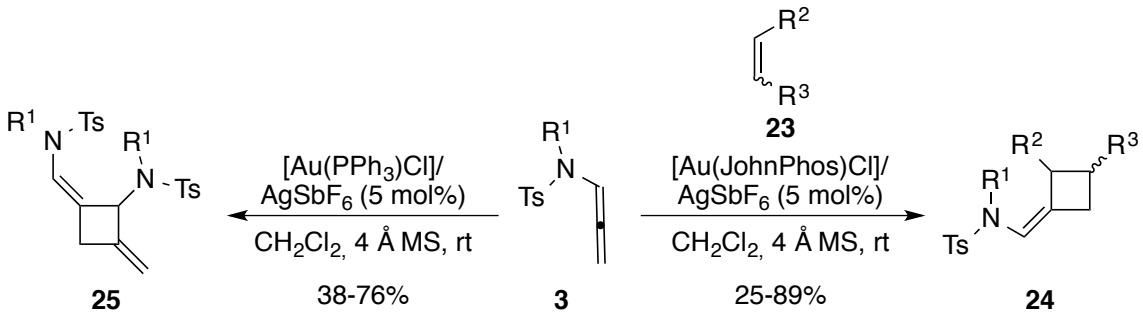




Scheme 3.9

The first examples of intermolecular [2+2] cycloaddition reaction catalyzed by gold were independently reported in 2012 by the groups of Chen,[146] González,[147] and Mascareñas.[148]

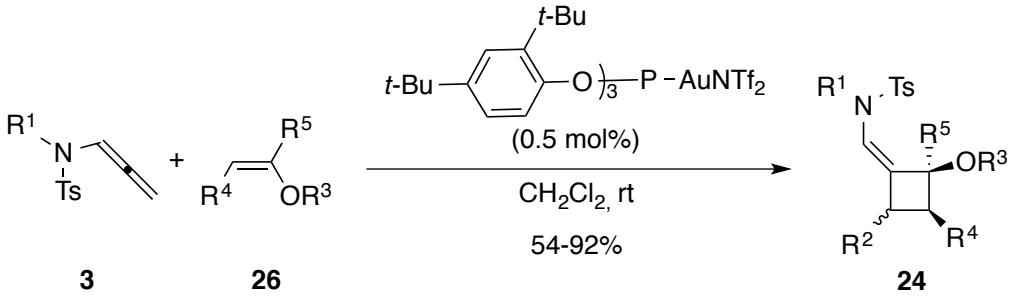
As described by Chen, a formal cycloaddition of *N*-tosylallenamides **3** with vinyl ethers or amides and electron-rich styrenes **23** afforded regioselectively functionalized cyclobutane adducts **24**. Furthermore, in the absence of the alkene, a dimerization of the allenamide **3** took place giving rise to cyclobutanes **25** (Scheme 3.10).



Scheme 3.10

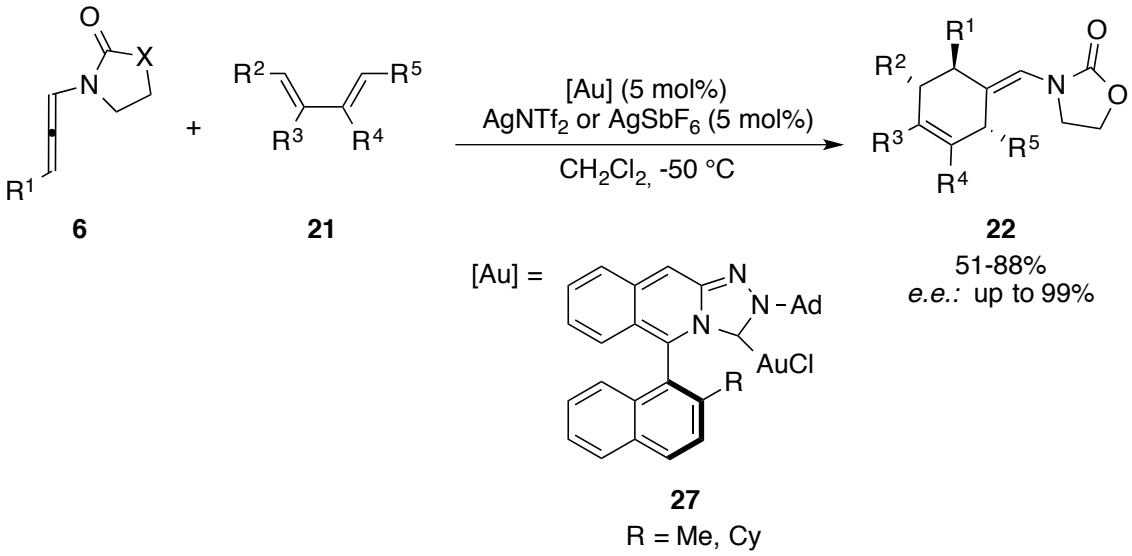
Moreover, González and coworkers established a more convenient reaction conditions as *N*-tosylallenamides **3** could also be employed in efficient and selective [2+2]-cycloadditions with enol ethers **26** using a phosphite cationic gold(I) catalyst having NTf_2^- as counter anion in a remarkable low catalyst loading of 0.5 mol% at ambient temperature (Scheme 3.11).

[146] X.-X. Li, L.-L. Zhu, Z. Chen, *Org. Lett.* **2012**, *14*, 436-439.
[147] S. Suarez-Pantiga, C. Hernandez-Díaz, M. Piedrafita, E. Rubio, J. M. Gonzalez, *Adv. Synth. Catal.* **2012**, *9*, 1651-1657.
[148] H. Faustino, P. Bernal, L. Castedo, F. López, J. L. Mascareñas, *Adv. Synth. Catal.* **2012**, *354*, 1658-1664.



Scheme 3.11

Subsequently, enantioselective versions of intermolecular [4+2] or [2+2] cycloaddition reactions were described. Mascareñas and coworkers reported in 2012 the first example of a highly enantioselective intermolecular [4+2] cycloaddition between allenamides **6** and acyclic dienes **21**, which also represents the first asymmetric intermolecular [4+2] cycloaddition promoted by a chiral carbophilic metal complex. A novel chiral gold catalyst **27** bearing a new class of C2-chiral ligands featuring a triazole unit embedded to rigid cyclic framework served to provide a variety of optically active cyclohexene derivatives **22** (Scheme 3.12).[149]

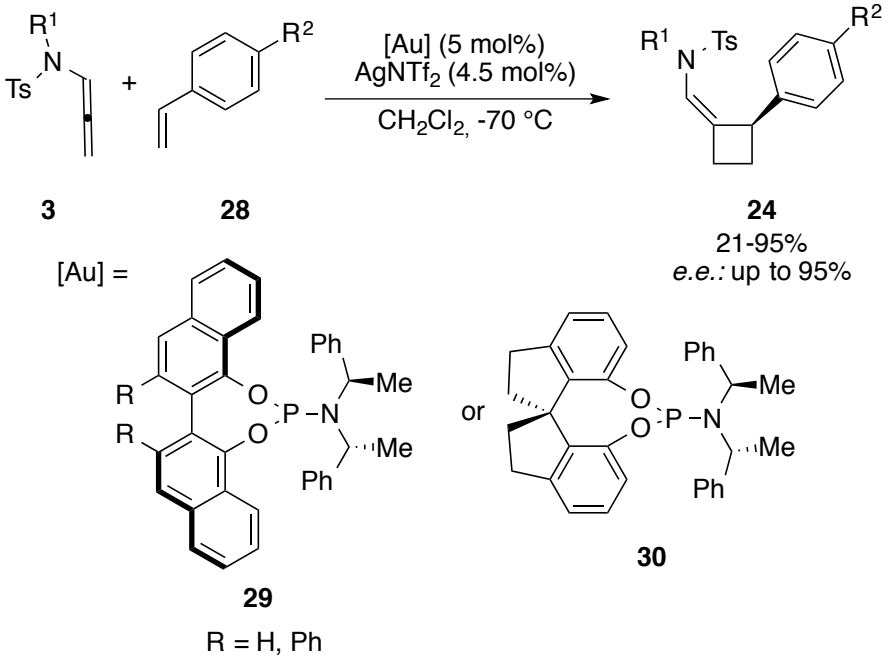


Scheme 3.12

González and coworkers reported the first example of the intermolecular gold-catalyzed asymmetric [2+2]-cycloaddition of *N*-sulfonylallenamides and styrenes (Scheme 3.13).[150] The high reactivity of the starting materials **3** and **28** towards gold catalysts required low reaction temperatures in order to avoid undesired reactions. These features were judiciously used by the authors to modulate the

[149] J. Francos, F. Grande-Carmona, H. Faustino, J. Iglesias-Sigüenza, E. Díez, I. Alonso, R. Fernandez, J. M.Lassaletta, F. López, J. L.Mascareñas, *J. Am. Chem. Soc.* **2012**, *134*, 14322-14325.
[150] S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2012,** *51*, 11552-11555.

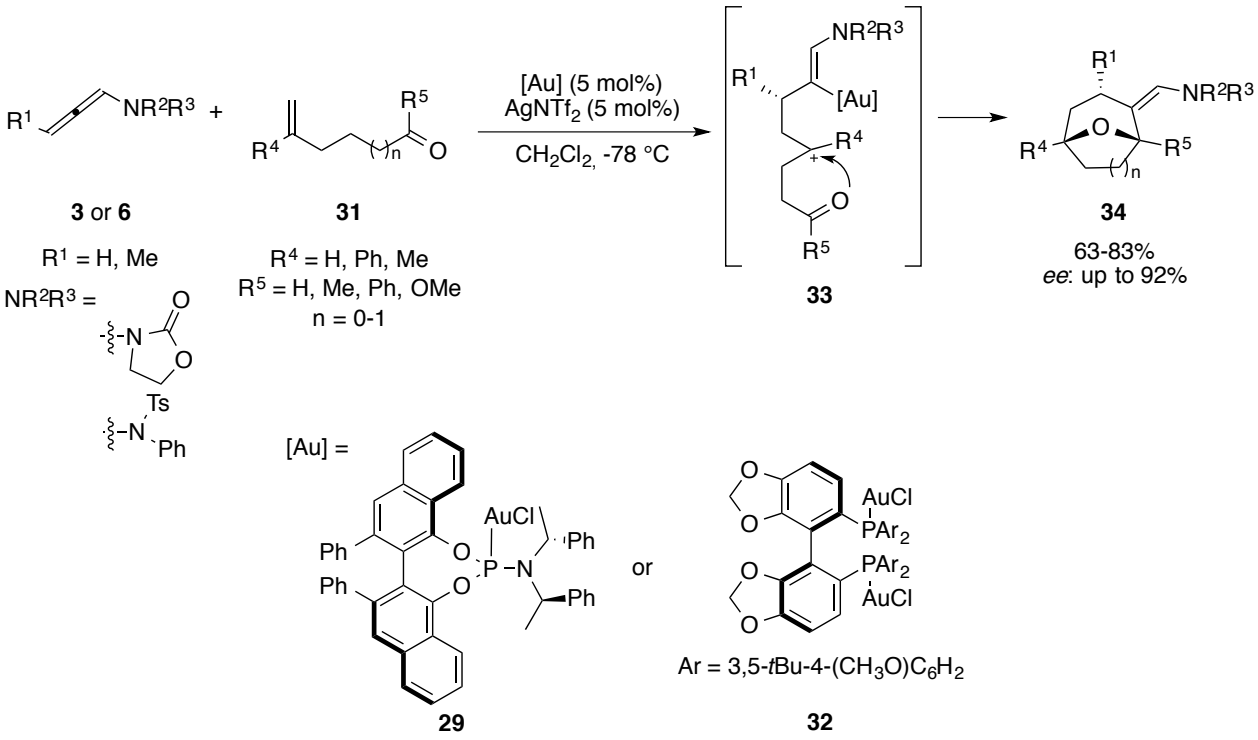
enantioselectivity of the process. Thus, ligands based on phosphoramidite scaffolds **29a** and **30** provided satisfactory stereocontrol to access optically active cyclobutane derivatives **24** with high yields and enantiomeric excesses up to 95%.



Scheme 3.13

Later, the group of Mascareñas described an interesting cascade cycloaddition between allenamides and carbonyl-tethered alkenes to provide oxa-bridged seven-, eight-, and even nine-membered carbocycles (Scheme 3.14).[151] The reaction proceeded by the interception of the carbocation **33**, formed during the addition of **3** or **6** to the alkene moiety of **31**, by the carbonyl group that acts as an internal nucleophile. In addition chiral diphosphine **32**/gold and/or phosphoramidite **29b**/gold catalysts led to 8-oxabicyclo[3.2.1]octanes **34** with relatively high enantiomeric excess.

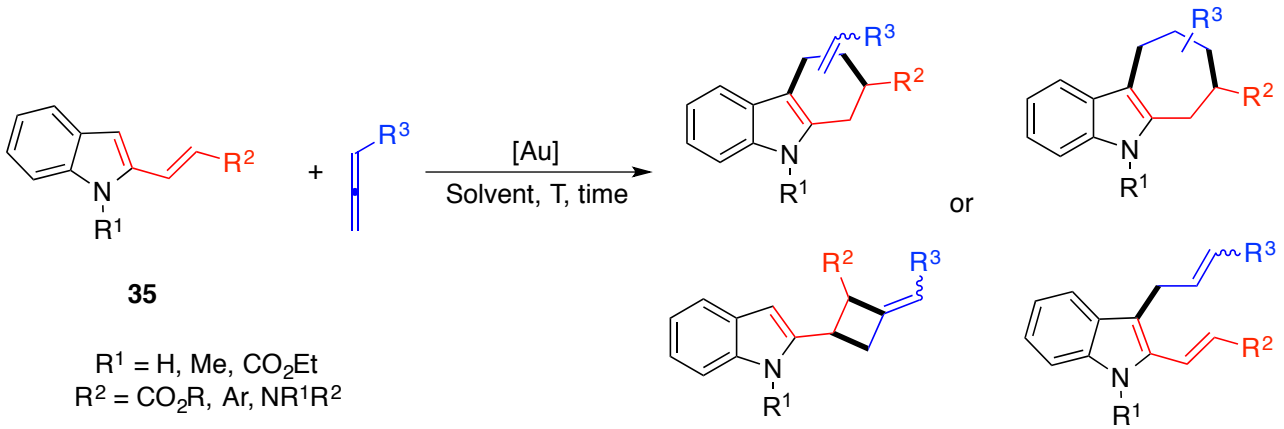
[151] H. Faustino, I. Alonso, J. L.Mascareñas, F. López, *Angew. Chem. Int. Ed.* **2013**, *52*, 6526-6530.


R1
NR2R3
+
R4
R5
n
O
[Au] (5 mol%)
AgNTf2 (5 mol%)
CH2Cl2, -78 °C
[Au]
3 or 6
31
R1 = H, Me
R4 = H, Ph, Me
R5 = H, Me, Ph, OMe
n = 0-1
NR2R3 =
Ts
Ph
33
34
63-83%
ee: up to 92%
[Au] =
AuCl
PAr2
or
Ar = 3,5-tBu-4-(CH3O)C6H2
29
32

Scheme 3.14

3.2 Objectives

On the basis of our preliminary studies on [4+2] cycloaddition reactions with 2-vinylindoles[152] and taking into account the recent literature on gold-catalyzed intermolecular cycloaddition reactions with allenes,[16-23] our objective was to test reactivity of vinylindoles **35** with allenes under gold catalysis. To this aim, a series of allenes bearing group with different electronic properties were prepared prepared and their reactivity tested in the presence of 2-vinylindoles **35** and a series of gold catalysts. According to the reactivity of the allenes, several features are challenging to achieve selective trasnformations. Thus, the reaction could lead to the formation of functionalized dehydrocarbazole derivatives through a [4+2] cycloaddition with various regio- and stereoselectivities. A [2+2]-cycloaddition with the vinyl group of the compound **35** could also be feasible. Moreover, as allenes can act as C3 synthons, a [4+3] cyclization pathway affording could also be operative.[14-15] In particular this last transformation would be attractive since, to the date, there are no reports involving an intermolecular [4+3] cycloaddition. Finally, hydroarylation of the allene by the electron-rich indole ring was also conceivable (Scheme 3.15).



Scheme 3.15

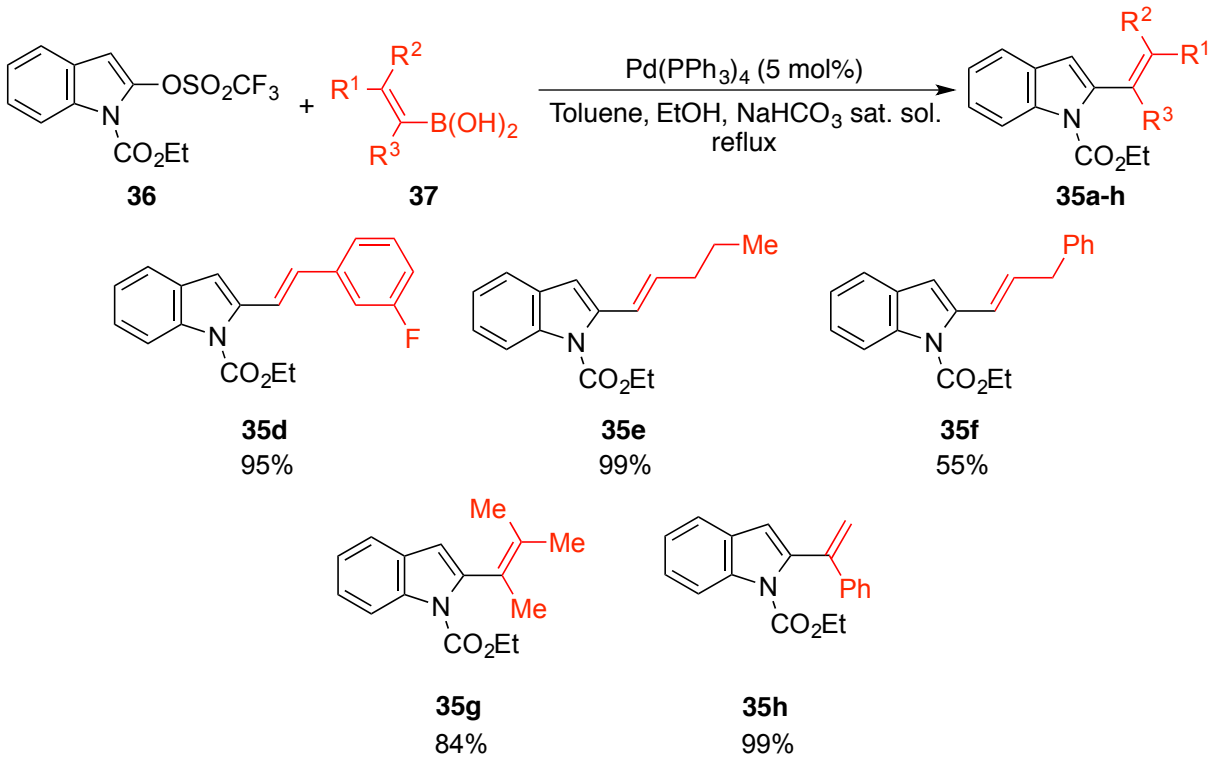
[152] a) G. Abbiati, V. Canevari, D. Facoetti, E. Rossi, *Eur. J. Org. Chem.* **2007**, 517-525; b) V. Pirovano, G. Abbiati, M. Dell'Acqua, D. Facoetti, M. Giordano, E. Rossi, *Synlett* **2012**, 2913-2918; c) V. Pirovano, M. Dell'Acqua, D. Facoetti, D. Nava, S. Rizzato, G. Abbiati, E. Rossi, *Eur. J. Org. Chem.* **2013**, 6267-6269.

3.3.1 Synthesis of starting materials

In this study, allenes bearing group with different electronical properties, as well as vinylindoles have been employed. Synthesis of 2-vinylindoles **35a-c, i, j**, 2-vinylbenzofuran derivative **TT**, as well as the precursor of these compounds has already been described in Chapter 2.

3.3.1.1 Synthesis of vinylindoles **35**

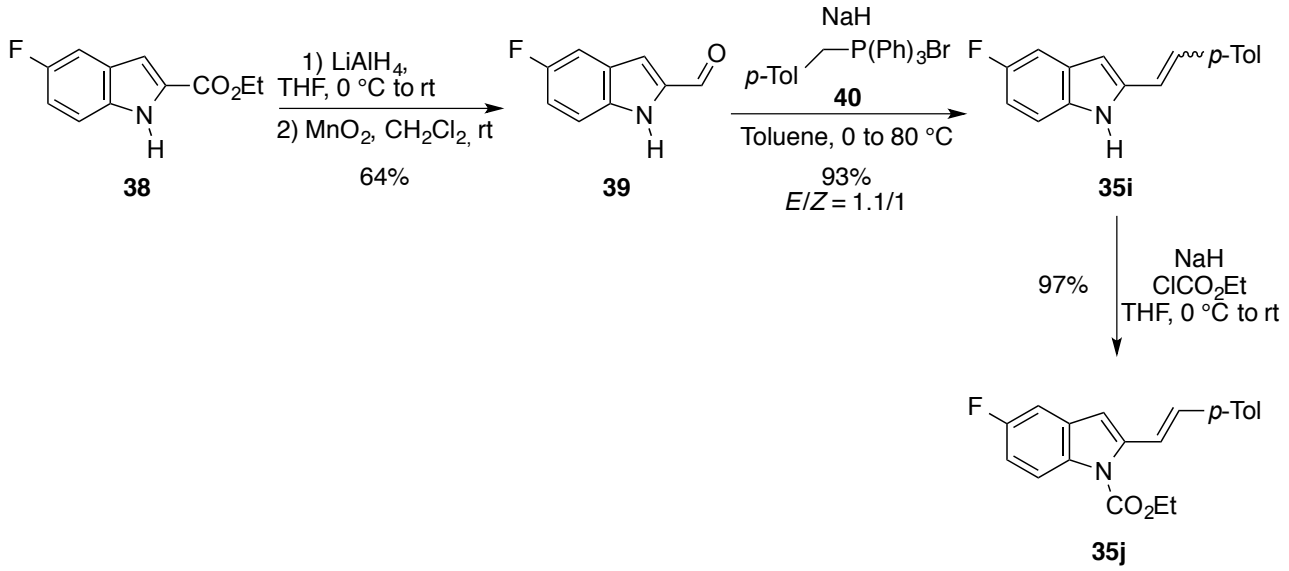
2-Vinylindoles **35a-h** were prepared according to the procedure described in Chapter 2.[153] Scheme 3.16 reports only the new indole derivatives that have been synthetized. These compounds were prepared via palladium-catalyzed cross-coupling reaction of 2-trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester **36** with the corresponding boronic acids **37**, in general high yields (Scheme 3.16).



Scheme 3.16

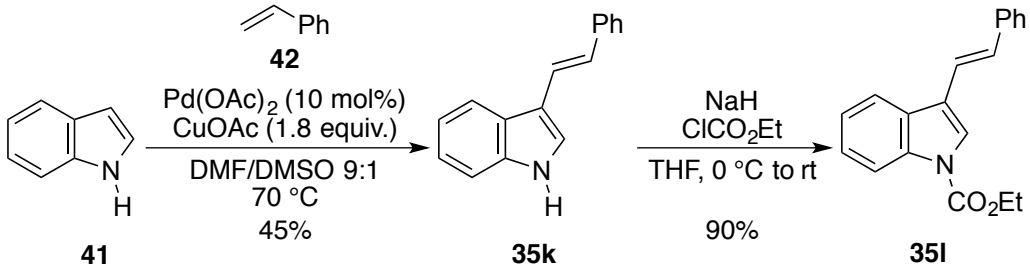
[153] E. Rossi, G. Abbiati, V. Canevari, G. Celentano, *Synthesis* **2006**, 299-304.

5-Fluoro 2-vinylindole (**35j)** was prepared starting from commercially available 5-fluoro-1*H*-indole-2-carboxylate (**38**) in four steps (Scheme 3.17). A reduction with lithium aluminum hydride and subsequent reoxidation yielded aldehyde **39**. A subsequent Wittig reaction with bromo(4-methylbenzyl)triphenylphosphorane (**40**) afforded a separable mixture of *E*- and *Z*-5-fluoro-2-(4-methylstyryl)-1*H*-indole isomers (**35i)** in 93% overall yield (*E:Z* = 1.1:1). Finally, protection of nitrogen atom, performed only on the *E*-isomer, led to the desired vinylindole **35j**.



Scheme 3.17

3-Vinylindole **35l** was obtained in two steps from indole (**41**). A palladium-catalyzed oxidative coupling on indole with styrene (**42)** led to **35k**,[154] which was protect as indicated above to yield **35l** in a useful overall yield (Scheme 3.18).

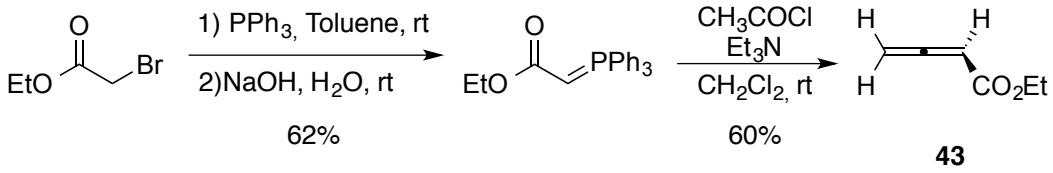


Scheme 3.18

[154] N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2005**, *44*, 3125-3129.

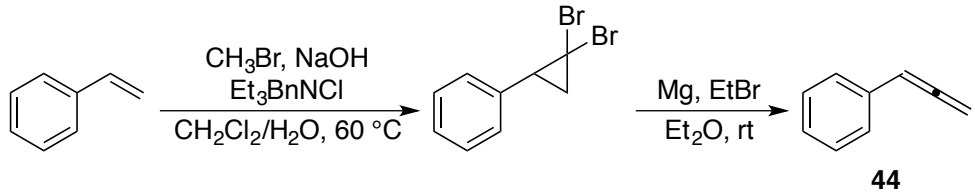
3.3.1.2 Synthesis of allenes

A series of allenes was synthesized following different known procedures. Allenic ester **43** was obtained via standard Wittig reaction as indicated in Scheme 3.19.[155]



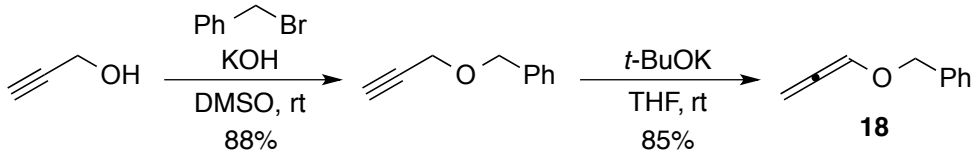
Scheme 3.19

Phenylallene (**44**) was prepared following the method described by Brandsma, via cyclopropanation of styrene with dibromocarbene followed by treatment with ethylmagnesium bromide 3.20.[156]



Scheme 3.20

The allenyl ether **18** was prepared from propargyl alcohol by a sequential alkylation with benzyl bromide followed by a base-catalyzed isomerization (Scheme 3.21).[157]



Scheme 3.21

N-Allenamides **3a, b** and **6a, b** were prepared in a similar manner from propargyl amides and their subsequent isomerization (Scheme 3.22, Eq. 1 and 2 for **3a, b** and Eq. 3 for **6a, b**).[158]

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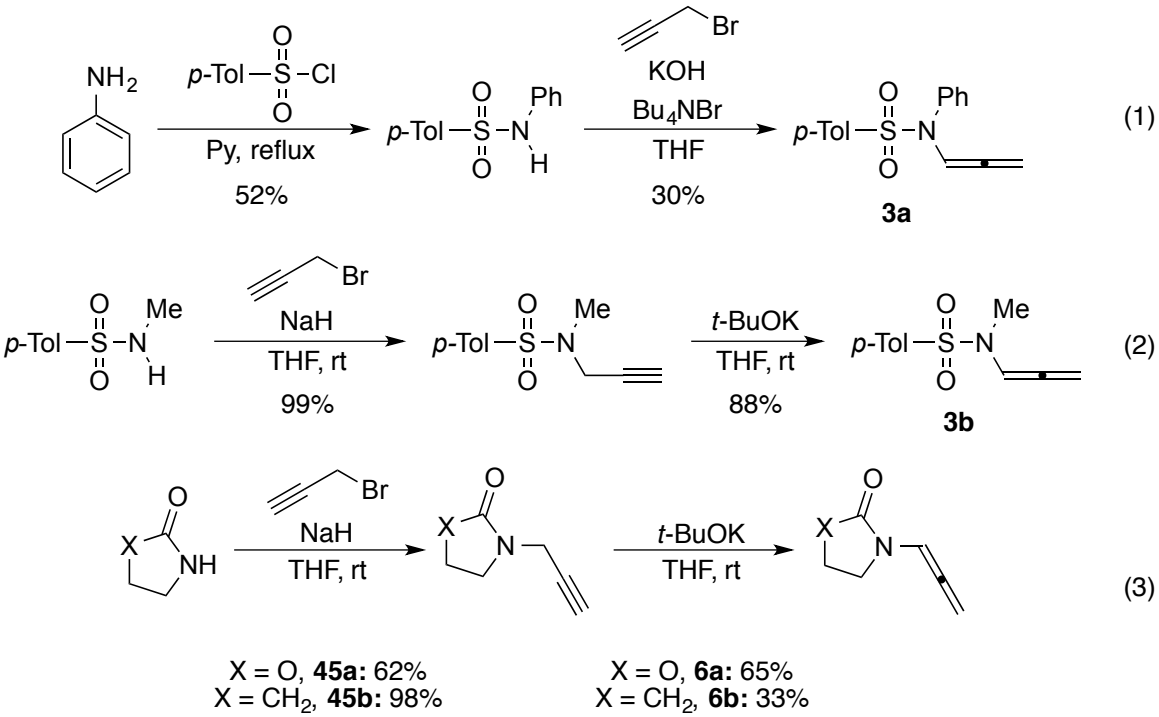
[155] L. Rout, A. M. Harned, *Chem. Eur. J.* **2009**, *15*, 12926-12928.
[156] R. J. de Lang, L. Brandsma, *Synth. Commun.* **1998**, *28*, 225-232.
[157] B. M. Trost, J. Xie, *J. Am. Chem. Soc.* **2006**, *128*, 6044-6045.

[158] a) A. González-Gómez, G. Domínguez, J. Pérez-Castells, *Eur. J. Org. Chem.* **2009**, 5057-5062; b) S. Suárez-Pantiga, C. Hernández-Díaz, M. Piedrafita, E. Rubio, J. M. González, *Adv. Synth. Catal.* **2012**, *354*, 1651-1657; c) L. L. Wei, J. A. Mulder, H. Xiong, C. A. Zificsak, C. J. Douglas, R. P. Hsung, *Tetrahedron* **2001**, *57*, 459-466.


NH2
p-Tol—S(=O)2—Cl
Py, reflux
52%
p-Tol—S(=O)2—N(Ph)H
Br
KOH
Bu4NBr
THF
30%
p-Tol—S(=O)2—N(Ph)
3a
(1)
p-Tol—S(=O)2—N(Me)H
Br
NaH
THF, rt
99%
p-Tol—S(=O)2—N(Me)
t-BuOK
THF, rt
88%
p-Tol—S(=O)2—N(Me)
3b
(2)
X
NH
Br
NaH
THF, rt
t-BuOK
THF, rt
(3)
X = O, 45a: 62%
X = CH2, 45b: 98%
X = O, 6a: 65%
X = CH2, 6b: 33%

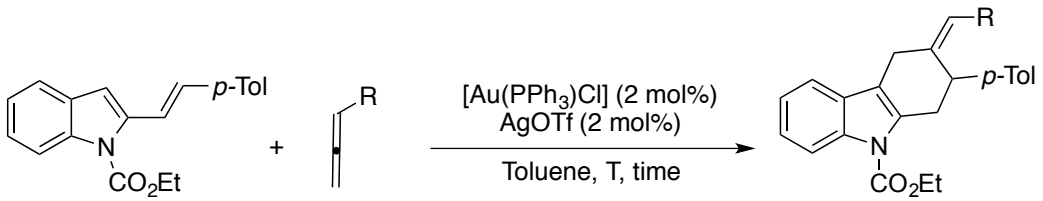
Scheme 3.22

3.3.2 Gold-catalyzed cycloaddition reactions between vinylindoles and allenes

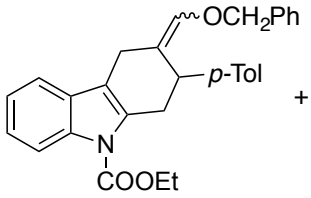
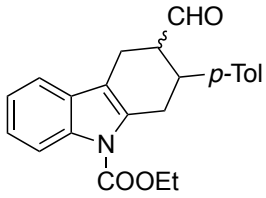
3.3.2.1 Initial studies

The reactivity of representative allenes **43**, **44** and **18** with diverse electronic properties towards indole **35a** in the presence of a cationic gold catalyst generated by the *in situ* reaction between [Au(PPh3)Cl] and AgOTf was tested (Table 3.1). The selection of the catalytic system was based on the proved effectivity in cycloaddition reactions of various 2-vinylindoles with α,β-unsaturated compounds, as disclosed in the previous chapter.

Table 3.1: Reaction between 2-vinylindole 35a and allenes 43, 44 and18 with various electronic properties



35a **43**, **44** or **18** **45**

Entry	R	Time, h	T, °C	Products, Yield, %	
1	CO_2Et **43**	24	rt to reflux	–	
2	Ph **44**	24	rt to reflux	–	
3	OCH_2Ph **18**	6	rt	 **45** 30%	 **46** 28%
4	OCH_2Ph **18**	1.5	-20	**45** 30%	**46** 15%

Reaction conditions: Entries 1 and 2, to a solution of the god catalyst in toluene (2 mL) **35a** and a solution of **43** or **44** were added and the mixture stirred for 6 h at rt and for 18 h at 110 °C. Entries 3 and 4, to a solution of gold catalyst in toluene (2 mL), **35a** and a solution of **18** in toluene (1.3 mL) were added at rt or at -20 °C and the mixture stirred at the same T for 6 or 1.5 h respectively.

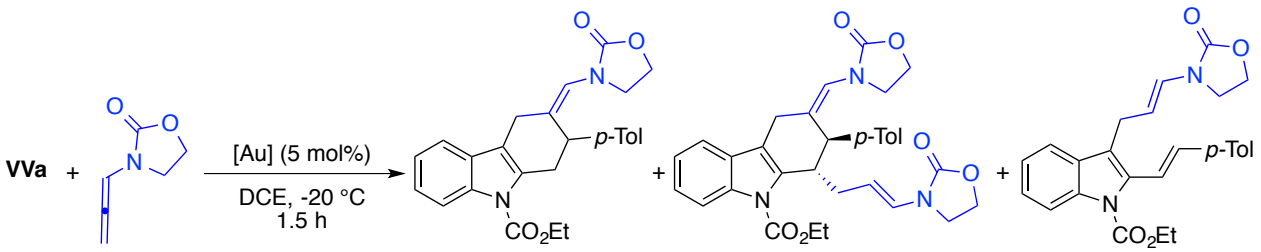
Under the evaluated reaction conditions, both ethyl 2,3-butadienoate (**43**) and phenylallene (**44**) did not give rise to any product, leading to the recovery of unreacted starting material **35a** and allene degradation. Even an increase of the reaction temperature to 110 °C was not effective (entry 1-2).

On the contrary, when ((propa-1,2-dien-1-yloxy)methyl)benzene (**18**) was employed, a mixture of [4+2] cycloadducts **45** and **46** was obtained in moderate combined yield. Tetrahydrocarbazole derivative **45** was obtained as a mixture of stereoisomers on the exocyclic double bond. Moreover, compound **46** likely arose from the hydrolysis of compound **45** during isolation and purification of the reaction mixture, probably due to the sensibility of the enol ether moiety. It is noteworthy that the reaction of the vinylindole **35a** with the allene **18** proceeded with complete chemo- and regioselectivity, being the terminal double bond of the allene the only one involved in the cycloaddition reaction. A decrease of the temperature until -20 °C was not reflected in any increase of the yield (entry 4).

Taking into account the ability of *N*-allenamides as C–2 synthon in gold-catalyzed cycloaddition reactions,[17-22] the behavior of these compounds towards vinylindoles in the presence of gold was then evaluated. Additionally, in the event of a cycloaddition reaction the new product should likely be more stable than the obtained in the reaction with alkoxyallene **18**, facilitating the purification steps.

In a preliminary experiment, vinylindole **35a** was reacted with 1.5 equivalents of *N*-allenamide **6a** in the presence of *in situ* generated cationic gold(I) catalyst $[Au(PPh_3)]^+$ in 1,2-dichloroethane at -20 ºC. Under this reaction conditions, the tetrahydrocarbazole **47a** arising from a [4+2] cycloaddition was isolated in 50% yield along with an unexpected tetrahydrocarbazole **48a** (15%) and the hydroarylation product **49a** (10%) In order to exclude any direct catalytic activity of the silver salt,[159] the reaction was performed under the previous conditions but using the preformed cationic gold catalyst $[Au(PPh_3)(NTf_2)]$. As before, the cationic gold species afforded **47a** in 48% yield and **48a** in 33%, while no hydroarylation product was observed (Scheme 3.23).

[159] D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012-9019.



35a (1.5 equiv.)	47a	48a	49a
[Au] = [Au(PPh$_3$)Cl]/AgOTf	50%	15%	10%
[Au(PPh$_3$)(NTf$_2$)]	48%	33%	-

Scheme 3.23

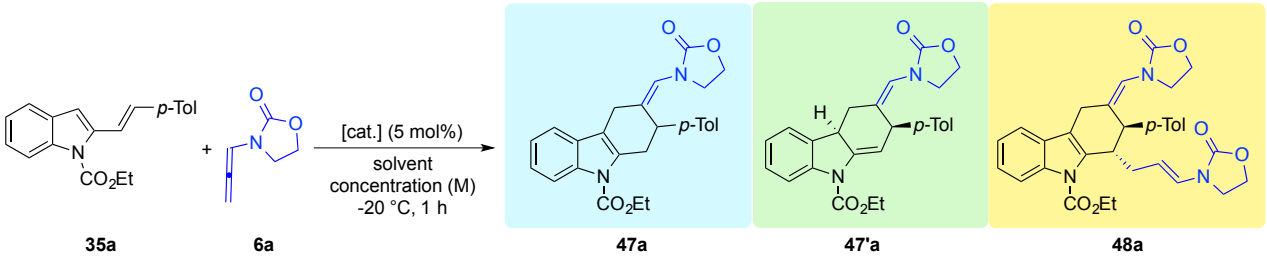
Interestingly, tetrahydrocarbazole **47a** was obtained as a single chemo-, regio- and stereoisomer, being the terminal double bond of the allene the only one involved in the reaction. Moreover, compound **48a** shows interesting features: (*i*) it was obtained also as a single isomer in a chemo-, regio- and stereoselective manner and, (*ii*) the overall reaction resulted in the formation of a three-component product (1 molecule of vinylindole and two molecules of the allene), a process which is less common in gold catalysis[160] and not reported before in cycloadditions with allenamides. Considering the interest of both products, a more detailed study directed towards the identification of reaction conditions that enabled the selective formation of **47a** or **48a** was then carried out.

3.3.2.2 Screening of reaction conditions

A screening of gold catalysts, solvents and temperatures was conducted in order to identify selective reaction conditions as disclosed in Table 3.2.

[160] For some recent examples on gold-catalyzed multicomponent reactions see: a) X. Zhang, A. Corma, *Angew. Chem. Int. Ed.* **2008**, *47*, 4358-4361; b) A. D. Melhado, W. E. Brenzovich, A. Lackner, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8885-8887; c) Y. Suzuki, S. Naoe, S. Oishi, F. Shinja, N. Fujii, H. Ohno, *Org. Lett.* **2012**, *14*, 326-329; d) D. M. Schultz, N. R. Babij, J. P. Wolfe, *Adv. Synth. Catal.* **2012**, *354*, 345-355; e) H. von Wachenfeld, P. Roese, F. Paulsen, N. Loganathan, D. Strand, *Chem. Eur. J.* **2013**, *19*, 7982-7988.

Table 3.2: Screening of conditions for the reaction between 35a and 6a



						Yield (%)[a]		
Entry	Eq. 35a	Eq. 6a	[cat.]	Solvent	C (M)	47a	47'a	48a
1	1	1.5	[Au(PPh$_3$)(NTf$_2$)]	DCE	0.1	48	-	33
2	1	1.5	[Au(IPr)(NTf$_2$)]	DCE	0.1	15	44	35
3	1	1.5	[Au(JohnPhos)NTf$_2$]	DCE	0.1	16	51	33
4	1	1.5	[Au((ArO)$_3$P)(NTf$_2$)]	DCE	0.1	44	19	32
5	1	0.9	[Au(PPh$_3$)(NTf$_2$)]	DCE	0.1	52	-	7
6	1	0.9	[Au(PPh$_3$)(NTf$_2$)]	DCE	0.1	54	-	9
7	1	0.9	[Au(PPh$_3$)(NTf$_2$)]	DCE	0.05	46	-	26
8	1	0.9	[Au(PPh$_3$)(NTf$_2$)]	PhMe	0.1	24	27	63
9	1	0.9	[Au(PPh$_3$)(NTf$_2$)]	THF	0.1	42	13	25
10	1	0.9	[Au(PPh$_3$)(NTf$_2$)]	CH_2Cl_2	0.1	55	-	13
11[b]	1	0.9	[Au(PPh$_3$)(NTf$_2$)]	CH_2Cl_2	0.1	68	-	13
12	1	0.9	[Au(IPr)(NTf$_2$)]	DCE	0.1	5	75	-
13	1	0.9	[Au((ArO)$_3$P)(NTf$_2$)]	DCE	0.1	65	18	-
14	1	0.9	[Au(JohnPhos)NTf$_2$]	DCE	0.1	-	81	8
15	1	0.9	[Au(JohnPhos)NTf$_2$]	DCE	0.05	-	79	-
16	1	0.9	[Au(JohnPhos)NTf$_2$]	CH_2Cl_2	0.05	-	80	-
17	1	0.9	[Au(PPh$_3$)Cl]	CH_2Cl_2	0.1	-	15	-
18	1	0.9	[Au(JohnPhos)SbF$_6$]	CH_2Cl_2	0.1	-	80	-
19	1	0.9	$AuCl_3$	CH_2Cl_2	0.1	74	-	-
20[c]	1	0.9	$AuCl_3$	CH_2Cl_2	0.1	83	-	-
21	1	2.5	[Au(PPh$_3$)(NTf$_2$)]	CH_2Cl_2	0.1	17	-	70
22	1	2.5	[Au(JohnPhos)NTf$_2$]	CH_2Cl_2	0.1	-	-	99
23	1	2.5	[Au(JohnPhos)SbF$_6$]	CH_2Cl_2	0.1	-	-	99

Reaction conditions:entries 1-5 and 21, to a solution of **35a** and **6a** in the indicated solvent (2 mL) at -20 ºC, catalyst was added and the mixture was stirred for 1h at the same temperature. Entries 6-20 and 22-23, to a solution of **35a** and the gold catalyst in the indicated solvent (1 mL) at -20 ºC, a solution of **6a** (1 mL) was added dropwise via syringe and the mixture was stirred for 1h at the same temperature.

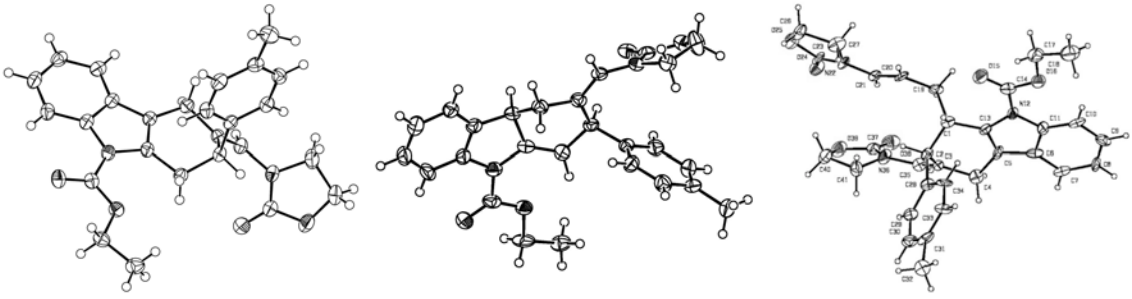
[a]: Isolated yields; [b]: at -70 °C; [c]: at -50 °C; [d]: reaction time was 24 h.

(IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; (ArO)$_3$P = tris(2,4-di-*tert*-butylphenyl) phosphite).

A first screening with various gold(I) catalysts was unsuccessful since both **47a** and **48a** were formed during the reaction, along with non-aromatized carbazole **47'a** which could be also detected and isolated (entries 1-4). In contrast, the reduction of the amount of *N*-allenamide **6a** to 0.9 equivalents in combination with an appropriate choice of the catalyst and the concentration turned out to be relevant for the selectivity (entries 5-20). In particular the use of simple $AuCl_3$ at -50 °C in dichloromethane afforded **47a** as single product in 83% yield (entry 20), while [Au(JohnPhos)(NTf_2)] at -20 °C led preferentially to the formation of **47'a** in 80% yield (entry 16). Dichloromethane revealed to be the best solvent (entry 8-10) and a dilution of the reaction mixture to 0.05 M demonstrated to be important for the selective synthesis of **47'a** (entry 14-15). It was also observed that better yields of product **47a** were obtained operating at lower temperatures (entries 19-20). Moreover, the dropwise addition of allene **6a** was preferred, since despite providing similar results in terms of yield, it provided cleaner and easy-to-purify reaction mixtures.

The selective synthesis of multicomponent product **48a** was also investigated. As supposed, this process was favored by the use of an excess of allene (entries 21-23). Thus, the use of 2.5 equivalents of the allene and [Au(JohnPhos)(NTf_2)] as catalyst at -20 °C in dichloromethane led to the exclusive formation of **48a**, being a quantitative transformation when the addition of the allene was accomplished dropwise (entries 21-22). No influence could be attributed to the presence of a different counterion such as SbF_6^- (entries 16 and 18, 22 and 23).

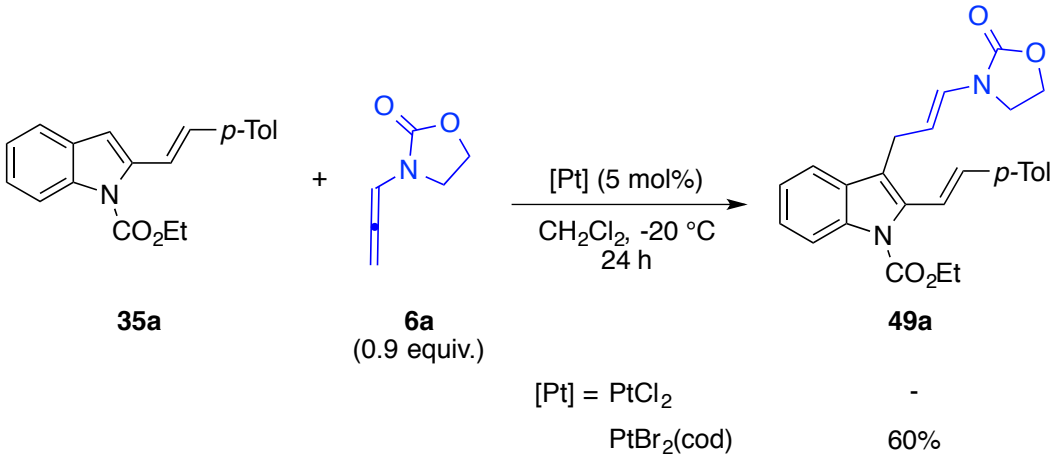
Structures of **47a-47'a** and of **48a** were determined by 1D-(^{1}H, APT) and 2D-NMR (COSY, NOESY, HETCOR, HMBC) analysis. Moreover, they were confirmed by X-ray analysis (Figure 3.1).



47a **47'a** **48a**

Figure 3.1

A comparison with platinum species was also accomplished. Interestingly, simple $PtCl_2$ did not afford any product even after prolonged reaction times, while in the presence of $PtBr_2$(cod) complex, the hydroarylation product **49a** was exclusively obtained in 60% yield (Scheme 3.24).



Scheme 3.24

According to the screening study, the following conditions from Table 3.2 were chosen to obtain selectively each of the three cycloadducts:

(a) Compound **47**, entry 20: $AuCl_3$ (5 mol%), CH_2Cl_2, -50 °C, 0.1 M;

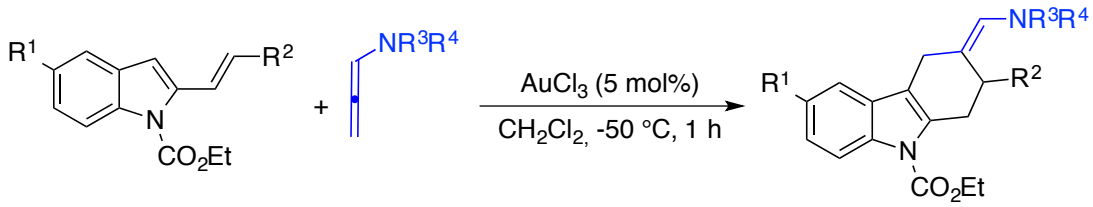
(b) Compound **47'a**, entry 16: [Au(JohnPhos)(NTf_2), CH_2Cl_2, -20 °C, 0.05 M;

(c) Compound **48a**, entry 22: [Au(JohnPhos)(NTf_2), CH_2Cl_2, -20 °C, 0.1 M.

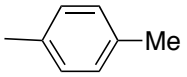
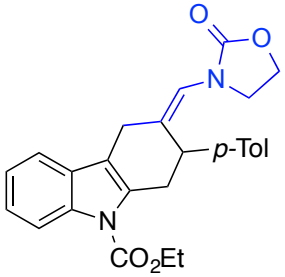
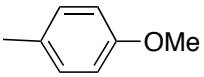
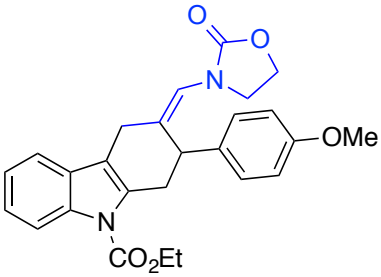
3.3.2.3 Scope for the synthesis of tetrahydrocarbazole derivatives **47**

Having in hand the optimized reaction conditions for the selective synthesis of **47a-47'a** and **48a**, we next evaluate the scope of these cycloadditions. Synthesis of various tetrahydrocarbazoles **47a-z** was achieved by the reaction of the corresponding vinylindoles **47** and *N*-allenamides **3a-b** and **6a-b** as summarized in Table 3.3.

Table 3.3: Scope for the synthesis of derivatives 47

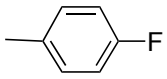
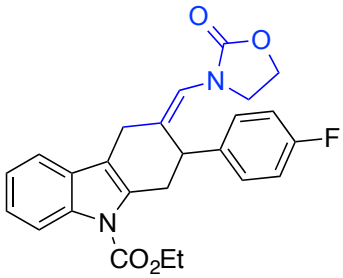
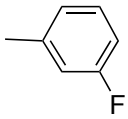
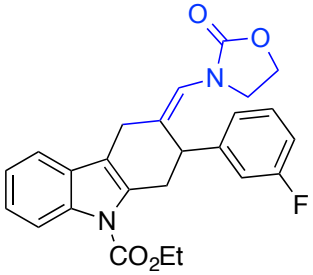
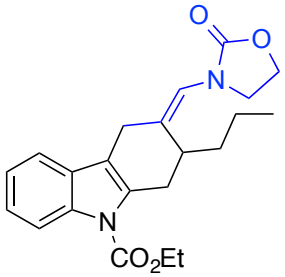
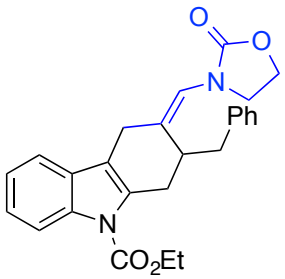
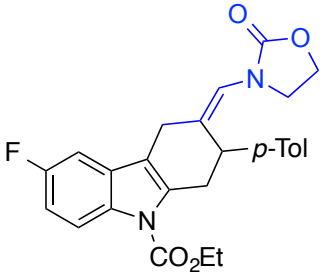


35 **3** or **6** **47**

Entry	35	R^1	R^2	3 or 6	Product	Yield,[a] %
1	**35a**	H		**6a**	 **47a**	83
2	**35b**	H		**6a**	 **47b**	83

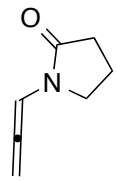
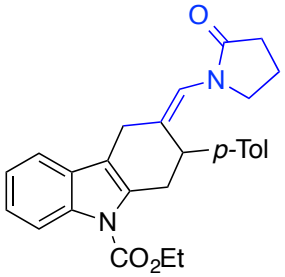
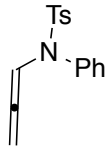
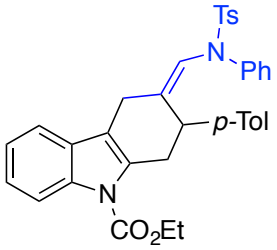
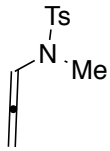
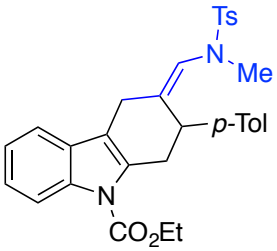
continues on the next page

Table 3.3: Scope for the synthesis of derivatives 47

Entry	35	R^1	R^2	3 or 6	Product	Yield,[a] %
3	**35c**	H		**6a**	 **47c**	72
4	**35d**	H		**6a**	 **47d**	75
5	**35e**	H	*n*-Pr	**6a**	 **47e**	44
6	**35f**	H	Bn	**6a**	 **47f**	32
7	**35j**	F	*p*-Tol	**6a**	 **47g**	92

continues on the next page

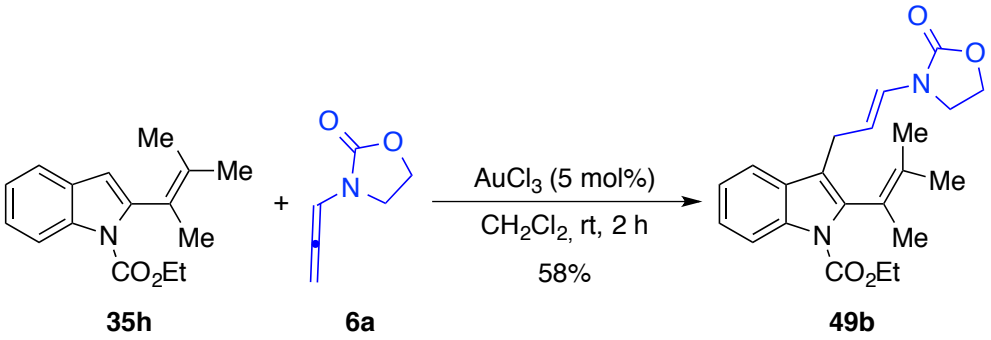
Table 3.3: Scope for the synthesis of derivatives 47

Entry	35	R^1	R^2	3 or 6	Product	Yield,[a] %
9	**35a**	H	*p*-Tol	 **6b**	 **47h**	75
10	**35a**	H	*p*-Tol	 **6a**	 **47i**	93[b] *E*:*Z* = 6:1
11	**35a**	H	*p*-Tol	 **3b**	 **47j**	91[b]

Reaction conditions: To a solution of **35** and $AuCl_3$ in dichloromethane (1 mL) at -50 ºC, a solution of allene **3** or **6** (1 mL) was added dropwise via syringe and the mixture was stirred for 1h at the same temperature. [a]:Isolated Yields; [b]:reaction was conducted at -70 °C, c = 0.01 M.

Firstly, we tested some vinylindoles bearing arenes with different electronic properties at β-position (entries 1-4) along with allenamide **6a**; the corresponding tetrahydrocarbazoles **35a-d** were always obtained in high yields, demonstrating that both electronwithdrawing as well as electrondonating groups on the aryl moiety were well tolerated. Under the optimized reaction condition β-alkyl substituted vinylindoles were also converted into the desired tetrahydrocarbazole **47e-f** albeit with lower yields (entries 5-6). Substitution of the C–5 of indole ring was allowed and indole **35j** was converted into tetrahydrocarbazole **47g** in high yield (entry 9). Modifications on the allenamide partner were subsequently tried. *N*-Allenyl amide derived from 2-pyrrolidone **6b** or tosylamides **3a,b** were employed obtaining the corresponding products **57h-j** in high yields (entries 9-11). The use of **3a,b** required the modification of the reaction conditions in order to avoid the formation of side-products derived from the dimerization of these substrates. In particular the reaction was diluted up to 0.01 M and the temperature was decreased to -70 °C (entries 10-11).

On the other hand, the use of β,β'-disubstituted vinylindole **35h** did not afford the desired cycloaddition product but the corresponding hydroarylated derivative **49b**, even when operating at room temperature (Scheme 3.25).



Scheme 3.25

Representative ^{1}H- and ^{13}C-NMR for product **47a** are showed in Figures 3.2 and 3.3, respectively.

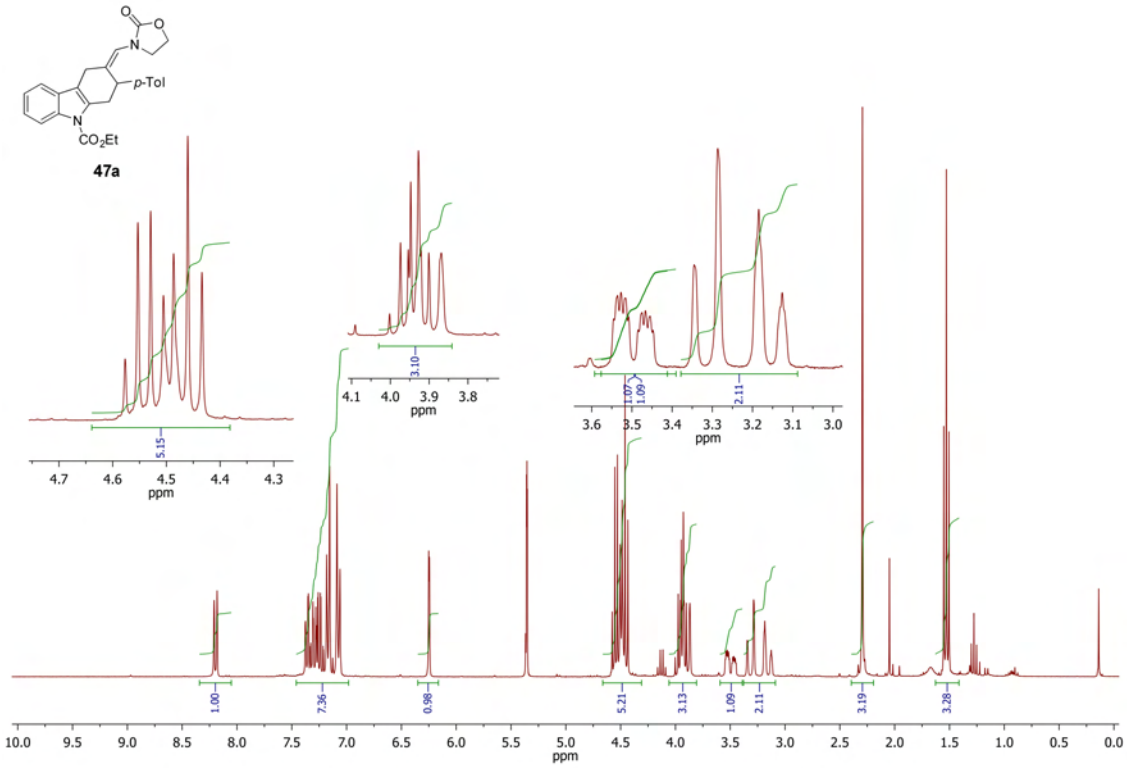


Figure 3.2

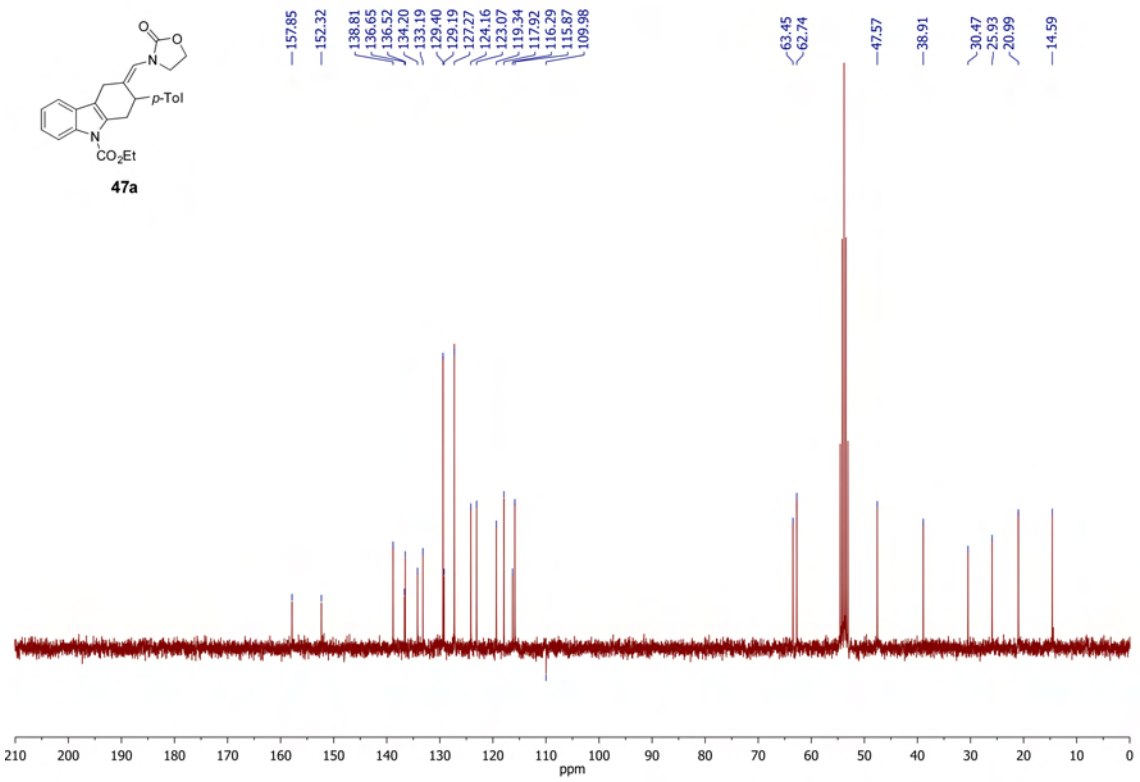
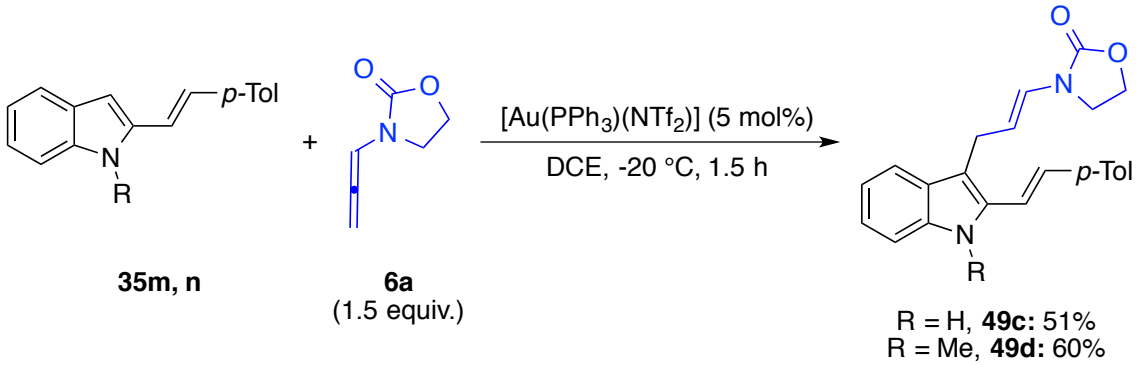


Figure 3.3

Interestingly, the presence of the ethoxycarbonyl moiety as protecting group on the indole demonstrated a enormous influence on the reaction outcome. Thus, when exploring the reactivity of *N*-H-free or *N*-Me vinylindoles (**35m, n**, respectively), a different reaction outcome was observed. Under reaction conditions tested, [Au(PPh$_3$)(NTf$_2$)] (5.0 mol%) in DCE at -20 ºC, the corresponding hydroarylation products **49c, d** were obtained in moderate yields (Scheme 3.26).

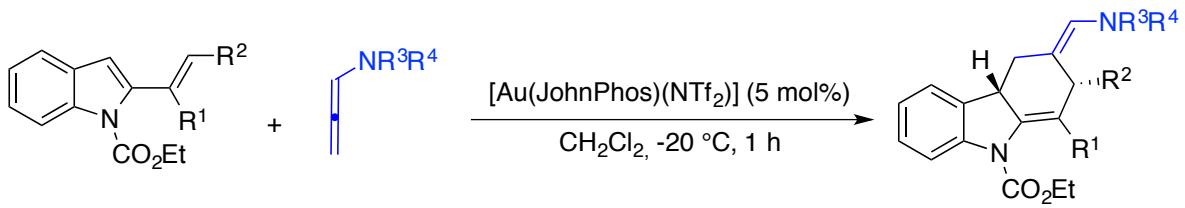


Scheme 3.26

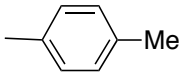
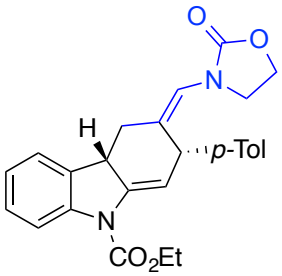
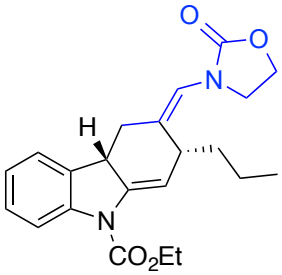
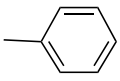
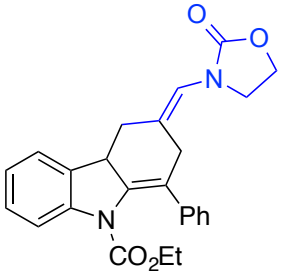
3.3.2.4 Scope for the synthesis of tetrahydrocarbazole derivatives **47'**

Then, the scope for the preparation of tetrahydrocarbazoles **47'** was carried out using [Au(JohnPhos)(NTf_2)] as catalyst and *N*-allenamides as limiting reagent. The results obtained are reported in Table 3.4.

Table 3.4: Scope for the synthesis of derivatives 47'

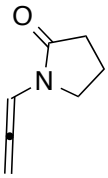
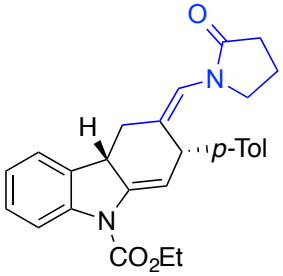
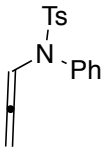
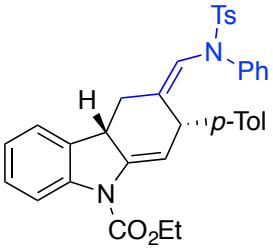
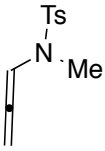
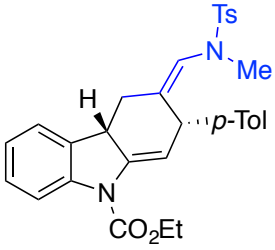


35 **3** or **6** **47'**

Entry	35	R^1	R^2	3 or 6	Product	Yield,[a] %
1	**35a**	H		**6a**	 **47'a'**	80
2	**35e**	H	*n*-Pr	**6a**	 **47'e**	37
3	**35h**		H	**6a**	 **47'k**	96

continues on next page

Table 3.4: Scope for the synthesis of derivatives 47'

Entry	35	R^1	R^2	3 or 6	Product	Yield,[a] %
4	**35a**	H	*p*-Tol	 **6b**	 **47'h**	75
5	**35a**	H	*p*-Tol	 **3a**	 **47'i**	81[b]
6	**35a**	H	*p*-Tol	 **3b**	 **47'j**	98[b]

Reaction conditions: To a solution of **35** and gold catalyst in dichloromethane (3 mL) at -20 ºC, a solution of **3** or **6** (0.9 equiv., 1 mL) was added dropwise via syringe and the mixture was stirred for 1 h at the same temperature.
[a]:Isolated Yields; [b]:reaction was conducted at -70 °C, c = 0.01 M.

While *β*-tolyl-substituted vinylindole **35a** gave rise to **47'a** in good yield, as observed before, the use of *β*-alkyl-substituted 2-vinylindoles such as **35e** led to the corresponding carbazole **47'e** in lower yield (entry 2). Interestingly, carbazole derivative **47'k** could be prepared in almost quantitative yield by means of the employment of α-phenyl-substituted 2-vinylindole **35h** (entry 3). Further modifications of the allenamide were carried out using allenes **6b** and **6a,b**. In this way, the corresponding derivatives **47'h-j** were selectively obtained in good yields (entries 4-6). However, as for $AuCl_3$ catalysis, tosylamides required a lower reaction temperature of -70 °C and a dilution of 0.01 M.

Representative ^{1}H- and ^{13}-C-NMR spectra for compound **47'a** are showed in Figures 3.4 and 3.5, respectively.

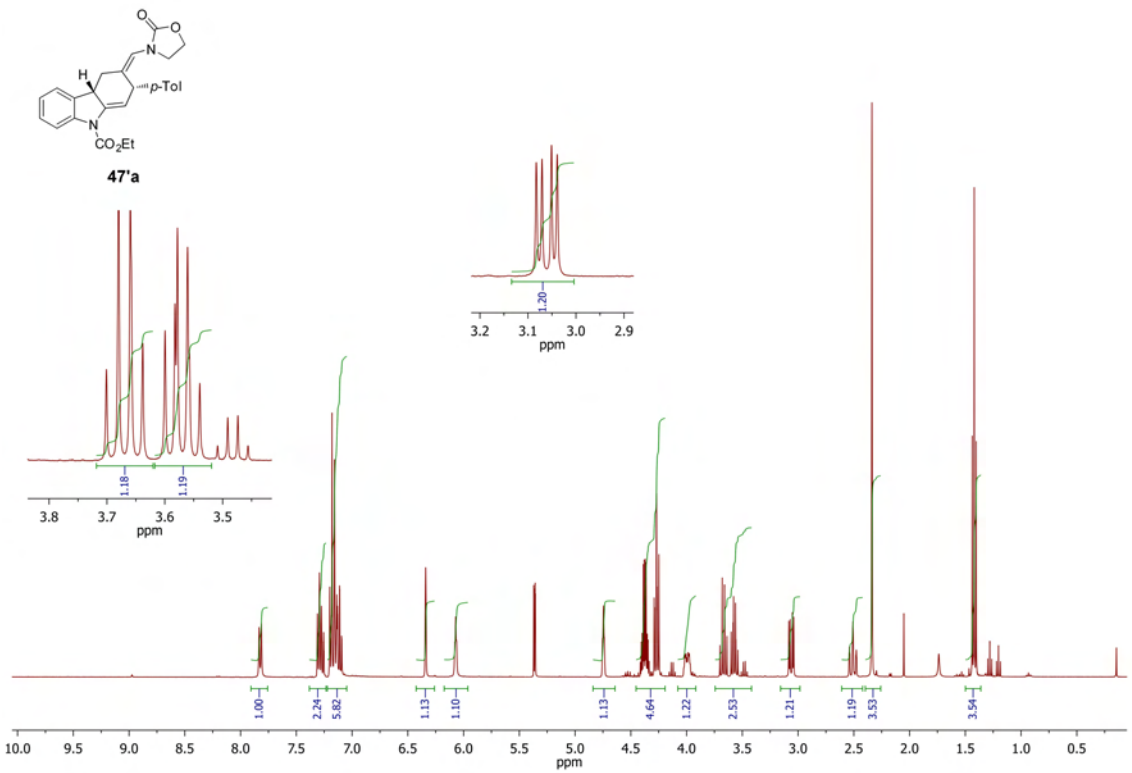


Figure 3.4

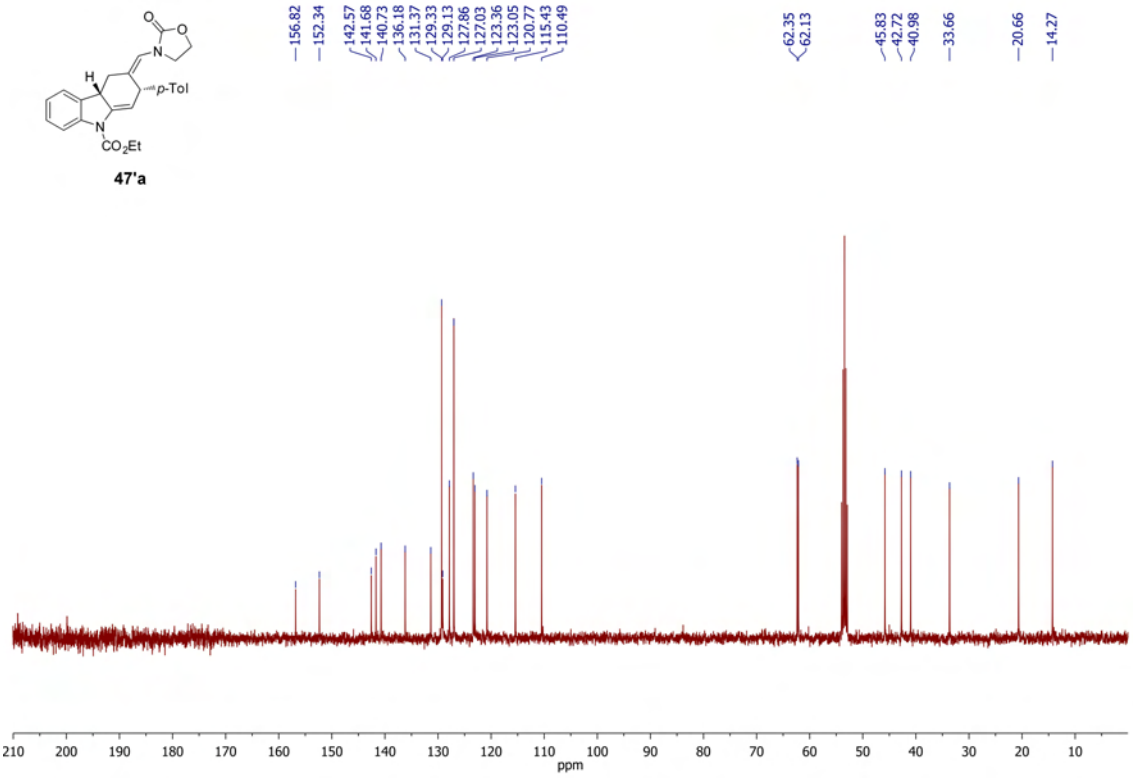
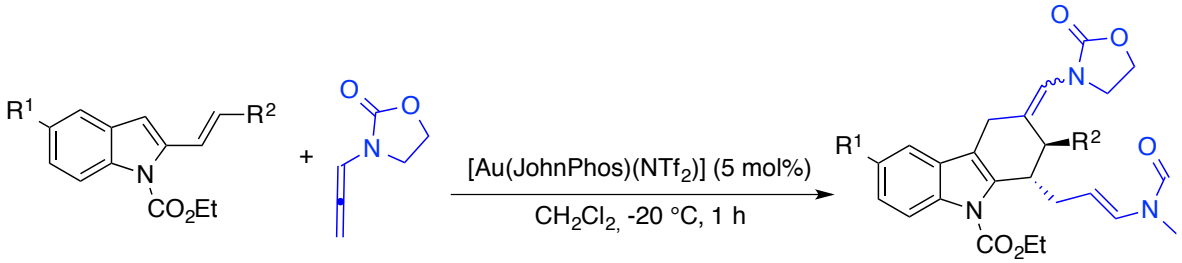


Figure 3.5

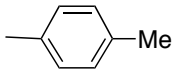
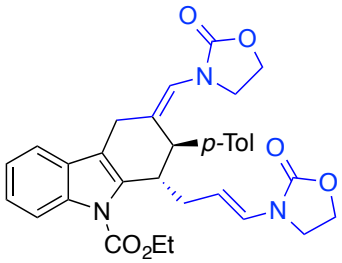
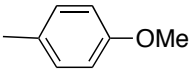
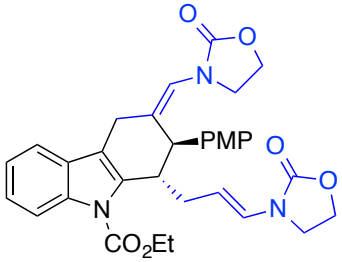
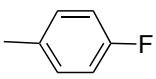
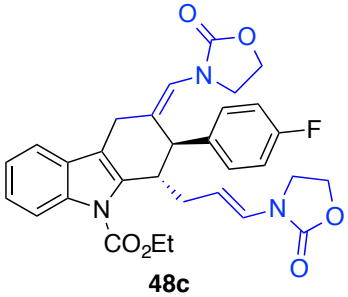
3.3.2.5 Scope for the synthesis of the multicompontent tetrahydrocarbazole derivatives **48**

Finally, a study on the scope of the multicomponent formation of tetrahydrocarbazole derivatives **48** was carried out. As before, various vinylindoles were evaluated using *N*-allenamide **6a** in excess (2.5 equiv.) and [Au(JohnPhos)(NTf_2)] as the catalyst. In Table 3.5 are shown the results of this study.

Table 3.5: Scope for the synthesis of derivatives 48

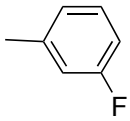
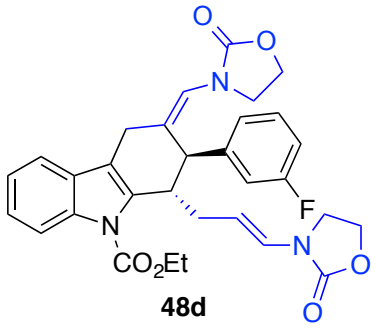
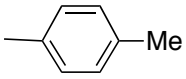
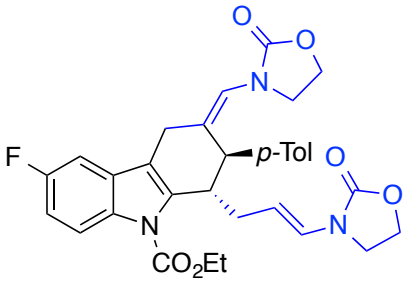
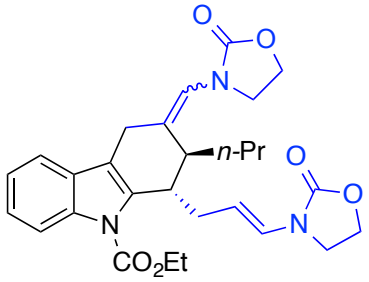
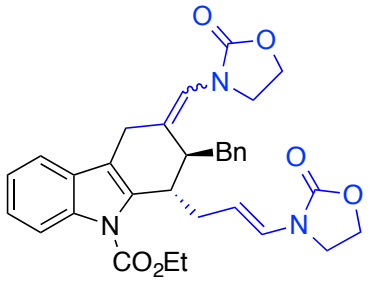


35 **6a** **48**

Entry	35	R^1	R^2	Product, 48	Yield,[a] %
1	**35a**	H		 **48a**	95
2	**35b**	H		 **48b**	99
3	**35c**	H		 **48c**	93

continues on next page

Table 3.5: Scope for the synthesis of derivatives 48

Entry	35	R^1	R^2	Product, 48	Yield,[a] %
4	**35d**	H		 **48d**	87
5	**35j**	F		 **48g**	92
6	**35e**	H	*n*-Pr	 **48e**	92 *E*/*Z* = 2.8:1
7	**35f**	H	Bn	 **48f**	66 *E*/*Z* = 1.5:1

Reaction conditions: To a solution of **35** and gold catalyst in dichloromethane (3 mL) at -20 ºC, a solution of **6a** (2.5 equiv., 1 mL) was added dropwise via syringe and the mixture was stirred for 1h at the same temperature.
[a]:Isolated Yields.

Hence, under the optimized conditions, highly substituted tetrahydrocarbazole derivatives **48a-g** bearing aryl substituents at β position were efficiently prepared (entries 1-5). Similarly,

vinylindoles with alkyl groups gave rise to compunds **48e-f** in good yield, but in this case as a separable mixture of *E* and *Z* isomers (entries 6-7) on the exocyclic double bond.

In Figures 3.6 and 3.7 are showed the representative ^{1}H- and ^{13}C-NMR spectra for compound **48a**.

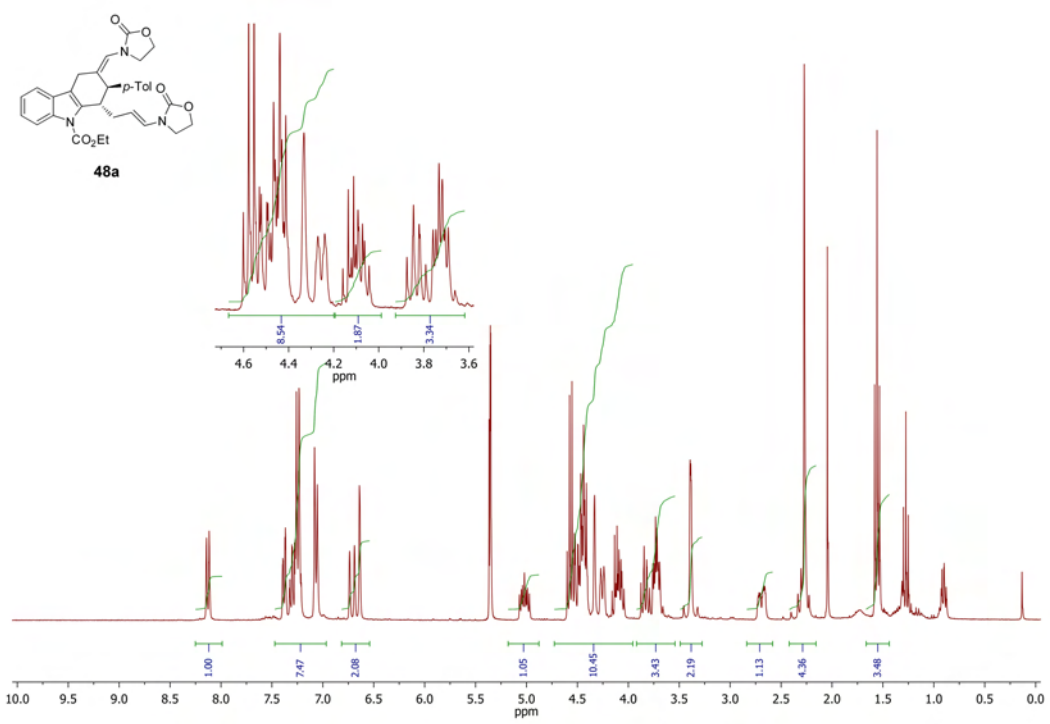


Figure 3.6

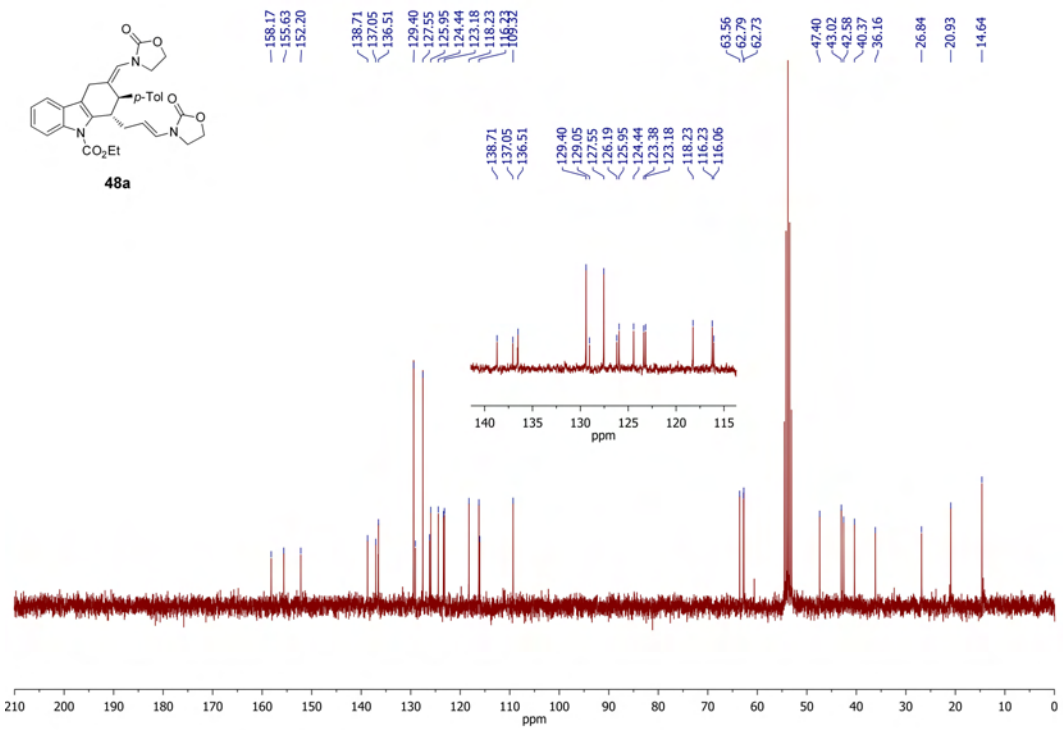
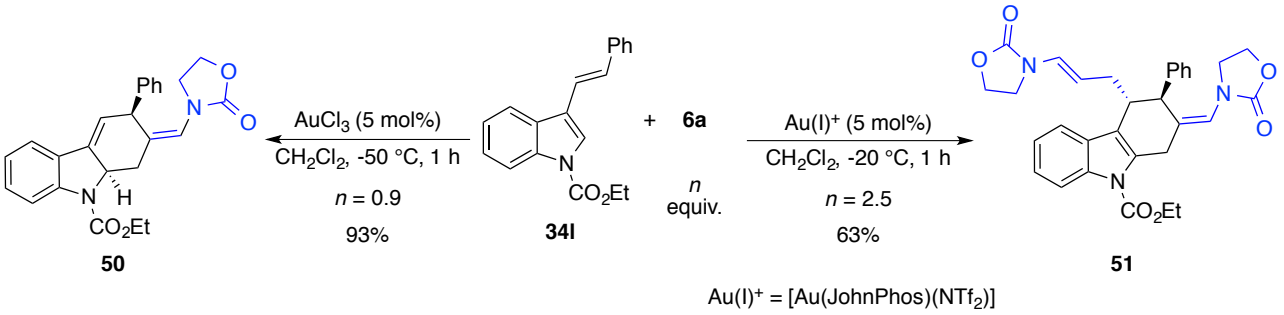


Figure 3.7

3.3.2.6 Gold-catalyzed cycloaddition of allenamides with 3-vinylindole and 2-vinylbenzofuran derivatives

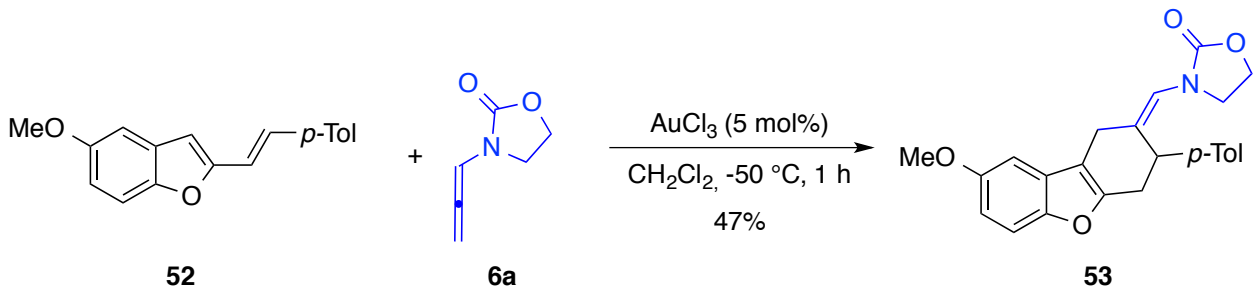
Besides 2-vinylindoles, in order to explore the potential of these transformations, the study was extended to other substrates. First, the reactivity of 3-vinylindole **34l** with allenamide **6a** was explored. Thus, the use of $AuCl_3$ (5.0 mol%) in CH_2Cl_2, at -50 ºC for 1 h afforded compound **50** in good yield, while the employ of [Au(JohnPhos)(NTf_2)] (5.0 mol%), in CH_2Cl_2, at -20 ºC, for 1 h, with an excess of **6a** (2.5 equiv.), gave rise to multicomponent product **51** in a reasonable yield (Scheme 3.27).



Scheme 3.27

Importantly, compounds **50-51** display a complementary substitution pattern to those obtained previously, when using 2-vinylindoles. This feature could be relevant for a rational synthetic design for these relevant scaffolds.

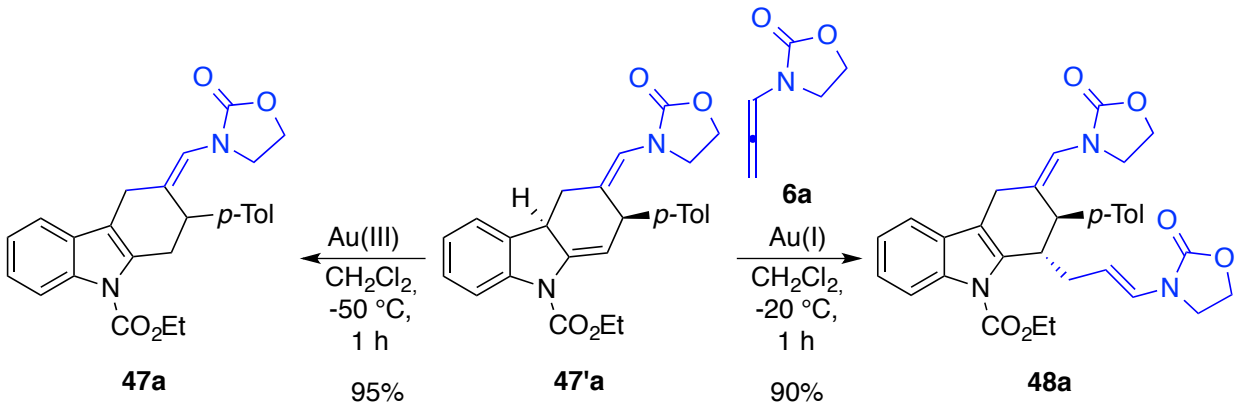
Not only indole scaffold but also benzofuran derivatives as compound **52** proved also capable to undergo a gold-catalyzed cycloaddition in the presence of *N*-allenamide **6a**. In this case, the $AuCl_3$ catalyzed reaction leadto the formation of tricyclic compound **53** in moderate yield (Scheme 3.28).



Scheme 3.28

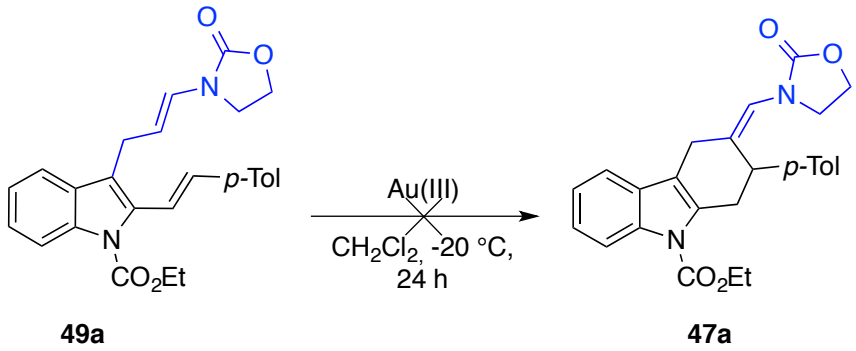
3.3.2.7 Additional experiments and proposed reaction mechanism

In order to gain insights into the formation of tetrahydrocarbazole derivatives **47**, **47'** and **48**, experiments were conducted and summarized in Scheme 3.29. Treatment of compound **47'a** in the presence of $AuCl_3$ or $[Au(PPh_3)(NTf_2)]$ resulted in the quantitative aromatization to **47a** within an hour. In addition,the addition of 0.9 equivalents of allenamide **6a** in the presence of $[Au(JohnPhos)(NTf_2)]$ to **47'a** led to multicomponent product **48a** in high yield.



Scheme 3.29

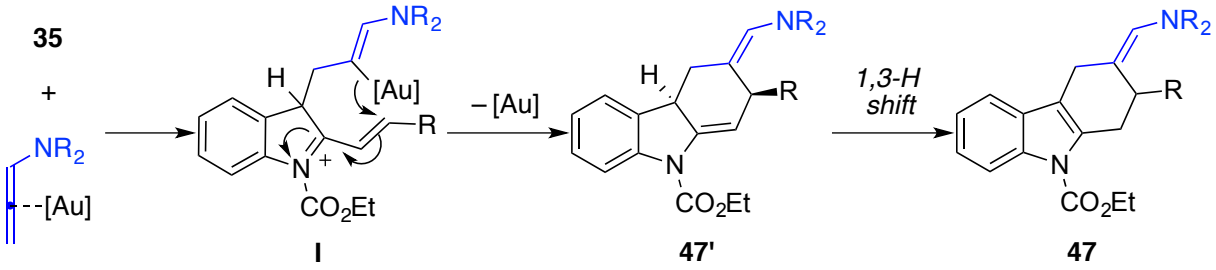
On the contrary, when using independently prepared hydroarylated indole **49a** the formation of the corresponding cycloaddition product **47a** was not detected by treatment with $AuCl_3$ even after 24 h at -20 °C (Scheme 3.30).



Scheme 3.30

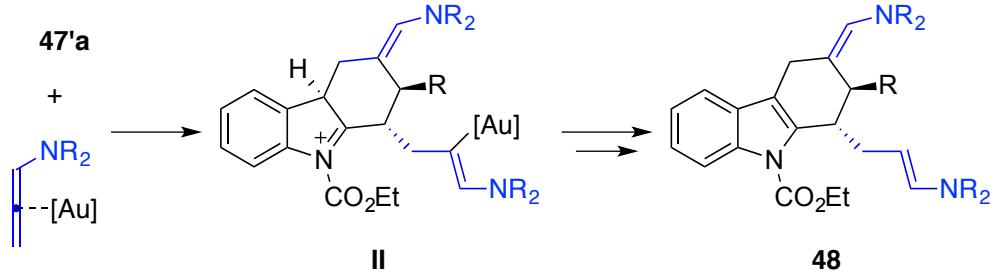
According to these experiments, and without further detailed studies, a plausible mechanistic rationale for these transformations is illustrated in Scheme 3.31. First, a gold-promoted activation of the allene triggers the nucleophilic attack of the indole through position C–3 to afford intermediate **I**. Since hydroarylation product **49a** is not competent to accomplish the cyclization, and considering

literature precedents, it is likely that the cyclization occurred from intermediate **I**, in a process which is faster than a protodemetallation. This cyclization leads to carbazole **47'**, which depending on reaction conditions could be isolated, or evolved to the aromatized indole **47**. This aromatization could be accomplished by some of the gold catalysts, although the presence of adventitious acid traces (especially in the case of $AuCl_3$) could also influence on this process. This mechanism accounts for the formation of benzofuran derivative **53** as well (Scheme 3.28).



Scheme 3.31

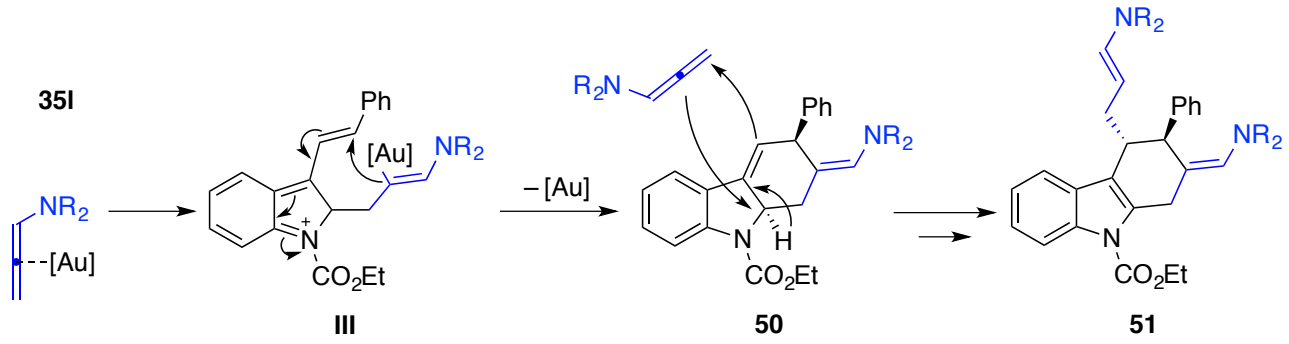
When an excess of the allene is employed, a second addition of the allene likely takes place from **47'** to afford carbazole **48**. A sequence comprising a hydroarylation of the allene through intermediate **II**, followed by a protodemetallation/aromatization might account for the results (Scheme 3.32).



Scheme 3.32

In the same manner, when using 3-vinylindole **35l**, the reaction might take place by means of a nucleophilic attack through position C-2 of the indole. Hydroarylation of allenamides at position C–2 has been previously reported for substrates bearing substituents at position C3.[10] A subsequent cyclization on intermediate **III** would afford carbazole **50**. When the reaction takes places in the presence of an excess of the allene, a second addition takes place leading to **51** (Scheme 3.33). This second addition cannot occur through a hydroarylation. However, an intermolecular ene-reaction can account for the formation of compound **51**. Aromatization of the indole ring might serve as a

driving force for this reaction. In the literature there are some reports on gold-catalyzed ene-reactions.[161]



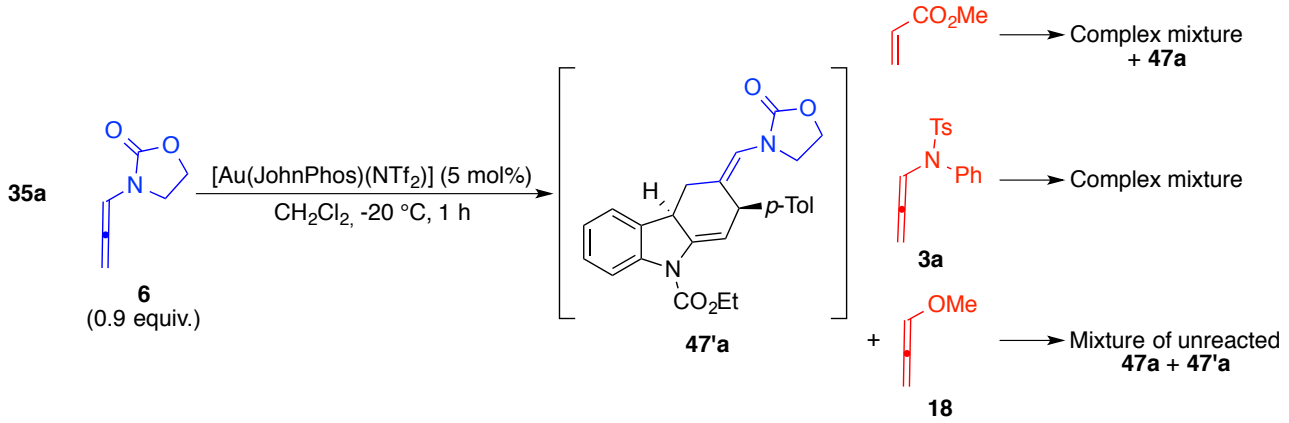
Scheme 3.33

[161] For an example of *intramolecular* gold-catalyzed Alder-ene reaction, see: G. Lemière, V. Gandon, N. Agenet, J. -P. Goddard, A. de Kozak, C. Aubert, L. Fensterbank, M. Malacria, *Angew. Chem. Int. Ed.* **2006**, *45*, 7596-7599.

3.3.2.8 Preliminary experiments on gold-catalyzed multicomponent reactions

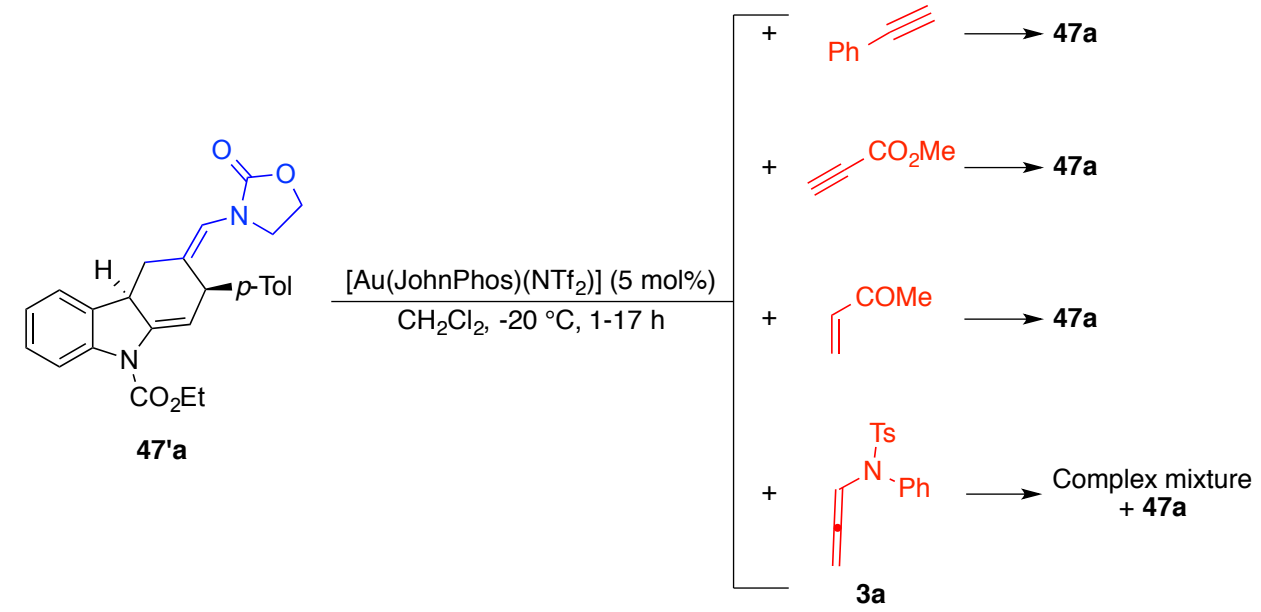
Considering the satisfactory results for the preparation of products **47'-48**, we got interested in the possibility of using two different molecules in the multicomponent reactions. Thus, the first addition of *N*-allenamide in the presence of cationic gold(I) catalyst would lead to **47'** that could react with a second molecule of allene, alkyne or alkene giving rise to other functionalized tetrahydrocarbazoles.

Thus, starting from **35a** and [Au(JohnPhos)(NTf_2)] as catalyst , the sequential addition of allenamide **6a** and α,β-unsatured ester or another allene such as **3a** or **18** were evaluated. However, only a complex reaction mixture was obtained from which we were only able to detect the formation of **47a** in some cases (Scheme 3.34).



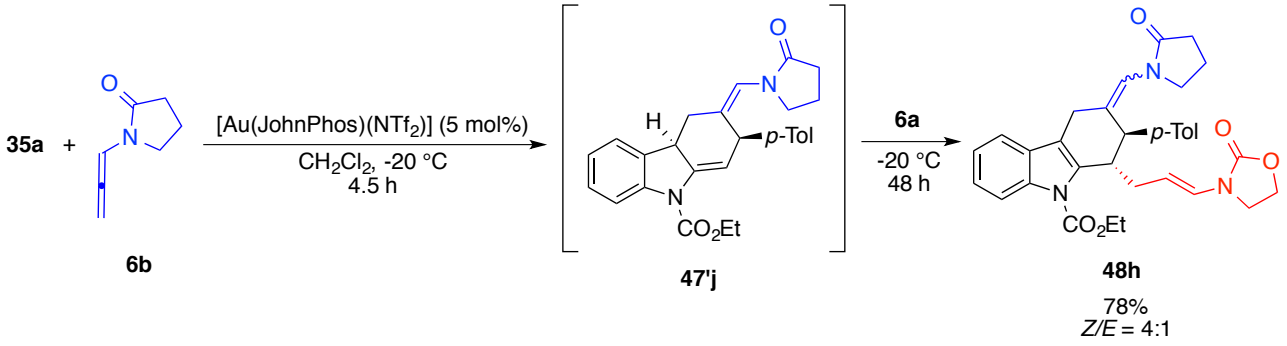
Scheme 3.34

The reactions performed on isolated **47'a** were again not successful, affording aromatized **47a** or complex mixture (Scheme 3.35).



Scheme 3.35

Among these transformations, the reaction between 2-vinylindole **35a** and allene **6b**, followed by addition to the reaction mixture of **6a** led to tetrahydrocarbazole **48h** in 78% yield (Scheme 3.36).



Scheme 3.36

3.4 Experimental data

3.4.1 Preface

3.4.1.1 General methods

All reactions were carried out under argon using standard Schlenck techniques.

3.4.1.2 Reagents

This study was carried out using 2-vinylindoles **35a-c,m,n** and 2-vinylbenzofuran **52**, which syntheses have already been described in Chapter 2, while preparation of vinylindoles **35d-h,j,l** will be illustrated in next paragraphs.
Allenes **18**, **43-44** and *N*-allenamides **3a,b** and **6a,b** are known compounds and their preparation was achieved following procedures reported in literature.[27-30]
$AuCl_3$, [$Au(PPh_3)Cl$], $PtCl_2$ and $PtBr_2(cod)$ were purchased from commercial suppliers and used as received, the rest of the gold catalysts were prepared according to literature procedures.[162]

3.4.1.3 Solvents

Solvents used for reactions sensitive to oxygen and hydrolysis were distilled and stored in a protected atmosphere of nitrogen, according to the following standard operations:
Dichloromethane: distilled on $CaCl_2$ under nitrogen atmosphere.
1,2-Dichloroethane: distilled on $CaCl_2$ under nitrogen atmosphere.
Toluene: distilled on Na using benzophenone as indicator under nitrogen atmosphere.
Tetrahydrofuran: distilled on Na using benzophenone as indicator under nitrogen atmosphere.

The other anhydrous solvents employed are available commercially.

[162] a) N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133-4136; b) L. Ricard, F. Gagosz, *Organometallics*, **2007**, *26*, 4704-4707.

3.4.1.4 Chromatography/purification of compounds

The chromatographic column separations were conducted by flash technique, using silica gel *Merck Grade 9385 60Å* (230-240 mesh).

For thin-layer chromatography (TLC), silica gel 60778-25EA *FLUKA* thin-layer plates were employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 365 nm), by basic solution of $KMnO_4$ (3.0 g $KMnO_4$, 20.0 g K_2CO_3 and 0.3 g KOH in 300 mL of H_2O) or with Ce/Mo solution (12 g of $(NH_4)_2MoO_4$, 0.5 g of $Ce(NH_4)_4(SO_4)_4{\cdot}2H_2O$ and 15 mL of concentrated H_2SO_4 in 235 mL of H_2O).

3.4.1.5 NMR spectroscopy

^{1}H-NMR analysis were performed with Bruker DPX-300, or Bruker AVANCE-300, 400 MHz instruments. at room temperature, respectively at 300, 400 MHz. The coupling constants (*J*) are expressed in Hertz (Hz), the chemical shifts (δ) in ppm. The multiplicities of the proton spectra were described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), dq (double quartet), dt (double triplet), td (triple doublet), ddd (double double doublet), bs (broad signal).

^{13}C-NMR analyses were performed with the same instruments at 75.45 and 100 MHz; carbon multiplicities were assigned by DEPT experiments.

^{19}F-NMR analyses were carried out with Bruker DPX-300 spectrometer at 282.4 MHz.

Two-dimensional NMR techniques (COSY, NOESY, HSQC, HMBC) were performed, where appropriate, to aid the correct assignment of structures.

3.4.1.6 Mass spectrometry

High-resolution mass spectra were recorded in an Agilent 6520Q-TOF and in a Finnigan Mat95 spectrometers.

3.4.1.7 Melting points

The melting points of the solid products were measured in capillary tube with the device *Stuart Scientific SMP3*.

3.4.1.8 X-ray diffraction

Single crystals suitable for X-ray diffraction were obtained by slow diffusion of Et_2O in a solution of **47a**, **47'a** or **48a** in CH_2Cl_2 at -20 °C. Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

3.4.2 Experimental data

3.4.2.1 Representative procedure for the synthesis of 2-vinylindoles **35d-h**:

(*E*)-Ethyl 2-(4-fluorostyryl)-1*H*-indole-1-carboxylate (35d):

To a solution of ethyl 2-(((trifluoromethyl)sulfonyl)oxy)-1*H*-indole-1-carboxylate (**36)** (0.5 g, 1.48 mmol) in anhydrous toluene (25 mL), $Pd(PPh_3)_4$ (86 mg, 0.074 mmol) was added. The reaction was stirred for 30 minutes at room temperature, then a solution of (*E*)-(3-fluorostyryl)boronic acid (**37d)** (0.37 g, 2.22 mmol) in EtOH-$NaHCO_3$ (sat.) (3:2, 25 mL) was added dropwise at room temperature. The mixture was then heated at reflux for 2 h, cooled at room temperature and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent evaporated under vacuum. The crude was purified by flash chromatography (SiO_2, hexane/ethyl acetate 50:1) to yield **35d** (0.434 g, 95%) as a yellow solid (m.p.: 64.1-64.5 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 16.2 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.38-7.22 (m, 5H), 7.07-6.95 (m, 2H), 6.91 (s, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 1.54 (t, *J* = 7.07 Hz, 3H) ppm.**^{13}C-NMR** (75 MHz, $CDCl_3$): δ =163.2 (d, J_{C-F} = 245 Hz, C), 152.1 (C), 139.5 (d, J_{C-F} = 7.7 Hz, C), 139.0 (C), 136.8 (C), 130.1 (d, J_{C-F} = 8.4 Hz, CH), 129.6 (C), 129.5 (CH), 124.6 (CH), 123.4 (CH), 122.6 (CH), 121.7 (CH), 120.5 (CH), 115.9 (CH), 114.7 (d, J_{C-F} = 21 Hz, CH), 112.9 (d, J_{C-F} = 22 Hz, CH), 107.5 (CH), 63.4 (CH_2), 14.4 (CH_3) ppm. **^{19}F-NMR** (282 MHz, $CDCl_3$): δ = -113.4 (s) ppm. **HR-MS** (EI) calc. for $[C_{19}H_{16}FNO_2]^+$ 309.1165, found 309.1168.

(*E*)-Ethyl 2-(pent-1-en-1-yl)-1*H*-indole-1-carboxylate (35e):

The representative procedure was followed using **36** (0.50 g, 1.48 mmol) and (*E*)-1-penten-1-ylboronic acid (**37e)** (0.25 g, 2.22 mmol). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 50:1) yielded **35e** (0.397 g, 99%) as a clear oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.30-7.18 (m, 2H), 6.97 (d, *J* = 15.7 Hz, 1H), 6.67 (s, 1H), 6.22 (dt, *J* = 15.6, 7.1 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 2.25 (q, *J* = 7.1 Hz, 2H), 1.54 (m, 5H), 1.01 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 152.1 (C), 139.9 (C), 136.4 (C), 134.0 (CH), 129.6 (C), 123.8 (CH), 123.1 (CH), 122.1 (CH), 120.1 (CH), 115.7 (CH), 106.4 (CH), 63.1 (CH_2), 35.1 (CH_2), 22.3 (CH_2), 14.4 (CH_3), 13.75 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{16}H_{19}NO_2]^+$ 257.1416, found 257.1420.

(*E*)-Ethyl 2-(3-phenylprop-1-en-1-yl)-1*H*-indole-1-carboxylate (35f):

The representative procedure was followed using **36** (0.50 g, 1.48 mmol) and (*E*)-3-phenyl-1-propen-1-ylboronic acid (**37f)** (0.36 g, 2.22 mmol). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 40:1) yielded **35f** (0.248 g, 55%) as a clear oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.12 (bs, 1H), 7.49 (bs, 1H), 7.40-7.19 (m, 7H), 7.04 (dd, *J* = 15.6, 1.6 Hz, 1H), 6.70 (s, 1H), 6.36 (dt, *J* = 15.6, 6.9 Hz, 1H), 4.52 (q, *J* = 7.1 Hz, 2H), 3.62 (dd, *J* = 6.9, 1.6 Hz, 2H), 1.48 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ =152.1 (C), 139.8 (C), 139.3 (C), 136.5 (C), 132.0 (CH), 129.5 (C), 128.8 (2 x CH), 128.6 (2 x CH), 126.3 (CH), 124.0 (CH), 123.2 (CH), 123.1 (CH), 120.2 (CH), 115.7 (CH), 106.9 (CH), 63.12 (CH_2), 39.5 (CH_2), 14.2 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{20}H_{19}NO_2]^+$ 305.1416, found 305.1417.

Ethyl 2-(1-phenylvinyl)-1*H*-indole-1-carboxylate (35g):

The representative procedure was followed using **36** (0.50 g, 1.48 mmol) and 1-phenylvinylboronic acid (**37g)** (0.33 g, 2.22 mmol). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 50:1) yielded **35g** (0.434 g, 99%) as a clear oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.36 (m, 1H), 7.32-7.24 (m, 6H), 6.74 (s, 1H), 5.72 (d, *J* = 1.2 Hz, 1H), 5.53 (d, *J* = 1.2 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 151.0 (C), 142.9 (C), 140.1 (C), 139.7 (C), 137.1 (C), 129.1 (C), 128.4 (2 x CH), 127.7 (CH), 125.9 (2 x CH), 124.6 (CH), 123.1 (CH), 120.6 (CH), 115.6 (CH), 115.3 (CH_2), 111.8 (CH), 62.9 (CH_2), 13.7 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{19}H_{17}NO_2]^+$ 291.1259, found 291.1561.

Ethyl 2-(3-methylbut-2-en-2-yl)-1*H*-indole-1-carboxylate (35h):

The representative procedure was followed using **36** (0.50 g, 1.48 mmol) and *E*-3-methyl-2-buten-2-ylboronic acid (**37h)** (0.25 g, 2.22 mmol). Purification by flash chromatography (SiO_2, hexane/ethyl acetate 50:1) yielded **35h** (0.321 g, 84%) as a clear oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.7 Hz, 1H), 7.51 (m, 1H), 7.34-7.18 (m, 2H), 6.29 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.93 (s, 3H), 1.84 (s, 3H), 1.66 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 151.9 (C), 142.8 (C), 136.6 (C), 131.3 (C), 130.1 (C), 124.0 (CH), 123.2 (CH), 120.5 (CH), 115.9 (CH), 108.5 (CH), 63.1 (CH_2), 22.7 (CH_3), 20.4 (CH_3), 14.6 (CH_3) (a signal corresponding to a C carbon is missing, probably due to overlapping) ppm. **HR-MS** (EI) calc. for $[C_{16}H_{19}NO_2]^+$ 257.1416, found 257.1418.

3.4.2.2 Synthesis of 5-fluoro-2-vinylindole **35j**

5-Fluoro-1*H*-indole-2-carbaldehyde (39):

To a solution of ethyl 5-fluoro-1*H*-indole-2-carboxylate (**38)** (0.925 g, 4.46 mmol) in THF (10 mL), $LiAlH_4$ (0.254 g, 6.70 mmol) was added slowly at 0 °C. After 1 h at room temperature the reaction was quenched by the addition of H_2O (2 mL) and NH_3 (15% aq. sol., 1 mL). The resulting mixture was filtered through celite and the water layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to yield (5-fluoro-1H-indol-2-yl)methanol (727 mg, 99%) used directly for the next step.
To a solution of (5-fluoro-1H-indol-2-yl)methanol (0.727 g, 4.4 mmol) in CH_2Cl_2 was added MnO_2 (1.9 g, 22 mol) and the resulting suspension was stirred vigorously at room temperature for 24 h. The mixture was filtered through celite and the solvent removed under vacuum. Purification by column chromatography (SiO_2, Hexane:EtOAc 5:1) yielded the corresponding aldehyde **39** (0.46 g, 64%) as a yellow solid (m.p.: 169.4-170.0 °C). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 9.88 (s, 1H), 9.35 (s, 1H), 7.48-7.37 (m, 2H), 7.27 (bs, 1H), 7.19 (td, *J* = 9.0, 2.5 Hz, 1H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$ + DMSO): δ = 187.0 (CH), 162.6 (d, J_{C-F} = 240 Hz, C), 142.2 (C), 140.0 (C), 131.83 (d, J_{C-F} = 11.6 Hz, C), 120.7 (d, J_{C-F} = 27.2 Hz, CH), 118.8 (CH), 118.7 (d, J_{C-F} = 3.1 Hz, CH), 111.7 (d, J_{C-F} = 21.5 Hz, CH) ppm. **^{19}F-NMR** (282 MHz, $CDCl_3$): δ = -122.0 (s) ppm. **HR-MS** (EI) calc. for $[C_9H_6FNO]^+$ 163.0433, found 163.0436.

5-Fluoro-2-(4-methylstyryl)-1*H*-indole (35k):

NaH (145 mg, 95% in mineral oil, 5.75 mmol) was added to a suspension of bromo(4-methylbenzyl)triphenylphosphorane (**40)** (2.47 g, 5.52 mmol) in toluene (20 mL) at 0 °C. The solution was stirred for 30 min at room temperature, followed by the addition of 5-fluoro-1*H*-indole-2-carbaldehyde (**39)** (0.75 g, 4.6 mmol). The mixture was heated at 80 °C for 2 h and quenched by saturated solution of NH_4Cl. The water phase was extracted with AcOEt (3 x 10 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vaccum. The crude product was purified by column chromatography (SiO_2, Hexane/ethyl acetate 20:1 to 5:1) to yield **35i-*E*-**isomer (0.51 g, 44%) as a yellow solid, (m.p.: 240.3-241.0 °C, dec.) and **35i-*Z*-**isomer (0.57 g, 49%) as a thick yellow oil. **35i-*E* isomer: ^{1}H-NMR** (300 MHz, acetone-D_6): δ = 10.59 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.36 (dd, *J*= 8.8, 4.5 Hz, 1H), 7.26-7.17 (m, 5H), 6.91 (td, *J* = 9.2, 2.5 Hz, 1H), 6.61 (s, 1H), 2.34 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, acetone-D_6): δ = 157.8 (d, J_{C-F} = 233 Hz, C), 138.9 (d, J_{C-F} = 10.2 Hz, C), 137.5 (C), 134.4 (C), 134.1 (d, J_{C-F} = 10.2 Hz, C), 129.4 (2 x

CH), 128.0 (CH), 126.3 (2 x CH), 118.1 (CH), 111.5 (d, J_{C-F} = 10.5 Hz, CH), 110.0 (d, J_{C-F} = 26.2 Hz, CH), 104.5 (d, J_{C-F} = 24.1 Hz, CH), 102.7 (d, J_{C-F} = 4.4 Hz, CH), 20.4 (CH_3) (one C signal is missing, probably due to overlapping) ppm. **^{19}F-NMR** (282 MHz, acetone-D_6): δ = -126.4 (s). **HR-MS** (EI) calc. for $[C_{17}H_{14}FN]^+$ 251.1110, found: 251.1115.

***Z*-isomer: ^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.94 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 7.7 Hz, 2H), 7.21 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.04 (dd, *J* = 8.8, 4.4 Hz, 1H), 6.90 (td, *J* = 9.1, 2.5 Hz, 1H), 6.66 (d, *J* = 12.2 Hz, 1H), 6.54 (d, *J* = 12.2 Hz, 1H), 6.49 (d, *J* = 1.9 Hz, 1H), 2.45 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 158.0 (d, J_{C-F} = 240 Hz, C), 137.9 (C), 136.9 (C), 134.6 (C), 132.8 (C), 129.7 (2 x CH), 128.9 (CH), 128.4 (2 x CH), 128.2 (C), 120.1 (CH), 111.3 (d, J_{C-F} = 9.5 Hz, CH), 110.9 (d, J_{C-F} = 25.1 Hz, CH), 105.4 (d, J_{C-F} = 4.1 Hz, CH), 105.1 (d, J_{C-F} = 24.1 Hz, CH), 21.36 (CH_3) ppm. **^{19}F-NMR** (282 MHz, $CDCl_3$): δ = -124.512 (s) ppm. **HR-MS** (EI) calc. for $[C_{17}H_{14}FN]^+$ 251.1110, found: 251.1156.

(*E*)-Ethyl 5-fluoro-2-(4-methylstyryl)-1*H*-indole-1-carboxylate (1g):

To a solution of (*E*)-5-fluoro-2-(4-methylstyryl)-1*H*-indole (**35i**) (350 mg, 1.39 mmol) in THF (6 mL), NaH (70.2 mg, 95% in mineral oil, 2.78 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. Ethylchloroformate (226 mg, 2.09 mmol) was then added. After 2 h at room temperature, the reaction mixture was diluted with H_2O (6 mL) and extracted with Et_2O (3 x 6 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vaccum. After column chromatography (SiO_2, hexane/ethyl acetate 20:1), **1g** (434 mg, 97%) was obtained as a yellow solid (m.p.: 240.3-241.0 ºC dec.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 9.1, 4.6 Hz, 1H), 7.72 (d, *J* = 16.2 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.24-7.15 (m, 3H), 7.07 (d, *J* = 16.2 Hz, 1H), 7.00 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.82 (s, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 1.53 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.5 (d, J_{C-F} = 239 Hz, C), 151.9 (C), 141.3 (C), 138.1 (C), 134.2 (C), 133.1 (C), 131.6 (CH), 130.5 (d, J_{C-F} = 10.1 Hz, C), 129.5 (2 x CH), 126.7 (2 x CH), 119.0 (CH), 116.8 (d, J_{C-F} = 8.6 Hz, CH), 111.8 (d, J_{C-F} = 24.6 Hz, CH), 106.3 (d, J_{C-F} = 3.8 Hz, CH), 105.6 (d, J_{C-F} = 23.7 Hz, CH), 63.4 (CH_2), 21.3 (CH_2), 14.4 (CH_3) ppm.

^{19}F-NMR (282 MHz, ($CDCl_3$): δ = -120.4 (s) ppm. **HR-MS** (EI) calc. for $[C_{20}H_{18}FNO_2]^+$ 323.1322, found 323.1326.

3.4.2.3 Synthesis of 3-vinylindole **35l**

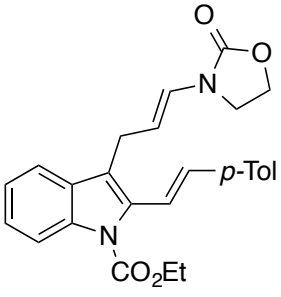
(*E*)-Ethyl 3-styryl-1*H*-indole-1-carboxylate (35l):

To a solution of (*E*)-3-styryl-1*H*-indole[26] (**35k**) (100 mg, 0. 46 mmol) in THF (2 mL), NaH (23.2 mg, 0.92 mmol, 95% mineral oil) was added at 0 °C and the mixture was stirred for 30 min at room temperature. Ethylchloroformate (75 mg, 0.69 mmol) was then added. After 2 h at room temperature, the reaction mixture was diluted with H_2O (2 mL) and extracted with Et_2O (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vaccum. After column chromatography (SiO_2, hexane/ethyl acetate 40:1), **8** (120 mg, 90%) was obtained as a yellow solid (m.p.: 88.2-88.7 ºC). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.86 (s, 1H), 7.60 (bs, 2H), 7.46-7.35 (m, 4H), 7.34-7.26 (m, 3H), 5.36 (bs, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 150.8 (C), 137.7 (2 x C), 136.1 (C), 128.9 (CH), 128.7 (2 x CH), 127.4 (CH), 126.1 (2 x CH), 124.9 (CH), 123.7 (CH), 123.2 (CH), 120.0 (CH), 119.7 (CH), 119.4 (C), 115.3 (CH), 63.2 (CH_2), 14.2 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{19}H_{17}NO_2]^+$ 291.3438, found 291.3441.

3.4.2.4 Platinum-catalyzed synthesis of **49a**

Ethyl 2-((*E*)-4-methylstyryl)-3-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-1*H*-indole-1-carboxylate (49a):

To a solution of the vinylindole **35a** (92 mg, 0.3 mmol) and Pt(cod)Br_2 (5.0 mol%) in CH_2Cl_2 at -50 ºC (0.1 M) was added dropwise via syringe a solution of **6a** (34 mg, 0.27 mmol) in CH_2Cl_2 (0.1 M, final concentration ca. 0.05 M). The mixture was stirred at the same temperature until disappearance of the starting reagents (checked by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, CH_2Cl_2/ethyl acetate 99:1 + 1% Et_3N), **49a** (69 mg, 60%) was obtained as white solid (m.p.: 144.8-145.5 °C).



^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.2 Hz, 1H), 7.55 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.47-7.24 (m, 5H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 14.5 Hz, 1H), 6.75 (d, *J* = 14.4 Hz, 1H), 5.05 (td, *J* = 14.4, 6.3 Hz, 1H), 4.52 (q, *J* = 7.1 Hz, 2H), 4.44 (dd, *J* = 8.1, 6.4 Hz, 2H), 3.72-3.64 (m, 4H), 2.40 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H) ppm.

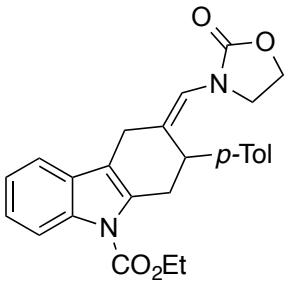
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.7 (C), 152.5 (C), 138.4 (C), 136.2

(C), 135.7 (C), 134.6 (C), 132.9 (CH), 130.6 (C), 129.9 (2 x CH), 126.9 (2 x CH), 125.4 (CH), 125.1 (CH), 123.4 (CH), 119.44 (CH), 119.37 (CH), 118.5 (C), 116.2 (CH), 109.7 (CH), 63.6 (CH_2), 62.6 (CH_2), 43.0 (CH_2), 26.1 (CH_2), 21.7 (CH_3), 14.9 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{26}H_{26}N_2O_4]^+$ 430.1893, found 430.1891.

3.4.2.5 General procedure for gold-catalyzed cycloadditions of vinylindoles **35** with allenamides **3** or **6**: synthesis of derivatives **47**

To a solution of the vinylindole **35** (0.2 mmol, 1.0 equiv.) and $AuCl_3$ (5.0 mol%) in CH_2Cl_2 at -50 ºC (0.1 M) was added dropwise via syringe a solution of the corresponding allene (0.18 mmol, 0.9 equiv.) in CH_2Cl_2 (0.1 M, final concentration ca. 0.05 M). The mixture was stirred at the same temperature until disappearance of the starting reagents (checked by TLC; 1 h). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 1:1 + 1% Et_3N) to yield the corresponding tetrahydrocarbazole derivatives **47** (for yields see table 3.2).

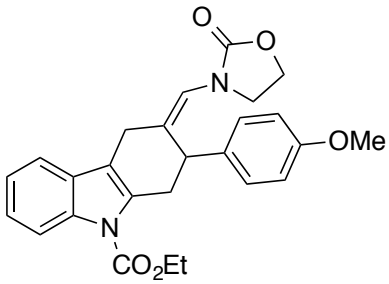
(*Z*)-Ethyl 3-((2-oxooxazolidin-3-yl)methylene)-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (4a):



White solid, m. p.: 163.7-164.3 °C.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.19 (d, *J* = 8.2 Hz, 1H), 7.39-7.20 (m, 3H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.25 (d, *J* = 1.7 Hz, 1H), 4.59-4.40 (m, 5H), 3.98-3.84 (m, 3H), 3.49 (bs, 1H), 3.32 (d, *J* = 17.5 Hz, 1H), 3.16 (d, *J* = 17.5 Hz, 1H), 2.28 (s, 3H), 1.53 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 157.9 (C), 152.3 (C), 138.8 (C), 136.7 (C), 136.5 (C), 134.2 (C), 133.2 (C), 129.4 (2 x CH), 129.2 (C), 127.3 (2 x CH), 124.2 (CH), 123.1 (CH), 119.4 (CH), 117.9 (CH), 116.3 (C), 115.9 (CH), 63.5 (CH_2), 62.7 (CH_2), 47.6 (CH_2), 38.9 (CH), 30.5 (CH_2), 25.9 (CH_2), 21.0 (CH_3), 14.6 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{26}H_{26}N_2O_4]^+$ 430.1893, found 430.1894.

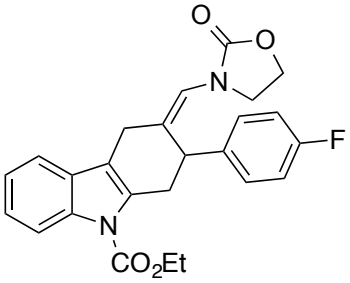
(*Z*)-Ethyl 2-(4-methoxyphenyl)-3-((2-oxooxazolidin-3-yl)methylene)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (47b):



Yellow solid, m.p.: 125 °C, (dec.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 1.1, 7.0 Hz, 1H), 7.33-7.19 (m, 3H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.77 (bs, 2H), 6.20 (d, *J* = 1.1 Hz, 1H), 4.56-4.42 (m, 5H), 3.99-3.82 (m, 2H), 3.79 (s, 1H), 3.73 (s, 3H), 3.47 (bs, 1H), 3.26 (d, *J* = 17.1 Hz, 1H), 3.12 (d, *J* = 17.1 Hz, 1H), 1.50 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 158.5 (C), 157.8 (C), 152.2 (C), 136.5 (C), 133.9 (C), 133.8 (C), 133.5 (C), 129.1 (C), 128.2 (2 x CH), 124.2 (CH), 123.1 (CH), 118.8 (CH), 117.8 (CH), 116.3 (C), 115.8 (CH), 114.1 (2 x CH), 63.2 (CH_2), 62.4 (CH_2), 55.4 (CH), 47.5 (CH_2), 38.5 (CH_3), 30.6 (CH_2), 25.9 (CH_2), 14.6 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{26}H_{26}N_2O_5]^+$ 446.1842, found 446.1847.

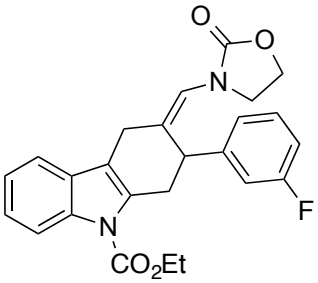
(*Z*)-Ethyl 2-(4-fluorophenyl)-3-((2-oxooxazolidin-3-yl)methylene)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (47c):



White solid; m.p.:158.5-160.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.6 Hz, 1H), 7.34-7.16 (m, 5H), 6.91 (t, *J* = 8.4 Hz, 2H), 6.18 (d, *J* = 1.5 Hz, 1H), 4.59-4.39 (m, 5H), 3.94-3.80 (m, 3H), 3.52 (bs, 1H), 3.26 (d, *J* = 17.6 Hz, 1H), 3.18 (d, *J* = 17.6 Hz, 1H), 1.50 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 161.8 (d, J_{C-F} = 245.1 Hz, C), 157.8 (C), 152.2 (C), 137.1 (d, J_{C-F} = 3.1 Hz, C), 136.4 (C), 133.9 (C), 133.5 (C), 129.0 (C), 128.8 (d, J_{C-F} = 7.9 Hz, 2 x CH), 124.3 (CH), 123.1 (CH), 119.1 (CH), 117.9 (CH), 116.3 (C), 115.9 (CH), 115.5 (d, J_{C-F} = 21.2 Hz, 2 x CH), 63.3 (CH_2), 62.4 (CH_2), 47.5 (CH_2), 38.6 (CH), 30.5 (CH_2), 25.8 (CH_2), 14.6 (CH_3) ppm. **^{19}F-NMR** (282 MHz, $CDCl_3$): δ = -116.6 (s) ppm. **HR-MS** (EI) calc. for $[C_{25}H_{23}FN_2O_4]^+$ 434.1642, found 434.1642.

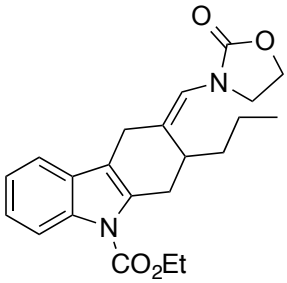
(*Z*)-Ethyl 2-(3-fluorophenyl)-3-((2-oxooxazolidin-3-yl)methylene)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (47d):



White solid; m.p.: 153.2-153.8 °C, (dec.).

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.19 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.31 (dd, *J* = 7.2, 1.4 Hz 1H), 7.28-7.22 (m, 2H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 10.6 Hz, 1H), 6.92 (td, *J* = 8.5, 2.5 Hz, 1H), 6.25 (d, *J* = 1.8 Hz, 1H), 4.59-4.50 (m, 3H), 4.48 (t, *J* = 7.8 Hz, 2H), 3.92 (m, 3H), 3.53 (m, 1H), 3.34 (d, *J* = 17.4 Hz, 1H), 3.16 (d, *J* = 17.6 Hz, 1H), 1.53 (q, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 162.9 (d, J_{C-F} = 242 Hz, C), 157.4 (C), 151.9 (C), 144.4 (d, J_{C-F} = 8.3 Hz, C), 136.3 (C), 133.4 (C), 132.3 (C), 129.8 (d, J_{C-F} = 8.4 Hz, CH), 128.7 (C), 123.9 (CH), 122.9 (CH), 122.7 (CH), 119.5 (CH), 117.6 (CH), 115.9 (C), 115.5 (CH), 114.1 (d, J_{C-F} = 21.8 Hz, CH), 113.3 (d, J_{C-F} = 21.1 Hz, CH), 63.1 (CH_2), 62.4 (CH_2), 47.1 (CH_2), 38.8 (CH), 29.9 (CH_2), 25.5 (CH_2), 14.2 (CH_3) ppm. **^{19}F-NMR** (282 MHz, CD_2Cl_2): δ = -113.85 (s) ppm. **HR-MS** (EI) calc. for $[C_{25}H_{23}FN_2O_4]^+$ 434.1642, found 434.1644.

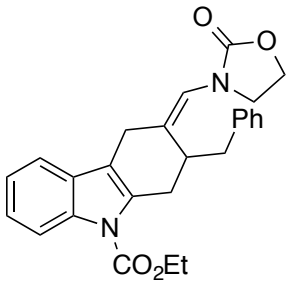
(*Z*)-Ethyl 3-((2-oxooxazolidin-3-yl)methylene)-2-propyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (47e):



Colorless oil.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.16 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.32-7.24 (m, 2H), 6.20 (d, *J* = 1.7 Hz, 1H), 4.54-4.42 (m, 4H), 3.93-3.79 (m, 2H), 3.48 (d, *J* = 17.6 Hz, 1H), 3.32 (d, *J* = 17.6 Hz, 1H), 3.25-3.13 (m, 3H), 1.49 (t, *J* = 7.2 Hz, 3H), 1.45-1.35 (m, 4H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 157.3 (C), 151.9 (C), 136.2 (C), 134.0 (C), 132.5 (C), 129.0 (C), 123.6 (CH), 122.6 (CH), 118.7 (CH), 117.5 (CH), 115.4 (CH), 115.0 (C), 62.9 (CH_2), 62.2 (CH_2), 47.1 (CH_2), 34.6 (CH_2), 34.4 (CH), 31.9 (CH_2), 25.3 (CH_2), 21.0 (CH_2), 14.2 (CH_3), 13.9 (CH_3). **HR-MS** (EI) calc. for $[C_{22}H_{26}N_2O_4]^+$ 382.1893, found 382.1899.

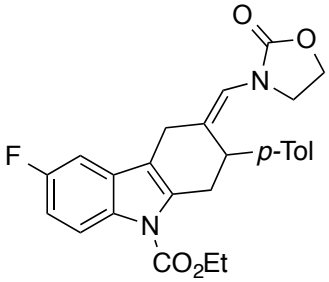
(*Z*)-Ethyl 2-benzyl-3-((2-oxooxazolidin-3-yl)methylene)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (47f):



Colorless oil.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.21 (d, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.28 (bs, 7H), 6.03 (d, *J* = 2.2 Hz, 1H), 4.48 (bs, 2H), 4.29 (t, *J* = 8.0 Hz, 2H), 3.68 (d, *J* = 18.0 Hz, 1H), 3.47-3.34 (m, 3H), 3.29 (bs, 2H), 3.18 (bs, 1H), 2.90 (dd, *J* = 13.3, 8.4 Hz, 1H), 2.78 (dd, *J* = 13.3, 7.1 Hz, 1H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 156.9 (C), 151.8 (C), 140.6 (C), 136.3 (C), 133.6 (C), 132.1 (C), 129.2 (2 x CH), 129.0 (C), 128.2 (2 x CH), 126.1 (CH), 123.7 (CH), 122.7 (CH), 119.0 (CH), 117.5 (CH), 115.5 (CH), 114.7 (C), 62.9 (CH_2), 62.2 (CH_2), 46.5 (CH_2), 38.6 (CH_2), 37.4 (CH), 31.0 (CH_2), 25.5 (CH_2), 14.1 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{26}H_{26}N_2O_4]^+$ 430.1893, found 430.1898.

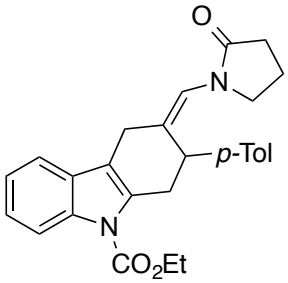
(*Z*)-Ethyl 2-(4-fluorophenyl)-3-((2-oxooxazolidin-3-yl)methylene)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (47g):



White solid; m.p.: 193.5-194.1 ºC.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.15 (dd, *J* = 9.7, 4.7 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 7.02 (bs, 2H), 6.24 (d, *J* = 1.5 Hz, 1H), 4.59-4.41 (m, 5H), 3.93 (bs, 2H), 3.87 (s, 1H), 3.49 (bs, 1H), 3.26 (d, *J* = 17.5 Hz, 1H), 3.12 (d, *J* = 17.5 Hz, 1H), 2.30 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 159.7 (d, J_{C-F} = 240 Hz, C), 157.8 (C), 152.1 (C), 138.7 (C), 136.6 (C), 136.2 (C), 133.0 (C), 132.7 (C), 130.1 (d, J_{C-F} = 9.4 Hz, C), 129.5 (2 x CH), 127.2 (2 x CH), 119.6 (CH), 116.9 (d, J_{C-F} = 8.9 Hz, CH), 116.1 (d, J_{C-F} = 3.4 Hz, C), 111.4 (d, J_{C-F} = 24.7 Hz, CH), 103.6 (d, J_{C-F} = 23.8 Hz CH), 63.6 (CH_2), 62.8 (CH_2), 47.5 (CH_2), 38.8 (CH), 30.5 (CH_2), 25.8 (CH_2), 21.0 (CH_3), 14.6 (CH_3). **^{19}F-NMR** (282 MHz, $CDCl_3$): δ = -121.4 (s). **HR-MS** (EI) calc. for $[C_{25}H_{25}FN_2O_4]^+$ 448.1798, found 448.1801.

(*Z*)-Ethyl 3-((2-oxopyrrolidin-1-yl)methylene)-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (47h):

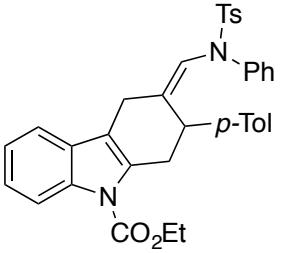


White solid; m.p.: 160.8-163.9 ºC.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 7.82 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.33-7.20 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.34 (s, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 4.44 (d, *J* = 5.9 Hz, 1H), 3.87 (d, *J* = 18.5 Hz, 1H), 3.78 (bs, 2H), 3.51 (bs, 1H), 3.31 (d, *J* = 17.5 Hz, 1H), 3.15 (d, *J* = 17.5 Hz, 1H), 2.47 (t, *J* = 8.1 Hz, 2H), 2.29 (s, 3H), 2.23 (bs, 2H), 1.53 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 175.3 (C), 152.4 (C), 146.6 (C), 139.2 (C), 136.7 (C), 136.4 (C), 134.4 (C), 132.0 (C), 129.3 (2 x CH), 127.3 (2 x CH), 124.1 (CH), 123.0 (CH), 119.9 (CH), 117.9 (CH), 116.6 (C), 115.9 (CH), 63.6 (CH_2), 50.2 (CH_2), 39.3 (CH), 31.0 (CH_2), 30.4 (CH_2), 26.1 (CH_2), 21.0 (CH_3), 19.2 (CH_2), 14.6 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{27}H_{28}N_2O_3]^+$ 428.2100, found 428.2105.

Note: reaction was conducted at -70 °C and with a final concentration of 0.01 M.

(*Z*)-Ethyl 3-((4-methyl-*N*-phenylphenylsulfonamido)methylene)-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (47i):

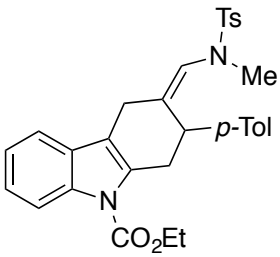


White solid; m.p.: 163.8-164.2 ºC (dec.).

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.12 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.32-7.16 (m, 7H), 7.17-7.04 (m, 7H), 6.12 (s, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.90 (t, *J* = 5.7 Hz, 1H), 3.63 (dd, *J* = 17.9, 5.6 Hz, 1H), 3.46 (dd, *J* = 17.9, 5.6 Hz, 1H), 3.37 (d, *J* = 19.9 Hz, 1H), 3.03 (d, *J* = 19.9 Hz, 1H), 2.33 (s, 6H), 1.47 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 151.9 (C), 143.7 (C), 141.3 (C), 139.8 (C), 138.3 (C), 136.2 (C), 136.1 (C), 134.6 (C), 133.6 (C), 129.3 (2 x CH), 129.1 (2 x CH), 129.0 (2 x CH), 128.8 (C), 127.8 (2 x CH), 127.4 (2 x CH), 126.9 (CH), 126.7 (2 x CH), 123.9 (CH), 123.0 (CH), 122.8 (CH), 117.7 (CH), 115.5 (CH), 115.0 (C), 62.9 (CH_2), 44.7 (CH), 31.1 (CH_2), 22.6 (CH_2), 21.5 (CH_3), 21.0 (CH_3), 14.4 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{36}H_{34}N_2O_4S]^+$ 590.2239, found 590.2243.

Note: reaction was conducted at -70 °C and with a final concentration of 0.01 M.

(*Z*)-Ethyl 3-((*N*,4-dimethylphenylsulfonamido)methylene)-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (47j):

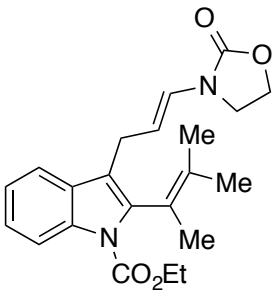


White solid; m.p.: 126.1-126.7 ºC (dec.). **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ = 8.26 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.43-7.22 (m, 5H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 5.45 (d, *J* = 1.6 Hz, 1H), 4.97 (d, *J* = 6.2 Hz, 1H), 4.56 (dd, *J* = 7.2, 1.7 Hz, 2H), 3.84 (d, *J* = 18.4 Hz, 1H), 3.57 (bs, 1H), 3.24 (d, *J* = 17.5 Hz, 1H), 3.11 (d, *J* = 17.5 Hz, 1H), 2.95 (s, 3H), 2.47 (s, 3H), 2.31 (s, 3H), 1.54 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 152.3 (C), 144.4 (C), 143.9 (C), 139.4 (C), 136.9 (C), 136.5 (C), 134.9 (C), 133.6 (C), 130.1 (2 x CH), 129.4 (2 x CH), 129.2 (C), 128.3 (2 x CH), 127.4 (2 x CH), 124.2 (CH), 123.1 (CH), 122.4 (CH), 117.8 (CH), 116.0 (CH), 115.6 (C), 63.5 (CH_2), 39.1 (CH), 30.5 (CH_2), 25.4 (CH_2), 22.0 (CH_3), 21.7 (CH_3), 21.0 (CH_3), 14.6 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{31}H_{32}N_2O_4S]^+$ 528.2083, found 528.2089.

3.4.2.6 Gold-catalyzed synthesis of **49b**

(*E*)-Ethyl 2-(3-methylbut-2-en-2-yl)-3-(3-(2-oxooxazolidin-3-yl)allyl)-1*H*-indole-1-carboxylate (49b):

To a solution of the vinylindole **35h** (52 mg, 0.2 mmol) and $AuCl_3$ (3.0 mg, 5.0 mol%) in CH_2Cl_2 at 25 ºC (0.1 M) was added dropwise via syringe a solution of **6a** (22 mg, 0.18 mmol) in CH_2Cl_2 (0.1 M, final concentration ca. 0.05 M). The mixture was stirred at the same temperature for 2 h (the disappearance of the starting reagents was checked by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:1 + 1% Et_3N) to yield **49b** (40 mg, 58%) as a colorless oil.



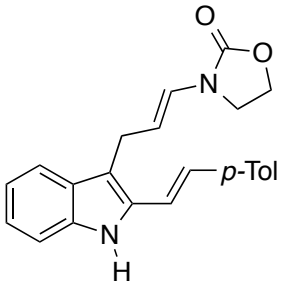
^{1}H-NMR (300 MHz, CD_2Cl_2): δ= 8.22 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.33-7.23 (m, 2H), 6.75 (d, *J* = 14.2 Hz, 1H), 4.95 (td, *J* = 14.2, 6.8 Hz, 1H), 4.45-4.37 (m, 4H), 3.64 (dd, *J* = 8.3, 7.8 Hz, 2H), 3.37 (dd, *J* = 6.9, 1.4 Hz, 2H), 1.92 (s, 3H), 1.88 (s, 3H), 1.57 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 155.2 (C), 151.4 (C), 138.5 (C), 136.1 (C), 131.9 (C), 129.8 (C), 124.6 (CH), 123.7 (CH), 122.4 (CH),

121.5 (C), 118.7 (CH), 116.1 (C), 115.5 (CH), 108.7 (CH), 62.6 (CH_2), 62.2 (CH_2), 42.5 (CH_2), 24.9 (CH_2), 22.1 (CH_3), 19.5 (CH_3), 19.5 (CH_3), 13.9 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{22}H_{26}N_2O_4]^+$ 382.1893, found 382.1894.

3.4.2.7 General procedure for gold-catalyzed reactions of 2-vinylindoles **35m,n**

To a solution of vinylindole **35m,n** (0.2 mmol) and allenamide **6a** (0.3 mmol, 1.5 equiv.) in DCE (0.1 M) at -20 ºC, $[Au(PPh_3)(NTf_2)]$ (5.0 mol%) was added. The resulting mixture was stirred at this temperature for 1 h (disappearance of the starting reagents was confirmed by TLC analysis). The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 4:1 + 1% Et_3N) to yield the corresponding derivative **49c,d** (for yields see Scheme 3.26).

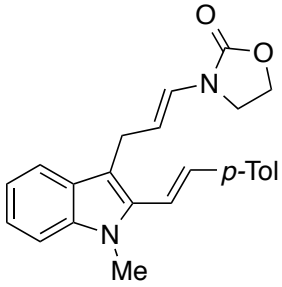
3-((*E*)-3-(2-((*E*)-4-Methylstyryl)-1*H*-indol-3-yl)prop-1-en-1-yl)oxazolidin-2-one (49c):



Yellow solid; m.p.: 168-169 ºC, (dec.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.27-7.03 (m, 5H), 6.87 (d, *J* = 4.2 Hz, 1H), 6.79 (d, *J* = 6.3 Hz, 1H), 4.98 (bs, 1H), 4.37 (dd, *J* = 9.0, 7.1 Hz, 2H), 3.63 (bs, 4H), 2.37 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 155.6 (C), 138.0 (C), 136.8 (C), 134.4 (C), 132.8 (C), 129.8 (2 x CH), 129.0 (C), 126.9 (CH), 126.4 (2 x CH), 124.5 (CH), 123.4 (CH), 120.0 (CH), 119.1 (CH), 116.0 (CH), 114.4 (C), 110.8 (CH), 110.4 (CH), 62.3 (CH_2), 42.8 (CH_2), 24.9 (CH_2), 21.5 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{23}H_{22}N_2O_2]^+$ 358.1681, found 358.1680.

3-((*E*)-3-(1-Methyl-2-((*E*)-4-methylstyryl)-1*H*-indol-3-yl)prop-1-en-1-yl)oxazolidin-2-one (49d):



White solid; m.p.: 130.9-132.5 °C.

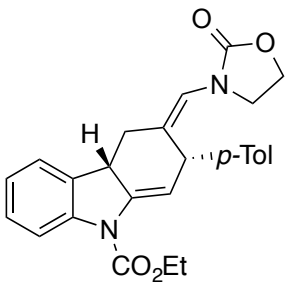
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.25 (bs, 4H), 7.13 (bs, 2H), 6.92 (d, *J* = 16.4 Hz, 1H), 6.83 (d, *J* = 14.3 Hz, 1H), 5.07 (dt, *J* = 14.2, 6.4 Hz, 1H), 4.39 (dd, *J* = 8.2, 6.5 Hz, 2H), 3.83 (s, 3H), 3.72 (dd, *J* = 6.5, 1.5 Hz, 2H), 3.67 (dd, *J* = 8.3, 6.5 Hz, 2H), 2.41 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 155.7 (C), 138.4 (C), 138.0 (C), 135.3 (C), 134.8 (C), 133.4 (CH),

129.9 (2 x CH), 128.2 (C), 126.7 (2 x CH), 124.7 (CH), 122.6 (CH), 119.8 (CH), 119.2 (CH), 116.6 (CH), 112.2 (C), 110.9 (CH), 109.5 (CH), 62.4 (CH_2), 43.1 (CH_2), 31.2 (CH_3), 26.0 (CH_2), 21.7 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{24}H_{24}N_2O_2]^+$ 372.1838, found 372.1844

3.4.2.8 General procedure for gold-catalyzed cycloadditions of vinylindoles **35** with allenamides **6**: Synthesis of carbazole derivatives **47'**

To a solution of the vinylindole **35** (0.2 mmol, 1.0 equiv.) and [Au(JohnPhos)(NTf_2)] (5.0 mol%) in CH_2Cl_2 at -20 ºC was added dropwise via syringe a solution of the corresponding allene (0.18 mmol, 0.9 equiv.) in CH_2Cl_2 (final concentration ca. 0.1 M). The mixture was stirred at the same temperature until disappearance of the starting reagents (checked by TLC; 1 h). The solvent was removed under reduced pressure and the resulting residue was purified by flash (SiO_2, hexane/ethyl acetate = 1:1 + 1% Et_3N) to yield the corresponding tetrahydrocarbazole derivatives **47'** (for yields see table 3.4).

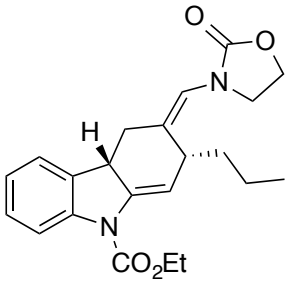
(*2R*,4aR*,Z*)-Ethyl 3-((2-oxooxazolidin-3-yl)methylene)-2-(*p*-tolyl)-4,4a-dihydro-2*H*-carbazole-9(3*H*)-carboxylate (47'a):



White solid; m.p.: 165-165.6 °C.

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 7.82 (d, *J* = 8.1 Hz, 1H), 7.32-7.25 (m, 2H), 7.21-7.07 (m, 5H), 6.34 (s, 1H), 6.07 (bs, 1H), 4.75 (bs, 1H), 4.42-4.34 (m, 2H), 4.28 (dt, *J* = 8.3, 1.4 Hz, 2H), 4.03-3.97 (m, 1H), 3.67 (q, *J* = 8.6 Hz, 1H), 3.57 (ddd, *J* = 8.6, 8.6, 6.9 Hz, 1H), 3.06 (dd, *J* = 12.7, 4.7 Hz, 1H), 2.51 (ddd, *J* = 12.0, 12.0, 1.6 Hz, 1H), 2.34 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, CD_2Cl_2): δ = 156.2 (C), 151.7 (C), 142.0 (C), 141.1 (C), 140.1 (C), 135.6 (C), 130.8 (C), 128.7 (2 x CH), 128.5 (C), 127.3 (CH), 126.4 (2 x CH), 122.7 (CH), 122.4 (CH), 120.2 (CH), 114.8 (CH), 109.9 (CH), 61.7 (CH_2), 61.5 (CH_2), 45.2 (CH_2), 42.1 (CH), 40.4 (CH), 33.0 (CH_2), 20.0 (CH_3), 13.7 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{26}H_{26}N_2O_4]^+$ 430.1893, found 43.1892.

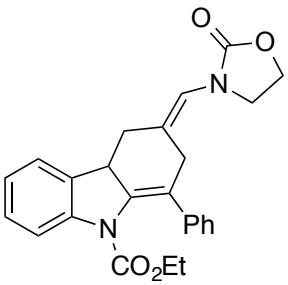
(*2R*,4aR*,Z*)-Ethyl 3-((2-oxooxazolidin-3-yl)methylene)-2-propyl-4,4a-dihydro-2*H*-carbazole-9(3*H*)-carboxylate (47'e):



Yellow oil.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 7.79 (d, *J* = 8.4 Hz, 1H), 7.28-7.22 (m, 2H), 7.08 (ddd, *J* = 8.4, 7.4, 1.0 Hz, 1H), 6.29 (s, 1H), 6.02 (dd, *J* = 3.3, 3.2 Hz, 1H), 4.46-4.36 (m, 4H), 4.03 (ddd, *J* = 8.5, 8.0, 7.3 Hz, 1H), 3.93-3.80 (m, 2H), 3.48 (bs, 1H), 2.85 (dd, *J* = 12.2, 4.8 Hz, 1H), 2.33 (dd, *J* = 12.2, 11.4 Hz, 1H), 1.60-1.40 (m, 4H, overlapping signal), 1.44 (t, *J* = 7.1 Hz, 3H, overlapping signal), 0.94 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 157.1 (C), 152.4 (C), 142.6 (C), 140.9 (C), 131.6 (C), 129.6 (C), 127.7 (CH), 123.3 (CH), 122.9 (CH), 119.3 (CH), 115.4 (CH), 110.3 (CH), 62.3 (CH_2), 62.0 (CH_2), 46.1 (CH_2), 43.6 (CH), 39.4 (CH_2), 35.5 (CH), 32.7 (CH_2), 19.9 (CH_2), 14.3 (CH_3), 14.1 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{22}H_{26}N_2O_4]^+$ 382.1893, found 382.1890.

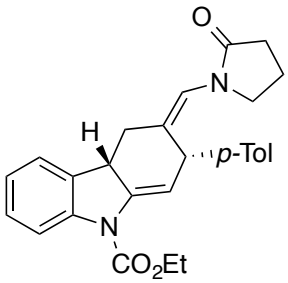
(*Z*)-Ethyl 3-((2-oxooxazolidin-3-yl)methylene)-1-phenyl-4,4a-dihydro-2*H*-carbazole-9(3*H*)-carboxylate (47'k):



White solid; m.p.: 132.5-132.9 °C, (dec.).

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 7.82 (d, *J* = 7.7 Hz, 1H), 7.40-7.22 (m, 7H), 7.13 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.68 (bs, 1H), 4.85 (bs, 1H), 4.45-4.32 (m, 2H), 4.15-4.04 (m, 2H), 3.91-3.79 (m, 1H), 3.54-3.40 (m, 1H), 2.77 (dddd, *J* = 11.6, 11.6, 4.0, 4.0 Hz, 1H), 2.53-2.44 (m, 2H), 2.33-2.23 (m, 1H), 0.82 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 157.4 (C), 152.0 (C), 142.9 (C), 142.7 (C), 135.9 (C), 133.4 (C), 128.7 (2 x CH), 128.0 (CH), 126.9 (CH), 126.6 (2 x CH), 124.8 (C), 124.3 (CH), 123.1 (C), 122.7 (CH), 122.0 (CH), 116.2 (CH), 62.9 (CH_2), 62.1 (CH_2), 45.3 (CH_2), 42.1 (CH), 31.5 (CH_2), 30.4 (CH_2), 14.0 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{25}H_{24}N_2O_4]^+$ 416.1736, found 416.1738.

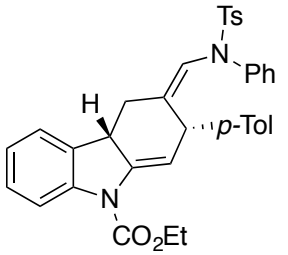
(*2R*,4aR*,Z*)-Ethyl 3-((2-oxopyrrolidin-1-yl)methylene)-2-(*p*-tolyl)-4,4a-dihydro-2*H*-carbazole-9(3*H*)-carboxylate (47'h):



White solid, mp.: 148.8-149.4 °C.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 7.82 (d, *J* = 8.1 Hz, 1H), 7.30-7.24 (m, 2H), 7.17-7.05 (m, 5H), 6.34 (s, 1H), 6.03 (dd, *J* = 3.2 ,3.2 Hz, 1H), 4.76 (bs, 1H), 4.37 (dq, *J* = 7.1, 2.0 Hz, 2H), 4.03-3.94 (m, 1H), 3.51 (ddd, *J* = 9.6, 6.8, 6.8 Hz, 1H), 3.36 (ddd, *J* = 9.6, 7.2, 7.2 Hz, 1H), 3.03 (dd, *J* = 12.7, 4.8 Hz, 1H), 2.49 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.39-2.30 (m, 2H, overlapping signal), 2.23 (s, 3H, overlapping signal), 2.02-1.90 (m, 2H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 174.5 (C), 152.8 (C), 143.0 (C), 142.3 (C), 141.1 (C), 136.4 (C), 131.9 (C), 129.9 (C), 129.5 (2 x CH), 128.2 (CH), 127.5 (2 x CH), 123.7 (CH), 123.4 (CH), 121.4 (CH), 115.8 (CH), 111.1 (CH), 62.5 (CH_2), 49.0 (CH_2), 43.3 (CH), 41.8 (CH), 34.1 (CH_2), 30.9 (CH_2), 21.0 (CH_3), 19.0 (CH_2), 14.6 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{27}H_{28}N_2O_3]^+$ 428.2100, found 428.2106.

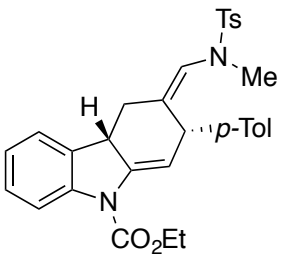
(*2R*,4aR*,Z*)-Ethyl 3-((4-methyl-*N*-phenylphenylsulfonamido)methylene)-2-(*p*-tolyl)-4,4a-dihydro-2*H*-carbazole-9(3*H*)-carboxylate (4i'):



White solid; m.p.: = 132.5-132.9 ºC, (dec.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.25-7.17 (m, 7H), 7.11-7.06 (m, 3H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.31 (s, 1H), 5.87 (dd, *J* = 3.4 ,3.4 Hz, 1H), 4.59 (dd, *J* = 3.4 ,3.4 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.92-3.86 (m, 1H), 2.90 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.48 (ddd, *J* = 12.4, 11.3 Hz, 1H, overlapping signal), 2.42 (s, 3H, overlapping signal), 2.27 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 152.4 (C), 143.8 (C), 142.6 (C), 140.9 (C), 140.0 (C), 139.9 (C), 138.9 (C), 135.8 (C), 134.2 (C), 131.1 (C), 129.4 (2 x CH), 128.9 (2 x CH), 128.8 (2 x CH), 128.1 (CH), 127.9 (2 x CH), 127.6 (2 x CH), 126.9 (CH), 126.8 (2 x CH), 123.4 (CH), 122.80 (CH), 122.75 (CH), 115.6 (CH), 110.7 (CH), 62.1 (CH_2), 42.9 (CH), 40.9 (CH), 32.4 (CH_2), 21.6 (CH_3), 21.0 (CH_3), 14.5 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{36}H_{34}N_2O_4S]^+$ 590.2239, found 590.2241.

(*2R*,4aR*,Z*)-Ethyl 3-((*N*,4-dimethylphenylsulfonamido)methylene)-2-(*p*-tolyl)-4,4a-dihydro-2*H*-carbazole-9(3*H*)-carboxylate (4j'):



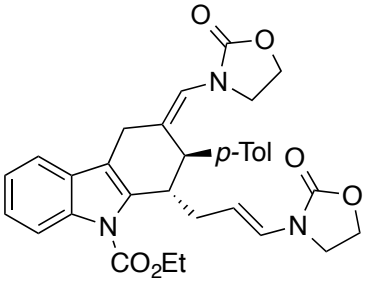
White solid; m.p.: 126.1-126.7 ºC, (dec.).

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 7.90 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.34-7.22 (m, 4H), 7.15-7.07 (m, 3H), 6.02 (bs, 1H), 5.32 (s, 1H), 5.13 (bs, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.07-3.94 (m, 1H), 2.84 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.61 (s, 3H), 2.50-2.42 (m, 1H, overlapped signal), 2.48 (s, 3H, overlapping signal), 2.33 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 152.8 (C), 144.6 (C), 144.4 (C), 143.3 (C), 141.5 (C), 141.0 (C), 136.6 (C), 133.6 (C), 131.6 (C), 130.0 (2 x CH), 129.4 (2 x CH), 128.3 (4 x CH), 123.69 (CH), 123.68 (CH), 123.2 (CH), 115.9 (CH), 110.6 (CH), 62.5 (CH_2), 43.4 (CH), 41.7 (CH), 37.8 (CH_3), 31.9 (CH_2), 21.7 (CH_3), 21.0 (CH_3), 14.7 (CH_3) (a signal corresponding to a C(sp^2)-H is overlapped) ppm. **HR-MS** (EI) calc. for $[C_{31}H_{32}N_2O_4S]^+$ 528.2083, found 528.2083.

3.4.2.9 General procedure for gold-catalyzed multicomponent cycloadditions of vinylindoles **35** with allenamides **6a**: synthesis of carbazole derivatives **48**

To a solution of the vinylindole **35** (0.2 mmol, 1.0 equiv.) and [Au(JohnPhos)(NTf_2)] (5.0 mol%) in CH_2Cl_2 at -20 ºC was added dropwise via syringe a solution of **6a** (0.5 mmol, 2.5 equiv.) in CH_2Cl_2 (final concentration of **35** ca. 0.1 M). The mixture was stirred at the same temperature until disappearance of the starting reagents (checked by TLC; 1 h). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO_2, CH_2Cl_2/ethyl acetate 99:1 + 1% Et_3N) to yield the corresponding tetrahydrocarbazole derivatives **48** (for yields see Table 3.5).

(*1S*,2R*,Z*)-Ethyl 1-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-3-((2-oxooxazolidin-3-yl)methylene)-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (48a):

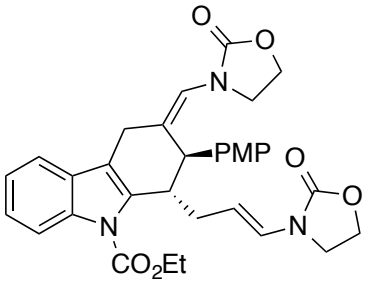


White solid; m.p.: 118.9-119.5 °C.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.13 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.33-7.21 (m, 4H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 14.4 Hz, 1H), 6.64 (s, 1H), 5.02 (ddd, *J* = 14.4, 9.0, 5.6 Hz, 1H), 4.56 (q, *J* = 7.2 Hz, 2H), 4.52-4.40 (m, 4H), 4.33 (s, 1H), 4.26 (d, *J* = 9.0 Hz, 1H), 4.15-4.04 (m, 1H), 3.84 (q, *J* = 8.9 Hz, 1H), 3.73 (dt, *J*

= 8.0, 4.3 Hz, 2H), 3.41 (d, *J* = 18.7 Hz, 1H), 3.37 (d, *J* = 18.7, 1H), 2.69 (dddd, *J* = 14.1, 7.2, 5.2, 2.6 Hz, 1H), 2.34-2.23 (m, 1H, overlapped signal), 2.27 (s, 3H, overlapped signal), 1.56 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 158.3 (C), 155.6 (C), 152.2 (C), 138.7 (C), 137.1 (C), 136.6 (C), 136.5 (C), 129.4 (2 x CH), 129.1 (C), 127.6 (2 x CH), 126.2 (C), 126.0 (CH), 124.4 (CH), 123.4 (CH), 123.2 (CH), 118.2 (CH), 116.2 (CH), 116.1 (C), 109.3 (CH), 63.6 (CH_2), 62.8 (CH_2), 62.7 (CH_2), 47.4 (CH_2), 43.0 (CH_2), 42.6 (CH), 40.4 (CH), 36.2 (CH_2), 26.8 (CH_2), 20.9 (CH_3), 14.6 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{32}H_{33}N_3O_6]^+$ 555.2369, found 555.2370.

(*1S*,2R*,Z*)-Ethyl 2-(4-methoxyphenyl)-1-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-3-((2-oxooxazolidin-3-yl)methylene)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (48b):

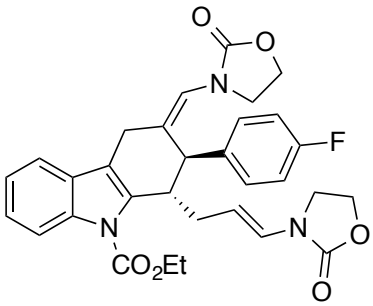


White solid; m.p.: 103.6-104.4 ºC.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.13 (d, *J* = 8.1 Hz, 1H), 7.38 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.33-7.21 (m, 4H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 14.1 Hz, 1H), 6.61 (s, 1H), 5.02 (ddd, *J* = 14.1, 9.2, 5.7 Hz, 1H), 4.57 (q, *J* = 7.1 Hz, 2H), 4.46-4.40 (m, 4H), 4.32 (s, 1H), 4.24 (d, *J* = 9.2 Hz, 1H), 4.14-4.05 (m, 1H), 3.83 (q, *J* = 8.3 Hz, 1H), 3.76-3.69 (m, 2H, overlapped signal), 3.73 (s, 3H, overlapped signal), 3.42 (d, *J* = 18.6 Hz, 1H), 3.34 (dd, *J* = 18.6, 1.9 Hz, 1H), 2.69 (ddd, *J* = 14.1, 5.0, 2.2 Hz, 1H), 2.27 (td, *J* = 14.1, 9.3 Hz, 1H), 1.56 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR (75 MHz, CD_2Cl_2): δ = 158.6 (C), 158.2 (C), 155.6 (C), 152.2 (C), 137.0 (C), 136.6 (C), 133.6 (C), 129.1 (C), 128.7 (2 x CH), 126.7 (CH), 125.9 (C), 124.4 (2 x CH), 123.2 (CH), 118.2 (CH), 116.2 (2 x CH), 116.1 (C), 114.0 (CH), 109.3 (CH), 63.6 (CH_2), 62.8 (CH_2), 62.7 (CH_2), 55.5 (CH_3), 47.5 (CH_2), 43.0 (CH_2), 42.2(CH), 40.5 (CH), 36.2 (CH_2), 26.8 (CH_2), 14.6 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{32}H_{33}N_3O_7]^+$ 571.2319, found 571.2325.

(*1S*,2R*,Z*)-Ethyl 2-(4-fluorophenyl)-1-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-3-((2-oxooxazolidin-3-yl)methylene)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (48c):

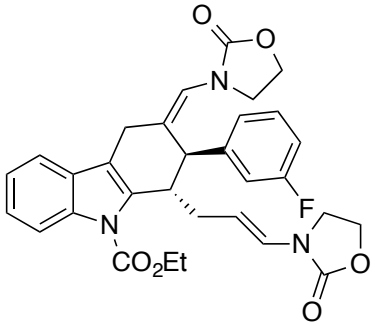


White solid; m.p.: 141.8-142.5 ºC.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.12 (d, *J* = 8.0 Hz, 1H), 7.40-7.34 (m, 3H), 7.30 (ddd, *J* = 8.0, 7.3, 1.5 Hz, 1H), 7.24 (ddd, *J* = 7.5, 7.3, 1.2 Hz, 1H), 6.94 (dd, *J* = 8.8, 8.7 Hz, 2H), 6.71 (d, *J* = 14.3 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 5.00 (ddd, *J* = 14.3, 9.2, 5.5

Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 4.54-4.41 (m, 4H), 4.34 (s, 1H), 4.22 (d, *J* = 9.4 Hz, 1H), 4.04 (ddd, *J* = 8.8, 8.8, 6.7 Hz, 1H), 3.82 (ddd, *J* = 8.8, 8.8, 7.8 Hz, 1H), 3.75-3.60 (m, 2H), 3.41 (d, *J* = 18.5 Hz, 1H), 3.31 (dd, *J* = 18.5, 2.3 Hz, 1H), 2.70 (dddd, *J* = 14.1, 5.4, 4.4, 1.7 Hz, 1H), 2.24 (ddd, *J* = 14.2, 9.3, 9.3 Hz, 1H), 1.55 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 161.5 (d, J_{C-F} = 242.3 Hz, C), 157.7 (C), 155.3 (C), 151.8 (C), 137.2 (d, J_{C-F} = 2.3 Hz, C), 136.4 (C), 136.2 (C), 129.1 (d, J_{C-F} = 8.3 Hz, 2 x CH), 128.6 (C), 126.4 (C), 125.6 (CH), 124.2 (CH), 123.0 (CH), 122.9 (CH), 117.90 (CH), 115.9 (CH), 115.7 (C) 115.0 (d, J_{C-F} = 21.2 Hz, 2 x CH), 108.8 (CH), 63.2 (CH_2), 62.4 (2 x CH_2), 47.1 (CH_2), 42.6 (CH_2), 41.9 (CH), 40.1 (CH), 35.8 (CH_2), 26.4 (CH_2), 14.2 (CH_3) ppm. **^{19}F-NMR** (282 MHz, CD_2Cl_2): δ = -117.41 (s) ppm. **HR-MS** (EI) calc. for $[C_{31}H_{30}FN_3O_6]^+$ 559.2119, found 559.2122.

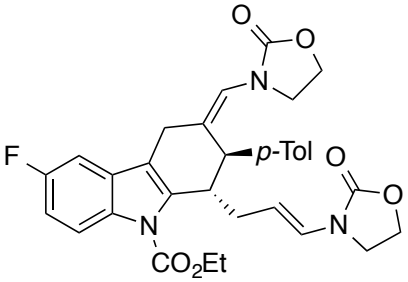
(*1S*,2R*,Z*)-Ethyl 2-(3-fluorophenyl)-1-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-3-((2-oxooxazolidin-3-yl)methylene)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (48d):



White solid; m.p.: 162.8-163.5 ºC.

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 8.13 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.27-7.17 (m, 3H), 7.13 (d, *J* = 10.7 Hz, 1H), 6.89 (t, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 14.3 Hz, 1H), 6.62 (s, 1H), 5.01 (ddd, *J* = 14.3, 9.3, 5.5 Hz, 1H), 4.57 (q, *J* = 7.2 Hz, 2H), 4.52-4.41 (m, 4H), 4.37 (s, 1H), 4.25 (d, *J* = 9.2 Hz, 1H), 4.04 (q, *J* = 8.8 Hz, 1H), 3.82 (q, *J* = 8.8 Hz, 1H), 3.77-3.67 (m, 2H), 3.43 (d, *J* = 18.7 Hz, 1H), 3.37 (dd, *J* = 18.7, 2.3 Hz, 1H), 2.71 (ddd, *J* = 14.2, 5.3, 2.5 Hz, 1H), 2.26 (td, *J* = 14.2, 9.5 Hz, 1H), 1.56 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, CD_2Cl_2): δ = 162.9 (d, J_{C-F} = 243.7 Hz, C), 157.69 (C), 155.25 (C), 151.81 (C), 144.32 (d, J_{C-F} = 6.6 Hz, C), 136.29 (C), 136.17 (C), 129.76 (d, J_{C-F} = 8.1 Hz, CH), 128.57 (C), 125.71 (CH), 125.47 (C), 124.18 (CH), 123.49 (CH), 123.16 (CH), 122.86 (CH), 117.90 (CH), 115.87 (CH), 115.70 (C), 114.53 (d, J_{C-F} = 22.2 Hz, CH), 113.22 (d, J_{C-F} = 21.2 Hz, CH), 108.69 (CH), 63.25 (CH_2), 62.37 (2 x CH_2), 47.02 (CH_2), 42.62 (CH_2), 42.38 (CH), 39.98 (CH), 35.76 (CH_2), 26.40 (CH_2), 14.24 (CH_3) ppm. **^{19}F-NMR** (282 MHz, CD_2Cl_2): δ = -113.74 (s) ppm. **HR-MS** (EI) calc. for $[C_{31}H_{30}FN_3O_6]^+$ 559.2119, found 559.2125.

(1*S*,2R*,Z*)-Ethyl 6-fluoro-1-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-3-((2-oxooxazolidin-3-yl)methylene)-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (48g):

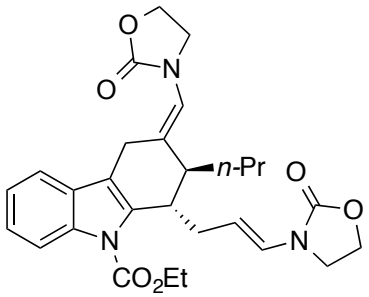


White solid; m.p.: 132.8-133.9 ºC.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.08 (ddd, *J* = 8.6, 4.6, 0.9 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.10-6.97 (m, 4H), 6.71 (d, *J* = 14.5 Hz, 1H), 6.65 (bs, 1H), 5.01 (ddd, *J* = 14.5, 9.2, 5.6 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 4.52-4.40 (m, 4H), 4.33 (s, 1H), 4.24 (ddd, *J* = 9.3, 2.3, 2.3 Hz, 1H), 4.07 (ddd, *J* = 8.9, 8.9, 6.1 Hz, 1H), 3.82 (ddd, *J* = 8.9, 8.9, 7.6 Hz, 1H), 3.77-3.68 (m, 2H), 3.34 (bs, 2H), 2.70 (dddd, *J* = 14.1, 4.4, 2.2, 1.7 Hz, 1H), 2.32-2.20 (m, 1H, overlapped signal), 2.27 (s, 3H, overlapped signal), 1.55 (t, *J* = 7.1 Hz, 3H)ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 159.3 (d, J_{C-F} = 239.6 Hz, C), 157.8 (C), 155.2 (C), 151.5 (C), 138.6 (C), 138.1 (C), 136.2 (C), 132.5 (C), 129.7 (d, J_{C-F} = 9.2 Hz, C), 129.1 (2 x CH), 127.1 (2 x CH), 125.7 (CH), 125.2 (C), 123.3 (CH), 116.9 (d, J_{C-F} = 9.0 Hz, CH), 115.4 (d, J_{C-F} = 3.7 Hz, C), 111.3 (d, J_{C-F} = 24.8 Hz, CH), 108.7 (CH), 103.6 (d, J_{C-F} = 23.5 Hz, CH), 63.4 (CH_2), 62.41 (CH_2), 62.35 (CH_2), 47.0 (CH_2), 42.6 (CH_2), 42.0 (CH), 40.0 (CH), 35.7 (CH_2), 26.3 (CH_2), 20.5 (CH_3), 14.2 (CH_3) ppm. **^{19}F-NMR** (282 MHz, CD_2Cl_2): δ = -121.16 (s) ppm. **HR-MS** (EI) calc. for $[C_{32}H_{32}FN_3O_6]^+$ 573.2275, found 573.2280.

(*1S*,2S*,Z*)-Ethyl 1-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-3-((2-oxooxazolidin-3-yl)methylene)-2-propyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (48e):

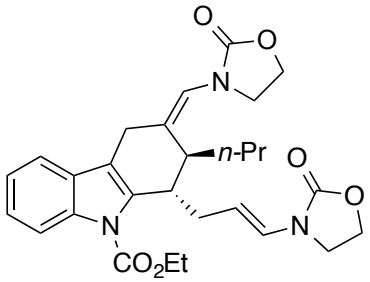
Spectroscopic Data for **(3*Z*)-48e**:



Clear oil.

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 8.13 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.34-7.24 (m, 2H), 6.62 (d, *J* = 14.6 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 4.93 (ddd, *J* = 14.6, 9.2, 5.6 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 4.50-4.40 (m, 4H), 4.01 (dd, *J* = 8.8, 6.2 Hz 1H), 3.81-3.67 (m, 3H), 3.58 (d, *J* = 9.8 Hz, 1H), 3.49 (dd, *J* = 18.4, 2.2 Hz, 1H), 3.35 (d, *J* = 18.4 Hz, 1H), 3.00 (dt, *J* = 7.3, 1.7 Hz, 1H), 2.54 (dddd, *J* = 14.2, 5.2, 4.6, 2.3 Hz, 1H), 2.09 (dd, *J* = 14.2, 9.4 Hz, 1H), 1.52 (t, *J* = 7.1 Hz, 3H, overlapped signal), 1.55-1.30 (m, 4H, overlapped signal), 0.90 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, CD_2Cl_2): δ = 157.6 (C), 155.2 (C), 151.7 (C), 136.9 (C), 136.2 (C), 128.9 (C), 127.9 (C), 125.1 (CH), 123.9 (CH), 122.6 (CH), 121.1 (CH), 117.8 (CH), 115.8 (CH), 115.2 (C), 109.3 (CH), 63.0 (CH_2), 62.3 (CH_2), 62.2 (CH_2), 47.2 (CH_2), 42.7 (CH_2), 40.5 (CH), 38.2 (CH), 35.6 (CH_2), 34.4 (CH_2), 26.0 (CH_2), 21.2 (CH_2), 14.2 (CH_3), 14.1 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{28}H_{33}N_3O_6]^+$ 507.2369, found 507.2366.

Spectroscopic Data for **(3*E*)-48e**:

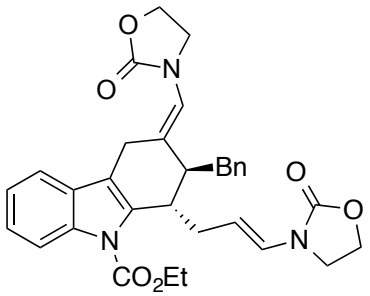


Clear oil.

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 8.19 (d, *J* = 7.4 Hz, 1H), 7.59 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.34-7.27 (m, 2H), 6.71 (d, *J* = 14.3 Hz, 1H), 6.33 (s, 1H), 4.90 (ddd, *J* = 14.3, 8.7, 6.2 Hz, 1H), 4.55 (q, *J* = 7.1 Hz, 2H), 4.44 (dd, *J* = 8.3, 7.8 Hz, 2H), 4.20 (ddd, *J* = 8.7, 8.7, 4.1 Hz, 1H), 4.14-4.07 (m, 1H), 3.70 (dd, *J* = 9.3, 7.1 Hz, 2H), 3.48-3.41 (m, 2H), 3.27 (q, *J* = 9.1 Hz, 1H), 2.66 (dd, *J* = 12.8, 2.8 Hz, 1H), 2.56 (ddd, *J* = 13.7, 8.7, 2.1 Hz, 1H), 2.24-2.09 (m, 3H), 1.53 (t, *J* = 7.2 Hz, 3H, overlapped signal), 1.55-1.30 (m, 4H, overlapped signal), 0.93 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, CD_2Cl_2): δ = 157.8 (C), 155.2 (C), 151.6 (C), 141.3 (C), 136.4 (C), 127.3 (C), 125.6 (CH), 124.1 (CH), 123.3 (CH), 120.9 (C), 119.7 (CH), 118.8 (CH), 116.0 (CH), 115.2 (C), 108.8 (CH), 63.5 (CH_2), 62.6 (CH_2), 62.3 (CH_2), 46.4 (CH_2), 42.6 (CH_2), 41.0 (CH), 35.8 (CH), 35.6 (CH_2), 35.3 (CH_2), 31.8 (CH_2), 20.2 (CH_2), 14.2 (CH_3), 14.1 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{28}H_{33}N_3O_6]^+$ 507.2369, found 507.2376.

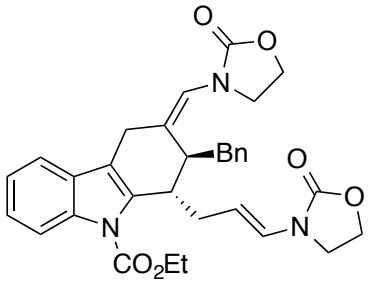
(*1S*,2R*,Z*)-Ethyl 2-benzyl-1-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-3-((2-oxooxazolidin-3-yl)methylene)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (48f):

Spectroscopic Data for **(3*Z*)-48f**:



^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.20 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.52 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.36-7.27 (m, 4H), 7.25-7.21 (m, 1H), 7.17 (dd, *J* = 8.2, 1.4 Hz, 2H), 6.54 (d, *J* = 14.3 Hz, 1H), 6.30 (d, *J* = 2.0 Hz, 1H), 4.62 (ddd, *J* = 14.3, 9.6, 5.4 Hz, 1H), 4.50-4.30 (m, 6H), 3.74-3.68 (m, 2H), 3.61-3.44 (m, 4H), 3.33 (ddd, *J* = 8.8, 8.8, 6.6 Hz 1H), 3.19 (dd, *J* = 8.0, 7.0 Hz, 1H), 3.04 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.67 (dd, *J* = 13.3, 8.9 Hz, 1H), 2.48 (dddd, *J* = 14.0, 7.6, 5.1, 2.7 Hz, 1H), 2.00 (ddd, *J* = 14.0, 9.6, 9.6 Hz, 1H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 157.3 (C), 155.2 (C), 151.6 (C), 140.6 (C), 136.5 (C), 136.4 (C), 129.4 (2 x CH), 128.9 (C), 128.2 (2 x CH), 128.0 (C), 126.1 (CH), 125.0 (CH), 124.0 (CH), 122.8 (CH), 121.4 (CH), 117.9 (CH), 115.9 (CH), 115.0 (C), 109.1 (CH), 63.0 (CH_2), 62.3 (CH_2), 62.2 (CH_2), 46.8 (CH_2), 42.5 (CH_2), 41.0 (CH), 39.3 (CH), 38.1 (CH_2), 35.6 (CH_2), 26.2 (CH_2), 14.1 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{32}H_{33}N_3O_6]^+$ 555.2369, found 555.2375.

Spectroscopic Data for **(3*E*)-48f**:

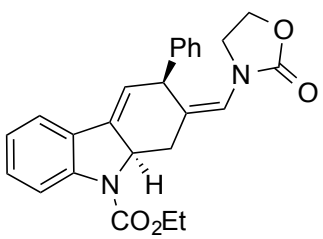


^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 8.23 (d, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.40-7.30 (m, 4H), 7.27-7.23 (m, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.64 (d, *J* = 14.3 Hz, 1H), 6.34 (s, 1H), 4.59 (ddd, *J* = 14.3, 8.8, 6.0 Hz, 1H, overlapped signal), 4.53-4.38 (m, 4H, overlapped signal), 4.27 (ddd, *J* = 8.7, 8.7, 4.2 Hz, 1H), 4.16 (q, *J* = 8.7 Hz, 1H), 3.60-3.45 (m, 4H), 3.42 (q, *J* = 9.0 Hz, 1H), 2.80-2.61 (m, 3H), 2.52-2.44 (m, 2H), 2.26 (dd, *J* = 13.0, 3.8 Hz, 1H), 2.13 (ddd, *J* = 14.6, 9.3, 9.3 Hz, 1H), 1.46 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, CD_2Cl_2): δ = 157.7 (C), 155.1 (C), 151.5 (C), 140.7 (C), 140.6 (C), 136.6 (C), 129.3 (2 x CH), 128.2 (2 x CH), 127.3 (C), 126.0 (CH), 125.5 (CH), 124.3 (CH), 123.3 (CH), 120.7 (C), 119.6 (CH), 119.2 (CH), 116.0 (CH), 115.3 (C), 108.6 (CH), 63.5 (CH_2), 62.6 (CH_2), 62.2 (CH_2), 46.5 (CH_2), 42.5 (CH_2), 39.3 (CH), 39.2 (CH_2), 38.2 (CH), 35.6 (CH_2), 32.3 (CH_2), 14.1 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{32}H_{33}N_3O_6]^+$ 555.2369, found 555.2377.

3.4.2.10 Gold-catalyzed reactions with 3-vinylindole **34l**: Synthesis of derivatives **50** and **51**

(*3S*,9aR*,Z*)-Ethyl 2-((2-oxooxazolidin-3-yl)methylene)-3-phenyl-2,3-dihydro-1*H*-carbazole-9(9a*H*)-carboxylate (50):

To a solution of the 3-vinylindole **34l** (58 mg, 0.2 mmol) and $AuCl_3$ (3.0 mg, 5.0 mol%) in CH_2Cl_2 at -50 ºC (0.1 M) was added dropwise via syringe a solution of **6a** (23 mg, 0.18 mmol) in CH_2Cl_2 (0.1 M, final concentration ca. 0.05 M). The mixture was stirred at the same temperature until disappearance of the starting reagents (checked by TLC; 1 h). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:1 + 1% Et_3N) to yield **50** (70 mg, 93%) as white solid (m.p.: 161.8-162.5 ºC).

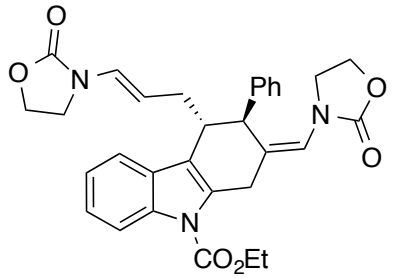


^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 7.88 (bs, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.37-7.20 (m, 6H), 7.0 (ddd, *J* = 7.5, 7.5, 0.8 Hz, 1H), 6.33 (bs, 1H), 5.94 (dd, *J* = 2.8, 2.8 Hz, 1H), 4.76-4.70 (m, 1H), 4.70 (d, *J* = 2.8 Hz, 1H), 4.44-4.32 (m, 2H), 4.24-4.14 (m, 2H), 3.58 (ddd, *J* = 8.8, .8.8, 6.3 Hz, 1H), 3.59-3.48 (m, 1H), 3.40 (ddd, *J* = 8.8, 8.8, 6.3 Hz, 1H), 2.50 (dd, *J* = 11.5, 11.4 Hz, 1H), 1.43 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 156.8 (C), 154.0 (C), 145.0 (C), 144.6 (C), 137.2 (C), 129.7 (CH), 129.2 (2 x CH), 128.7 (C), 128.1

(C), 127.6 (2 x CH), 127.0 (CH), 123.2 (CH), 123.1 (CH), 120.3 (CH), 119.8 (CH), 115.7 (CH), 62.7 (CH_2), 62.3 (CH), 62.2 (CH_2), 46.1 (CH_2), 42.9 (CH), 36.6 (CH_2), 14.8 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{25}H_{24}N_2O_4]^+$ 416.1736, found 416.1740.

(*3S*,4R*,Z*)-Ethyl 4-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-2-((2-oxooxazolidin-3-yl)methylene)-3-phenyl-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (51):

To a solution of the 3-vinylindole **34l** (58 mg, 0.2 mmol) and [Au(JohnPhos)(NTf_2)] (7.5 mg, 5.0 mol%) in CH_2Cl_2 at -20 ºC (0.1 M) was added dropwise via syringe a solution of **6a** (64 mg, 0.5 mmol) in CH_2Cl_2 (0.1 M, final concentration ca. 0.05 M). The mixture was stirred at the same temperature until disappearance of the starting reagents (checked by TLC; 1 h). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:1 + 1% Et_3N) to yield **51** (68 mg, 63%) as a yellow oil.



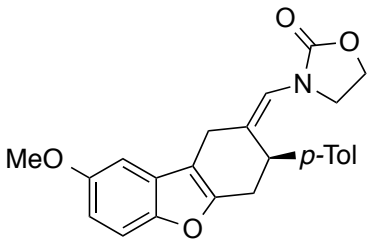
^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 8.19-8.15 (m, 1H), 7.57-7.53 (m, 1H), 7.34-7.14 (m, 7H), 6.71 (d, *J* = 14.1 Hz, 1H), 6.65 (d, *J* = 2.1 Hz, 1H), 4.95 (ddd, *J* = 14.1, 8.8, 6.3 Hz, 1H), 4.53-4.35 (m, 6H), 4.30 (bs, 1H), 4.14-4.06 (m, 1H), 3.90-3.83 (m, 2H), 3.69-3.58 (m, 4H), 2.63 (dddd, *J* = 15.1, 4.9, 4.9, 1.7 Hz, 1H), 2.42 (ddd, *J* = 15.1, 8.6, 8.6 Hz, 1H), 1.47 (t, *J* = 7.1 Hz, 3H) (trans configuration was established based on the NOE observed between the benzyl H and the exocyclic CH_2) ppm. **^{13}C-NMR** (100 MHz, CD_2Cl_2): δ = 157.7 (C), 155.2 (C), 151.7 (C), 141.4 (C), 136.3 (C), 133.6 (C), 128.8 (C), 128.4 (2 x CH), 127.2 (2 x CH), 126.4 (CH), 126.0 (C), 125.3 (CH), 123.8 (CH), 123.6 (C), 122.6 (CH), 118.0 (CH), 115.7 (CH), 108.9 (CH), 63.1 (CH_2), 62.4 (CH_2), 62.3 (CH_2), 47.0 (CH_2), 42.5 (CH_2 + CH), 37.5 (CH), 36.4 (CH_2), 31.2 (CH_2), 14.1 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{31}H_{31}N_3O_6]^+$ 541.2213, found 541.2216.

3.4.2.11 Gold-catalyzed reactions with 2-vinylbenzofuran **52**: synthesis of benzofuran derivative **53**

(*Z*)-3-((8-Methoxy-3-(*p*-tolyl)-3,4-dihydrodibenzo[*b,d*]furan-2(1*H*)-ylidene)methyl) oxazolidin-2-one (53):

To a solution of the benzofuran **52** (53 mg, 0.20 mmol) and $AuCl_3$ (3.0 mg, 5.0 mol%) in CH_2Cl_2 at -20 ºC (0.1 M) was added dropwise via syringe a solution of **6a** (23 mg, 0.18 mmol) in CH_2Cl_2 (0.1

M, final concentration ca. 0.05 M). The mixture was stirred at the same temperature until disappearance of the starting reagents (checked by TLC; 1 h). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) to yield **53** (39 mg, 50%) as a white solid (m.p.: 169.8-170.2 ºC, dec.).

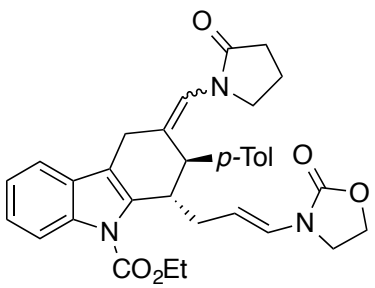


^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 9.5 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.84-6.75 (m, 2H), 6.22 (s, 1H), 4.50-4.39 (m, 3H), 3.89 (dd, *J* = 9.0, 7.7 Hz, 2H), 3.81 (s, 3H), 3.36-3.30 (m, 2H), 3.20-3.13 (m, 2H), 2.27 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 157.8 (C), 156.0 (C), 153.1 (C), 150.1 (C), 138.0 (C), 136.5 (C), 133.4 (C), 129.5 (2 x CH), 128.6 (C), 127.0 (2 x CH), 119.9 (CH), 112.2 (C), 111.7 (CH), 111.6 (CH), 101.7 (CH), 62.4 (CH_2), 56.2 (CH_3), 47.5 (CH_2), 38.6 (CH), 28.4 (CH_2), 25.6 (CH_2), 21.1 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{24}H_{23}NO_4]^+$ 389.1627, found 389.1631.

3.4.2.12 Gold-catalyzed sequential reaction between 2-vinylindole **35a** and *N*-allenamides **6b** and **6a**: synthesis of derivative **48h**

(*1S*,2R*,Z*)-Ethyl 1-((*E*)-3-(2-oxooxazolidin-3-yl)allyl)-3-((2-oxopyrrolidin-1-yl)methylene)-2-(*p*-tolyl)-3,4-dihydro-1*H*-carbazole-9(2*H*)-carboxylate (48h):

To a solution of the vinylindole **35a** (61 mg, 0.2 mmol) and [Au(JohnPhos)(NTf_2)] (7.8 mg, 5.0 mol%) in CH_2Cl_2 at -20 ºC (0.1 M) was added dropwise via syringe a solution of **6b** (24 mg, 0.2 mmol) in CH_2Cl_2 (0.1 M). The mixture was stirred at the same temperature for 4.5 h. Then, a solution of **6a** (28 mg, 0.22 mmol) in CH_2Cl_2 (0.1M) was added and the resulting mixture was stirred 48 h at -20 ºC. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate/CH_2Cl_2 1:2:1 + 1% Et_3N) to yield **48h** (86 mg, 78%, inseparable *Z*/*E* mixture, *Z*:*E* = 4:1) as a white solid (m.p.: 113.6-114.2 ºC of the mixture).



^{1}H-NMR (400 MHz, CD_2Cl_2, Major isomer): δ = 8.12 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.32-7.20 (m, 4H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.80 (s, 1H), 6.66 (d, *J* = 14.6 Hz, 1H), 4.97 (ddd, *J* = 14.6, 9.3, 5.6 Hz, 1H), 4.56 (q, *J* = 7.2 Hz, 2H), 4.49-4.34 (m, 2H), 4.32 (s, 1H), 4.25 (d, *J* = 9.2 Hz, 1H), 3.92 (ddd, *J* = 14.7, 7.8, 7.8 Hz, 1H), 3.77-3.63 (m, 3H), 3.42 (d, *J* = 18.6 Hz, 1H), 3.36 (dd, *J* = 18.6, 1.5 Hz, 1H), 2.69-2.59 (m, 2H), 2.47-2.25 (m, 2H, overlapped signal), 2.27 (m, 3H,

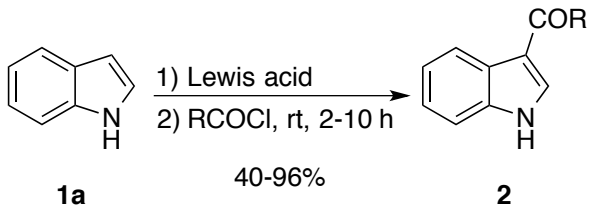
overlapped signal), 2.16-2.08 (m, 2H), 1.56 (t, *J* = 7.2 Hz, 3H). Minor isomer (only assignable signals are listed): 6.88 (d, *J* = 14.5 Hz, 1H), 5.07 (ddd, *J* = 14.5, 9.3, 5.4 Hz, 1H), 4.33 (s, 1H), 3.55 (ddd, *J* = 7.8, 7.8, 1.4 Hz, 1H) ppm. **^{13}C-NMR** (75 MHz, CD_2Cl_2, Major isomer): δ = 175.7 (C), 155.1 (C), 151.8 (C), 138.6 (C), 136.8 (C), 136.2 (C), 136.0 (C), 129.0 (2 x CH), 128.7 (C), 127.2 (2 x CH), 125.5 (CH), 124.2 (CH), 124.0 (CH), 123.6 (CH), 117.8 (CH), 115.9 (C), 115.8 (CH), 108.9 (CH), 63.1 (CH_2), 62.3 (CH_2), 49.7 (CH_2), 42.6 (CH_2), 42.5 (CH), 39.9 (CH), 35.7 (CH_2), 30.2 (CH_2), 26.7 (CH_2), 20.6 (CH_3), 19.1 (CH_2), 14.3 (CH_3). Minor isomer (only assignable signals are listed): 175.6 (C), 172.5 (C), 125.4 (CH), 123.8 (CH), 123.4 (CH), 122.8 (CH), 109.6 (CH), 45.2 (CH_2), 35.9 (CH_2), 31.1 (CH_2), 20.8 (CH_3), 17.5 (CH_2), 14.0 (CH_3) ppm. **HR-MS** (EI) calc. for $[C_{33}H_{35}N_3O_5]^+$ 553.2577, found 553.2584 (of the mixture).

Chapter 4. Gold- and silver- catalyzed synthesis of α-indolylacrylates

4.1 Introduction

The chemical modification of indoles through direct functionalization of their C–H bonds constitute a widespread research area of continuous interest for organic synthesis since this scaffold is present in a huge variety of natural product families, medicines or drug candidates, among others.[163] The most reactive position of indole towards electrophilic substitution is the C-3 site;[164] however the functionalization of N-1 and C-2 positions can also be accomplished, even when position C-3 is unsusbstituted.

In particular, the formation of a new C–C bond at C–3 position of the indole has been traditionally achieved by Friedel-Crafts alkylation and acylation reactions featuring the well-recognized reactivity of this electron-rich heteroaromatic system. A standard Friedel-Crafts reaction[1c] of unsubstituted indole **1a** with different acylating agents such as acid chlorides, anhydrides, nitriles and amino-acid derivatives in the presence of Lewis acid ($AlCl_3$, $TiCl_4$, $SnCl_4$) gives 3-acylindoles **2** regioselectively and in a good yields without laborious work-up (Scheme 4.1).



Scheme 4.1

However, these transformation require stoichiometric amount of Lewis Acids with consequent drawbacks related with functional groups compatibilities. In addition strong acylating agents are usually necessary.

More recently the introduction of innovative catalytic systems widened the scope of these reactions allowing the use of less toxic reagents than acyl chlorides and operating under milder conditions.[165]

The use of gold catalysts for the functionalization of the indole ring has been also explored in the last years.[166] Among these transformations, intermolecular hydroarylation of alkenes and alkynes

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[163] a) R. J. Sundberg, *Indoles*, Academic Press, London, **1996**; b) R. K. Brown, *Indoles* (Ed.: W. J. Houlihan), Wiley-Interscience, New York, **1972**; c) B. A. Trofimov, N. A. Nedolya, *Comprehensive Heterocyclic Chemistry*; (Eds.: G. Jones, C. A. Ramsden), Elsevier, Oxford, **2008**, vol. 3, pp. 88-168; d)J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, *Modern Heterocyclic Chemistry*, Wiley-VCH, Weinheim, **2011**, p. 377.

[164] S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, 71, 9088.

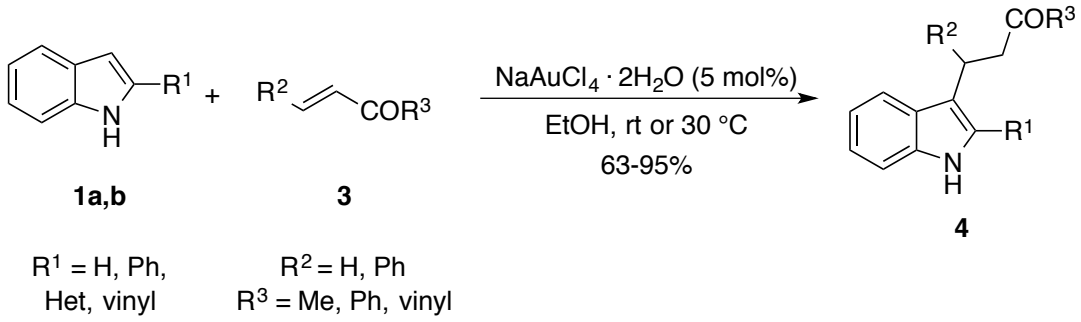
[165] a) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, *8*, 1199-1222; b) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *49*, 9608-9644.

[166] M. Dell'Acqua, D. Facoetti, V. Pirovano, G. Abbiati, E. Rossi, *Targets in Heterocyclic Systems* **2011**, *15*, 86-139.

with indoles are particularly interesting since allow efficient and selective functionalizations from simple starting materials and, importantly, occurs with atom economy.

4.1.1 Gold-catalyzed intermolecular reactions between indoles and activated alkenes and alkynes

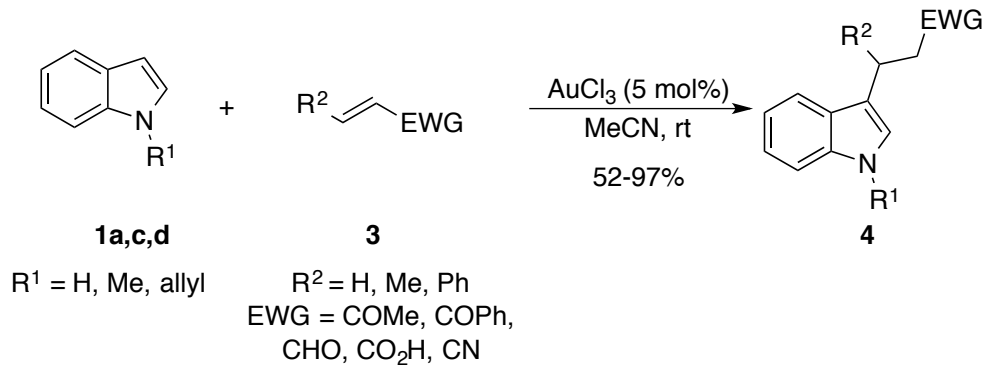
First examples of gold(III)-catalyzed functionalization of furans by Micheal-type reaction with methyl vinyl ketone were reported by Hashmi,[167] but it's only in 2004 that Arcadi and coworkers developed a procedure for the addition of α,β-enones **3** to indoles **1** (Scheme 4.2).[168] The reactions were performed in ethanol at room temperature or at 30 °C in the presence of 5 mol% of $NaAuCl_4 \cdot H_2O$. C–3 alkylated indoles **4** were obtained with high selectivity in the case of C–2 or N–1 unsubstituted starting materials. The process was later extended to the alkylation of 7-azaindoles.[169] However, possessing a much less activated C–3 position than indoles, these substrates required higher temperatures and longer reaction times.



Scheme 4.2

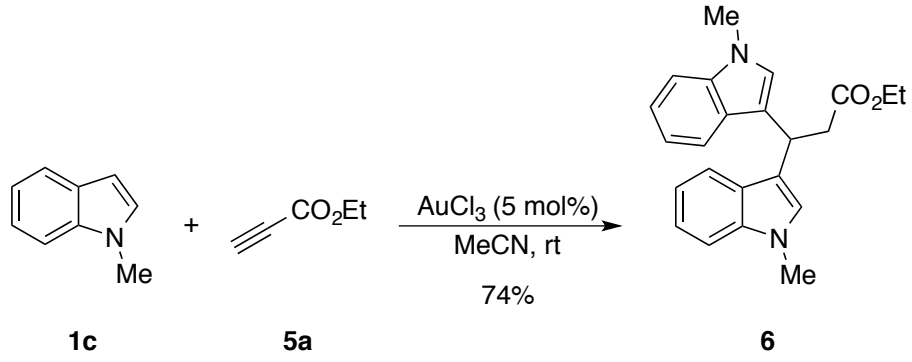
Also α,β-unsatured compounds other than enones can be employed, as reported by He. And coworkers.[171] Theyaccomplished the hydroarylation of several electron-rich arenes and heteroarenes with α,β-enones, acrylic acid and acrylonitrile in moderate to excellent yields. As catalyst 5 mol% of $AuCl_3$ was employed, using acetonitrile as solvent at room temperature. However, acrylic acid and acrylonitrile were less effective than acroleine, crotonaldehyde and methylvinylketone, which generally afforded higher yields of the corresponding products (Scheme 4.3).

[167] G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *Adv. Synth. Catal.* **2003**, *345*, 1247-1252.
[168] A. Arcadi, G. Bianchi, M. Chiarini, G. D'Anniballe, F. Marinelli, *Synlett* **2004**, 944-950.
[169] M. Alfonsi, A. Arcadi, G. Bianchi, F. Marinelli, A. Nardini, *Eur. J. Org. Chem.* **2006**, 2393-2402.
[171] Z. Li, Z. Shi, C. He, *J. Organomet. Chem.* **2005**, *690*, 5049-5054.



Scheme 4.3

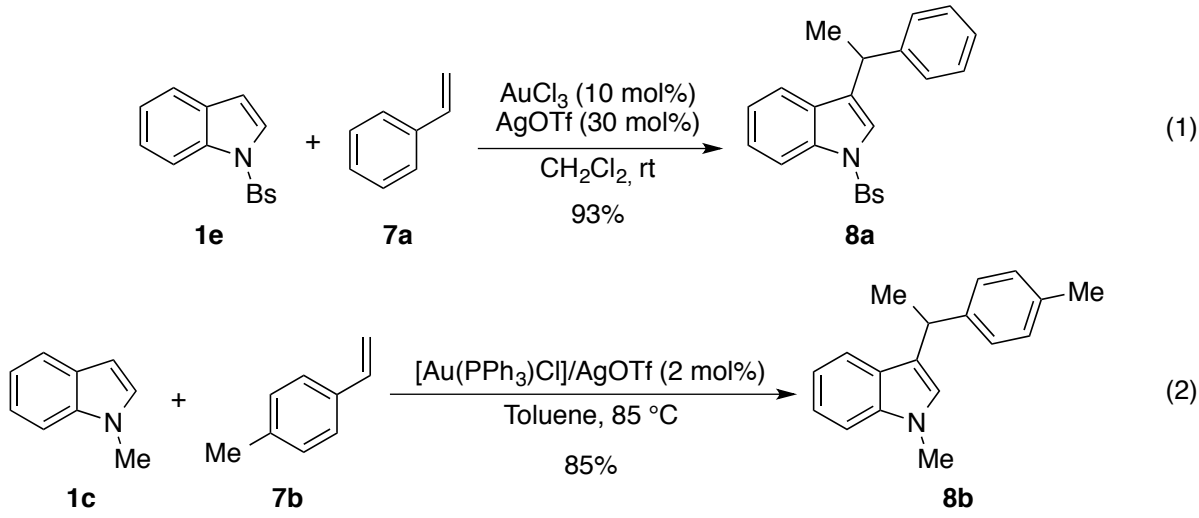
In the same work,[8] the authors described the reaction between indoles and activated alkynes such as ethyl propriolate **5a** as well. The reaction yielded only the double addition products **6** (Scheme 4.4). These results may indicate that the first hydroarylation reaction gives an activated alkene, which reacts faster then the alkyne with the second equivalent of arene to afford the bis-substituted product.



Scheme 4.4

4.1.2 Gold-catalyzed intermolecular reactions between indoles and unactivated alkenes and alkynes

The intermolecular hydroarylation of unactivated alkenes has been reported for various arenes[172] as well as for indoles. A first example was described by Liu and coworkers that reported the reaction of **1e** and styrene **7a** in the presence of $AuCl_3$/AgOTf. The reaction proceeded with high yield affording the corresponding Markovnikov derivative **8a**. Nevertheless, this hydroarylation reaction was limited to *N*-phenylsulfonyl-protected indole and could be catalyzed also by TfOH with similar yield (Scheme 4.5, Eq. 1).[173] On the other hand, Che reported an efficient intermolecular hydroarylation of unactivated alkenes with indoles using the system [(PPh_3)AuCl]/AgOTf as catalyst. First, the authors examined the coupling reaction between *N*-methylindole **1c** and *p*-methylstyrene **7b** and then, they extended the protocol to a variety of styrenes bearing electron-withdrawing, electron-donating and sterically bulky substituents to give the corresponding products in good to high yields (Scheme 4.5, Eq. 2). Unactivated aliphatic alkenes reacted under the reaction conditions described above only under microwave irradiation and coupling with indoles gave the corresponding adducts in up to 90% yield.[174]

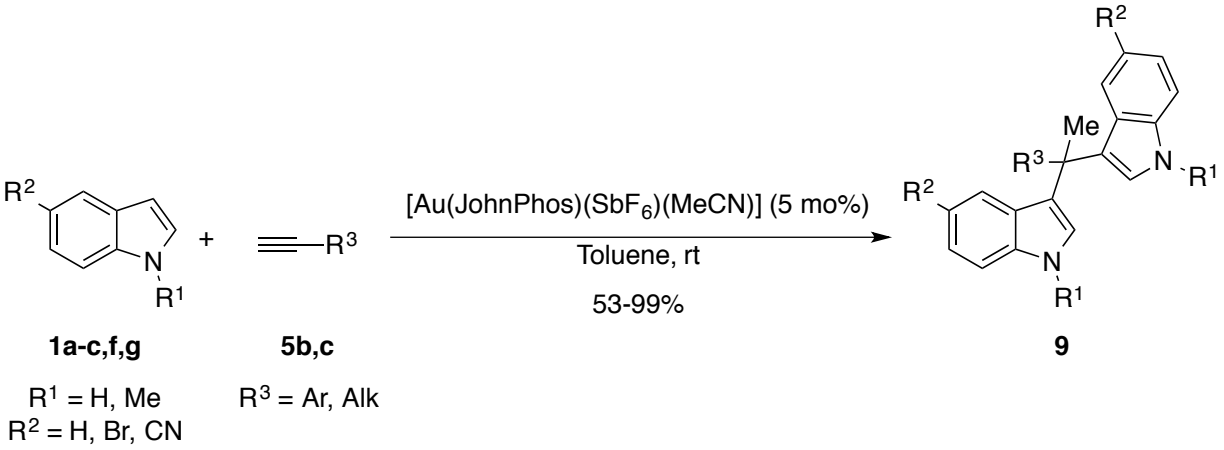


Scheme 4.5

Electronically unbiased terminal alkynes can also be employed in intermolecular reaction with indoles **1a-c,f,g** as investigated by Echavarren.[175] These transformations proceed satisfactorily in the

[172] Y.-P. Xiao, X.-Y. Lui, C.-M. Che, *J. Organomet. Chem.* **2009**, *694*, 494-501.
[173] M. M. Rozenman, M. W. Kanan, D. R. Liu, *J. Am. Chem. Soc.* **2007**, *129*, 14933-14938.
[174] M.-Z. Wang, M. -K. Wong, C. -M. Che, *Chem. Eur. J.* **2008**, *14*, 8353-8364.
[175] a) C. Ferrer, C. H. M. Amijs, A. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358-1373; b) J. Barluenga, A. Fernandez, R. Rodriguez, F. Fañánas, *J. Organomet. Chem.* **2009**, *694*, 546-550.

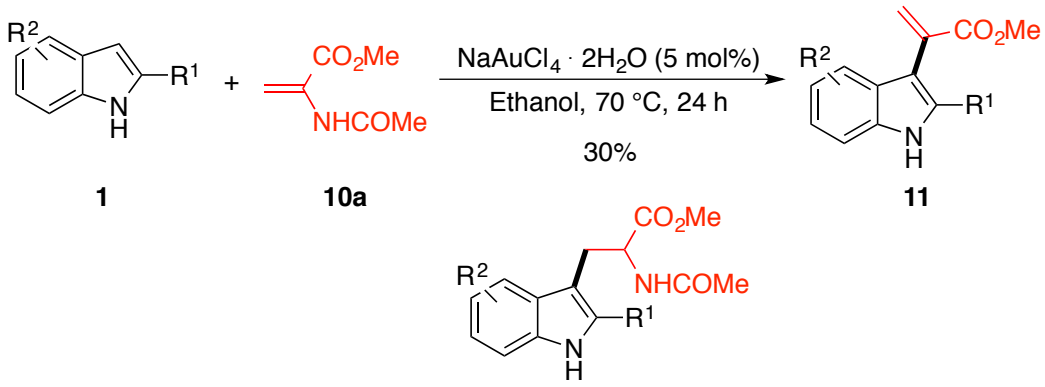
presence of cationic gold(I) catalyst to give bisindoles **9** in general high yields (Scheme 4.6). A single regioisomer was obtained in all cases, regardless on the nature of the substituents on the alkyne. This regiochemistry is opposite to that found by He in the reaction of *N*-methylindole **1c** with ethyl propriolate using $AuCl_3$ as catalyst (see Scheme 4.4).[8]



Scheme 4.6

4.2 Objectives

Taking in account the precedents described in the previous section, and based on the work described in Chapter 2, we planned to investigate the reactivity of indoles towards α-amidoacrylates,[176] as specific class of α,β-enones, in the presence of gold catalysts. According to the results obtained by Arcadi on the C–3 regioselective alkylation of indoles through gold-catalyzed conjugated addition-type reactions with enones,[6] the alkylation of the indole at position C–3 could be a feasible process that should provide an efficient modular access to relevant tryptophan analogues. In contrast, we have observed an unexpected reaction outcome, since no alkylation product was detected, but a new acrylate derivative **11**. This Chapter describes these findings (Scheme 4.7).



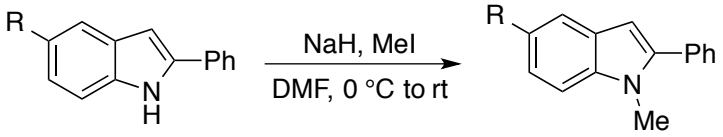
Scheme 4.7

[176] For an example on the use of α-acetamidoacrylates in the presence of Lewis acids see: E. Angelini, C. Balsamini, F. Bartoccini, S. Lucarini, G. Piersanti, *J. Org. Chem.* **2008**, *73*, 5654-5657.

4.3.1 Synthesis of starting materials

4.3.1.1 Synthesis of substituted indoles

Not commercially available 2-substituted indoles were prepared according to literature procedures as follows. *N*-methyl indoles **1i** and **1j** were obtained by simple methylation of the corresponding *NH*-free **1b,h** by treatment with NaH and iodomethane in DMF at 0 ºC (Scheme 4.8).[177]

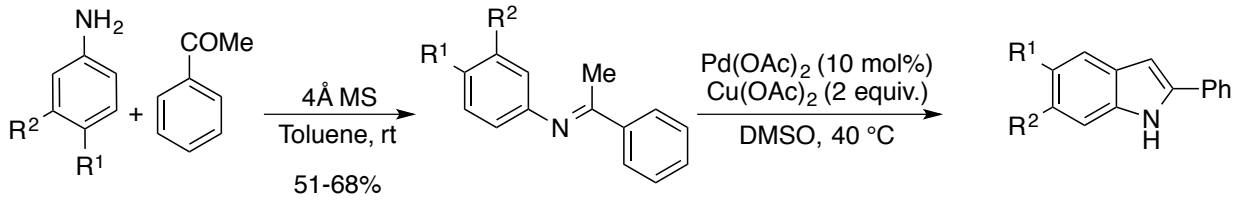


1b, h

R = H, **1i:** 84%
R = OMe, **1j:** 89%

Scheme 4.8

Indoles **1h,k,l** were prepared in two steps, as shown in Scheme 4.9. First, the imines were synthesized by condensation of the corresponding aniline with acetophenone.[178] Subsequently, the obtained *N*-aryl imines were converted into the corresponding indoles in good yields by means of an intramolecular oxidative coupling using $Pd(OAc)_2$ (10 mol%) as catalyst and $Cu(OAc)_2$ as oxidant in DMSO (Scheme 4.9).[179]



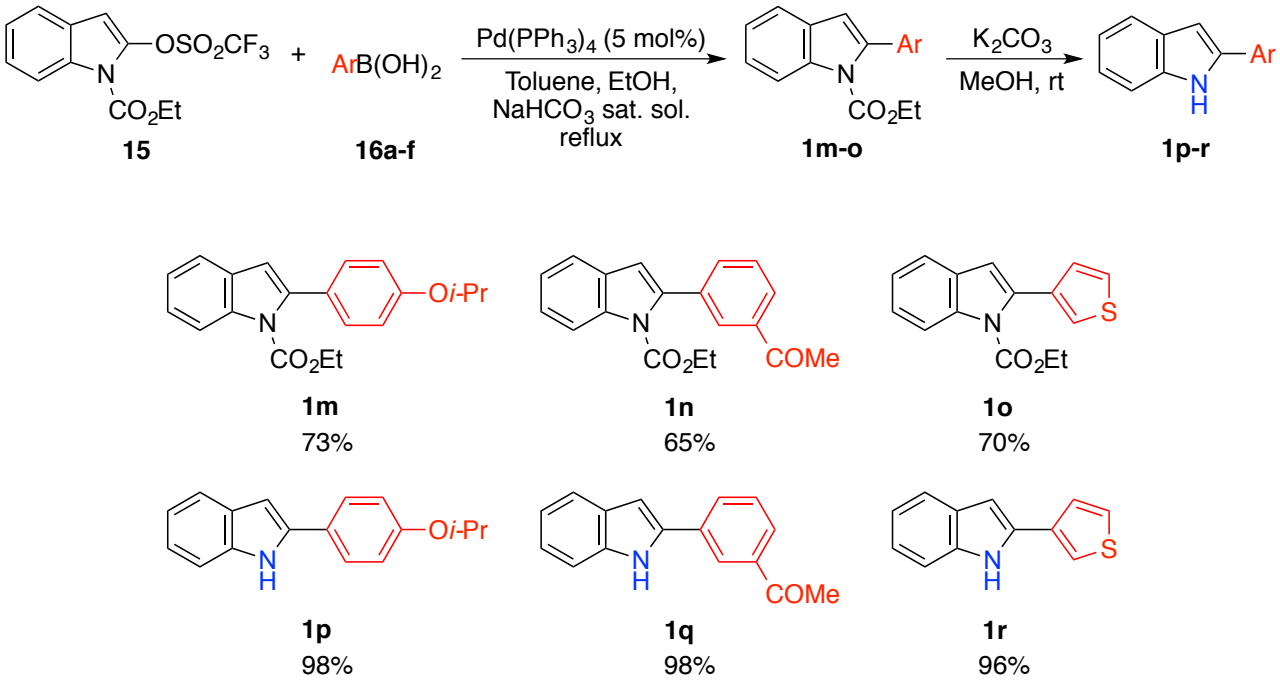
12 **13** **14a-c**

R^1 = OMe, R^2= H , **1h:** 62%
R^1 = H, R^2 = CF_3, **1k:** 69%
R^1 = NHAc, R^2 = H, **1l:** 60%

Scheme 4.9

[177] E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578-9579.
[178] F. M. Gautier, S. Jones, S. J. Martin, *Org. Biomol. Chem.* **2009**, 7, 229.
[179] Y. Wei, D. Indubhusan, Y. Naohiko, *J. Am. Chem. Soc.* **2012**, 134, 9098.

Finally, other 2-(hetero)aryl-substituted indoles **1p-r** were prepared in good to excellent yield by palladium-catalyzed Suzuki cross-coupling reactions of indole derivative **15** with the corresponding boronic acids **16a-f** followed by basic hydrolysis (Scheme 4.10).[180]

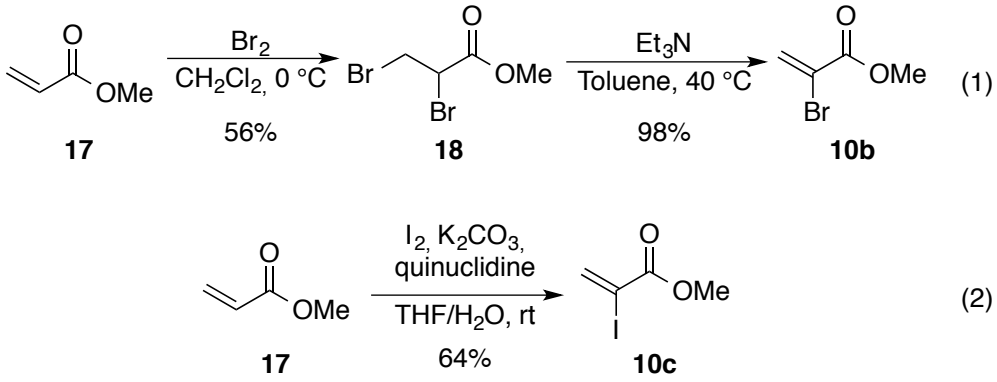


Scheme 4.10

4.3.1.2 Synthesis of acrylates

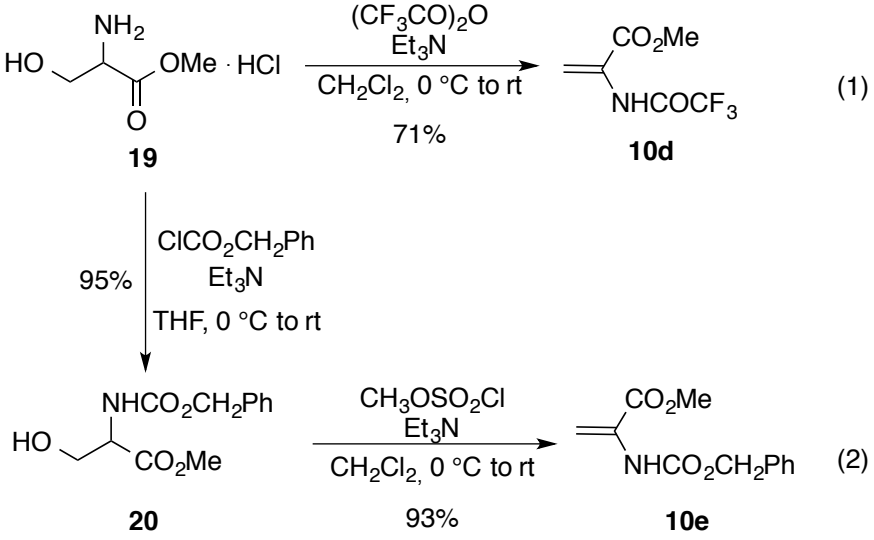
Not commercially available acrylates were prepared generally by know procedures as follows. Methyl 2-bromoacrylate (**10b**) was synthetized from methyl acrylate (**17**) through a bromination/elimination sequence (Scheme 4.11, Eq. 1).[181] The corresponding iodo-derivative **10c** was also prepared in one-pot from **17** by reaction with iodine in basic conditions (Scheme 4.11, Eq. 2).[182]

[180] E. Rossi, G. Abbiati, V. Canevari, G. Celentano, *Synthesis* **2006**, 299-304.
[181] a) B. Moon, S. Han, D. Kim, *Org. Lett.* **2005**, *7*, 3359-3361; b) A. R. Al Dulayymi, J. R. Al Dulayymi, M. S. Baird, M. E. Gerrard, G. Koza, S. D. Harkins, E. Roberts, *Tetrahedron* **1996**, *52*, 3409-3424.
[182] M. E. Krafft, J. W. Cran, *Synlett* **2005**, 1263-1266.



Scheme 4.11

Acrylate **10d** was prepared from serine methyl ester hydrochloride (**19**) by treatment with trifluoroacetic anhydride in the presence of triethylamine. This transformation yielded 2-trifluoroacetamidoacrylic acid methyl ester **10d** efficiently (Scheme 4.12, Eq. 1).[183] The synthesis of **10e** was accomplished in two steps from **19** via acetylation followed by elimination (Scheme 4.12, Eq. 2). [184]



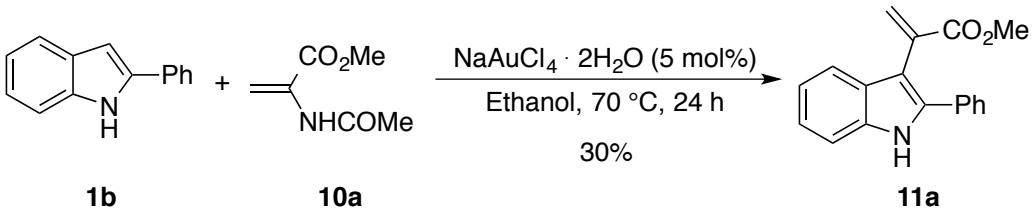
Scheme 4.12

[183] A. Avenoza, J. H. Busto, N. Canal, J. I. GarcÍa, G. Jiménez-Oses, J. M. Peregrina, M. Pérez-Fernández, *New J. Chem*. **2007**, *31*, 224-229.

[184] a) M. Iwashita, K. Makide, T. Nonomura, Y. Misumi, Y. Otani, M. Ishida, R. Taguchi, M. Tsujimoto, J. Aoki, H. Arai, T. Ohwada, *J. Med. Chem*. **2009**, 52, 5837-5863; b) L. Navarre, R. Martinez, J.-P. Genet, S. Darses, *J. Am. Chem. Soc*. **2008**, 130, 6159-6169.

4.3.2 Gold(I) and or silver catalyzed synthesis of α-indolylacrylates

Preliminary experiments on indole C–3 functionalization with acrilates were carried under conditions similar to those reported by Arcadi in the study of gold-catalyzed conjugated addition of indoles to enones.[6] These reactions, performed in ethanol at room temperature and in the presence of 5 mol% of $NaAuCl_4 \cdot H_2O$ afforded the corresponding alkylated indoles in good yields. However, when 2-phenylindole **(1b)** was treated with compound **10a** in the presence of $NaAuCl_4$ at room temperature, the expected tryptophan derivative was not detected in the reaction mixture and starting materials were recovered unaltered. In contrast, when the reaction was carried out at 70 °C, a new compound identified as indolylacrylate **11a** was isolated in 30% yield (Scheme 4.13).



1b **10a** **11a**

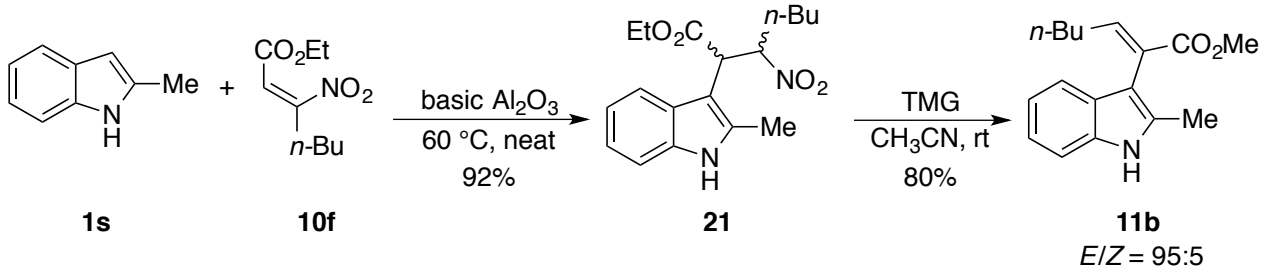
Scheme 4.13

Despite the modest yield, the reaction outcome is remarkable since it represents a new reactivity pattern in gold catalysis.

Moreover, the structure of compound **11a** is interesting as acrylate derivatives are compounds of relevance in chemistry.[185] These reasons justified a deeper study in order to establish optimized conditions and determine the scope of the reaction. In addition, 2-(1*H*-indol-3-yl)acrilates are scarcely described in literature and mainly prepared by addition/elimination sequences as reported for example by Petrini in 2008 (Scheme 4.14).[186]

[185] a) J. M. J. Frechet, *Science* **1994**, *263*, 1710-1715; b) E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor, M. A. Gallop, *J. Med. Chem.* **1994**, *37*, 1385-1401; c) E. Sackmann, *Science* **1996**, *271*, 43-48; d) R. Langer, D. A. Tirrell, *Nature* **2004**, *428*, 487-492.

[186] a) E. Conchon, F. Anizon, B. Aboab, R. M. Golsteyn, S. Leonce, B. Pfeiffer, M. Prudhomme, *Eur. J. Med. Chem.* **2008**, *43*, 282-292; b) R. Ballini, S. Gabrielli, A. Palmieri, M. Petrini, *Tetrahedron* **2008**, *64*, 5435-5541; c) R. J. Sundberg, J. Hong, S. Q. Smith, M. Sabat, I. Tabakovic, *Tetrahedron* **1998**, *54*, 6259-6292.



1s **10f** **21** **11b**

E/*Z* = 95:5

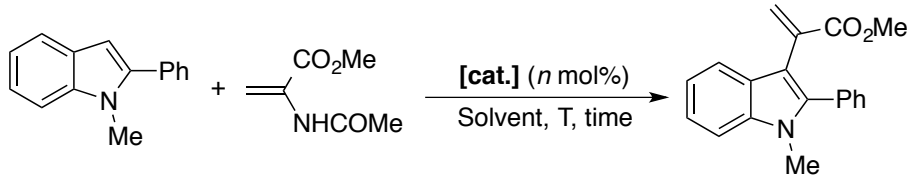
TMG = 1,1,3,3-Tetramethylguanidine

Scheme 4.14

4.3.2.1 Screening of reaction conditions

Using indole **1i** and acetamido acrylate **10a** as a model reaction, a series of reaction conditions were tested to optimized the synthesis of **11c** (Table 4.1).

Table 4.1:Screening of reaction conditions for the synthesis of 11c



1i **10a** **11c**

Entry	Catalyst, mol%	Solvent	T, °C	time, h	Yield, %[a]
1	$NaAuCl_4{\cdot}2H_2O$, 5	EtOH	70	24	30
2	–	Toluene	130 (mw)	6	–
3	$NaAuCl_4{\cdot}2H_2O$, 4	CH_2Cl_2	60	30	–
4	$AuCl_3$, 4	Toluene	130	48	–
5	$[Au(PPh_3)Cl]/AgOTf$, 2	EtOH	70	30	–
6	$[Au(PPh_3)Cl]/AgOTf$, 2	EtOH	100 (mw)	6	–
7	$[Au(PPh_3)Cl]/AgOTf$, 2	DMF	100 (mw)	6	–
8	$[Au(PPh_3)Cl]/AgOTf$, 2	DCE	130 (mw)	6	31
9	$[Au(PPh_3)Cl]/AgOTf$, 2	CH_3CN	100 (mw)	6	48
10	$[Au(PPh_3)Cl]/AgOTf$, 2	CH_3Cl	100 (mw)	6	60
11	$[Au(PPh_3)Cl]/AgOTf$, 2	Toluene	130	6	74
12	$[Au(PPh_3)Cl]/AgOTf$, 2	Toluene	130 (mw)	6	70
13	$[Au(PPh_3)Cl]/AgOTf$, 4	Toluene	130	6	80
14	[Au(IPr)Cl]/AgOTf, 4	Toluene	130	6	76
15	$[Au(PPh_3)(OTf)]$, 4	Toluene	130	6	75
16	$[Au(PPh_3)(NTf_2)]$, 4	Toluene	130	6	79
17	AgOTf, 4	Toluene	130	6	74
18	$AgSbF_6$, 4	Toluene	130	3	83
19	$AgNTf_2$, 4	Toluene	130	3	85

Reaction conditions: To a solution of the catalyst in the appropriate solvent (5 mL) **1i** and **10a** were added and the mixture stirred at the stated temperature for 3-48 h.
[a]:Isolated yields.

The reaction between **1i** and **10a** failed in the absence of catalysts, or using $NaAuCl_4{\cdot}H_2O$ in dichloromethane (sealed tube) or $AuCl_3$ in toluene at a higher temperature (entries 2-4). On the

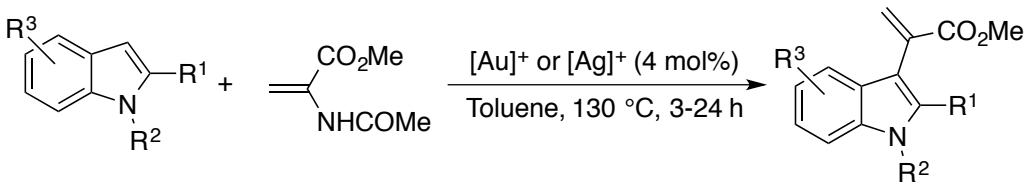
other hand, cationic gold(I) complex generated in situ from [Au(PPh_3)Cl] and AgOTf, led to poor results when ethanol or dimethylformamide were used as solvents (entries 5-7). Interestingly, the same catalytic system showed a reasonable performance to access the desired compound **11c** when using 1,2-dichloroethane, acetonitrile and chloroform, which enabled to obtain **11c** in a practical yield of 60% (entries 8-10). Interestingly, the use of toluene under conventional heating (sealed tube, 130 °C) or under microwave irradiation (130 °C) (entries 11-12) allowed the preparation of **11c** in 74% and 70% yield, respectively. In addition, increasing the catalyst loading up to 4 mol% led to the desired product in 80% yield (entry 13). The use of different type of cationic gold(I) did not affected particularly the reaction course and similar yields were obtained using phosphines (PPh_3) or *N*-heterocyclic carbene (IPr) as ligands (entries 13-14). Generation of the cationic species in situ[187] or use of the preformed cationic gold [Au(PPh_3)(NTf_2)] did not influence the formation of the product (entries 13 and 15-16). A different experiment showed that AgOTf was catalytically active as well, yielding **11c** in 74% (entry 17). Other commonly employed silver salts as $AgSbF_6$ and $AgNTf_2$ were subsequently tested and provided slightly better yields in shorter reactions (entries 18-19).

4.3.2.2 Scope of the reaction

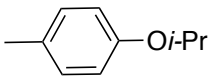
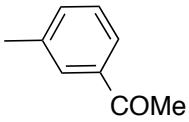
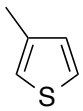
Using the best reactions conditions described in Table 4.1 the study of the scope of this transformation was then carried out. Both gold- and silver-catalyzed transformations were in parallel evaluated. Thus, reaction conditions described in Table 4.1, entry 16 were used for gold-catalyzed reactions to avoid interferences with the adventitious presence of silver. In the case of silver, cheap $AgSbF_6$ was the catalyst of choice considering the similar yields obtained and taking into account that higher price of $AgNTf_2$. As dielectric heating did not offer advantages according to the experiments performed before, conventional heating was selected. In the Table 4.2 are shown the results of the investigation on the gold- and silver-catalyzed reactions.

[187] The catalyst was prepared by mixing an equimolecular amount of [Au(PPh_3)Cl] and AgOTf in dry toluene. The obtained suspension was filtered through a syringe fitted with a Whatman Anotop 10 IC filter to remove the AgCl precipitate. The solution was then charged with the reactants as reported in Table 4.1.

Table 4.2: Scope of the reaction between 1 and 10a



1 **10a** **11**

Entry	1	R^1	R^2	R^3	Time, h	[cat.]	11	Yield, %[a]
1	**1i**	Ph	Me	H	3	$AgSbF_6$	**11c**	83
					6	$[Au(PPh_3)(NTf_2)]$		79
2	**1b**	Ph	H	H	6	$AgSbF_6$	**11a**	60
					6	$[Au(PPh_3)(NTf_2)]$		93
3	**1j**	Ph	Me	5-OMe	23	$AgSbF_6$	**11d**	76
					23	$[Au(PPh_3)(NTf_2)]$		71
4	**1h**	Ph	H	5-OMe	23	$AgSbF_6$	**11e**	62
					23	$[Au(PPh_3)(NTf_2)]$		70
5	**1k**	Ph	H	6-CF_3	6	$AgSbF_6$	**11f**	46
					6	$[Au(PPh_3)(NTf_2)]$		50
6	**1l**	Ph	H	5-NHAc	6	$AgSbF_6$	**11g**	53
					6	$[Au(PPh_3)(NTf_2)]$		58
7	**1p** 		H	H	6	$AgSbF_6$	**11h**	76
					24	$[Au(PPh_3)(NTf_2)]$		21
8	**1q** 		H	H	6	$AgSbF_6$	**11i**	76
					6	$[Au(PPh_3)(NTf_2)]$		78
9	**1r** 		H	H	6	$AgSbF_6$	**11l**	51
					5	$[Au(PPh_3)(NTf_2)]$		82
10	**1t**	Me	Me	H	4	$AgSbF_6$	**11m**	63
					4	$[Au(PPh_3)(NTf_2)]$		73
11	**1s**	Me	H	H	6	$AgSbF_6$	**11n**	62
					6	$[Au(PPh_3)(NTf_2)]$		87

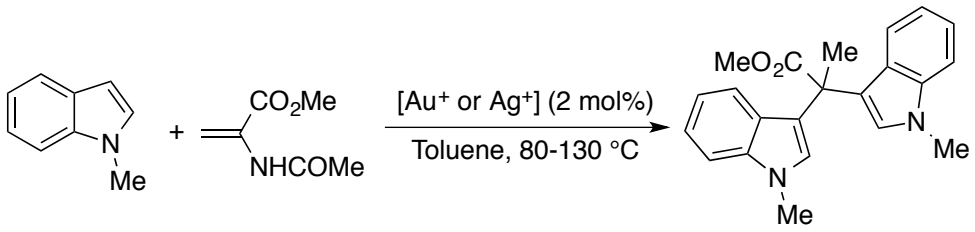
Reaction conditions: to a solution of the catalyst in toluene (5 mL) **1** and **10a** (1.1 equiv.) were added and the mixture was stirred at 130 °C for 4-24 h.
[a]:Isolated yields.

The reaction worked well with both *N*-methyl and *N*-unsubstituted indole **1b**,**i**. In the case of the *N*–*H*-free indole **1b**, cationic gold(I) catalyst was superior to the silver one (entry 2). Good results

were obtained with 2-phenylindoles bearing both electron-withdrawing or donating substituents at positions 5 or 6 of the indole (entries 3-6) or at the aryl moiety (entries 7-8). Remarkably, the presence of an additional electron-rich heteroarene as 3-thiophenyl at position C–2 was tolerated and the reaction proceeded exclusively on the indole ring (entry 9). 2-Methyl-substituted indoles were also suitable substrates affording the corresponding acrylates **11m,n**, being gold catalyst more effective in these cases (entries 10-11).

The reaction outcome was completely altered when 2-unsubstituted *N*-methylindole **1c** was chosen as substrate (Table 4.3.). Thus, under optimized conditions for gold catalysis, methyl 2,2-bis(1-methyl-1*H*-indol-3-yl)propanoate (**22**) was isolated in modest yield along with unreacted **1c** and a mixture of unidentified tarry compounds. A search of more convenient reaction conditions to access **22** was then performed. Thus, when the reaction was carried out with excess of **1c** at 80 °C **22** was obtained in a useful yield using both gold- and silver catalysis.

Table 4.3: Reaction between 1c and 10a: synthesis of derivative 22



1c **10a** **22**

Entry	1c/10a	[cat.]	T, °C	Time, h	Yield, %[a]
1	1:1.1	[Au(PPh_3)Cl]/AgOTf	130	6	26
2	2:1	[Au(PPh_3)Cl]/AgOTf	80	48	59
3	2:1	AgOTf	80	48	56

Reaction conditions: to a solution of the catalyst in toluene (5 mL) **1c** and **10a** were added and the mixture was stirred at the stated temperature for 6-48 h.
[a]: Isolated yields.

This chemical behavior is noteworthy as allow to access selectively to 2,2-disubstituted propanoate **22**, which is not accessible through intermolecular hydroarylation of propiolates, which led to the 3,3-disubstituted isomer (see Scheme 4.4).[8]

Acrylate derivatives **11a-m** were characterized based on ^{1}-H and ^{13}C-NMR analysis. Representative spectra for **11c** are reported in Figures 4.1 and 4.2, respectively.

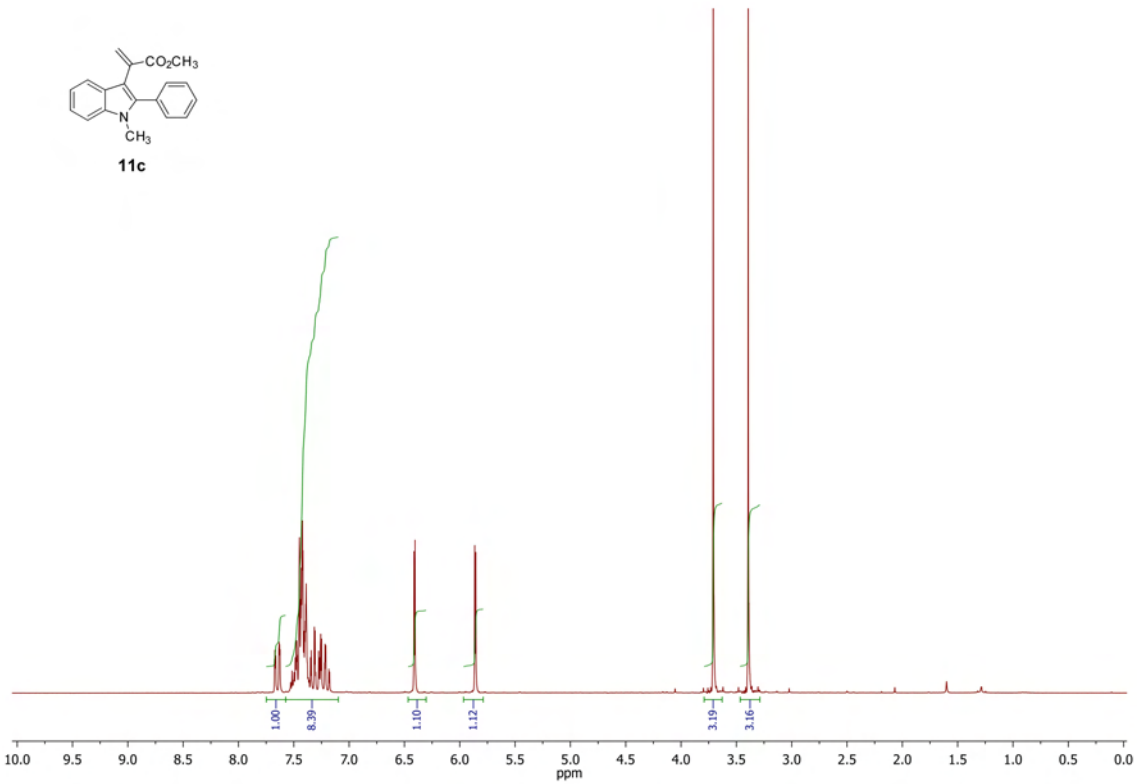


Figure 4.1

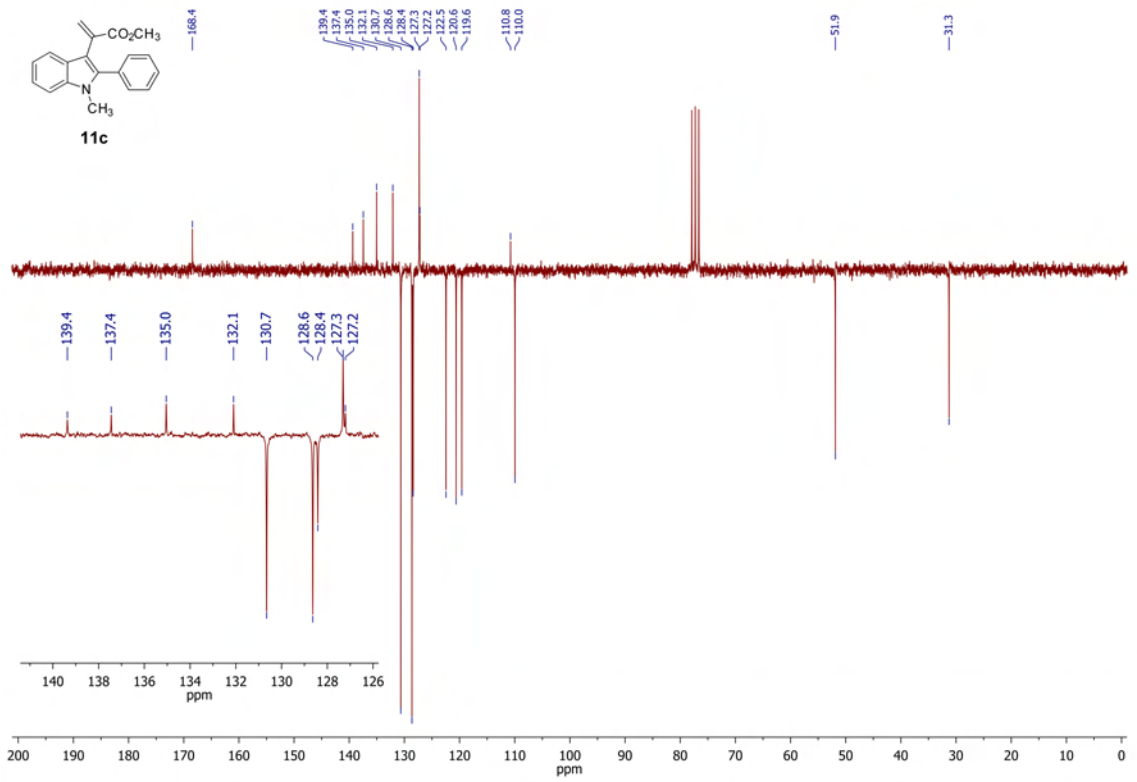
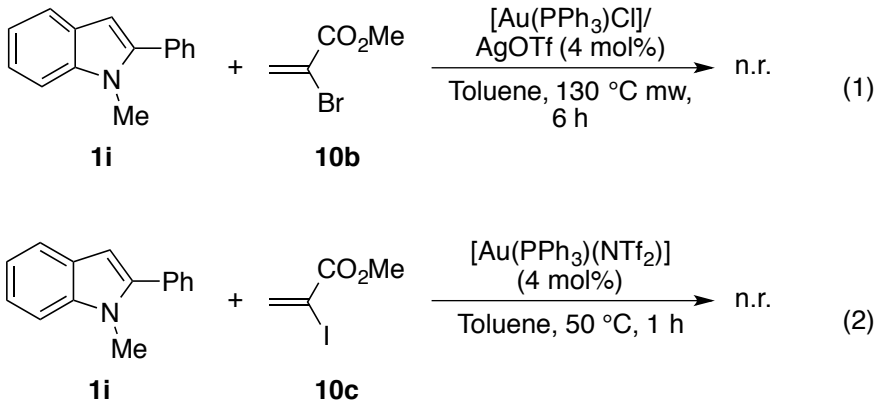


Figure 4.2

The influence of the structure of the enone derivative was also evaluated with the aim to understand the role of the leaving group on the reaction course and to develop milder conditions for the preparation of **ZZ** derivatives.

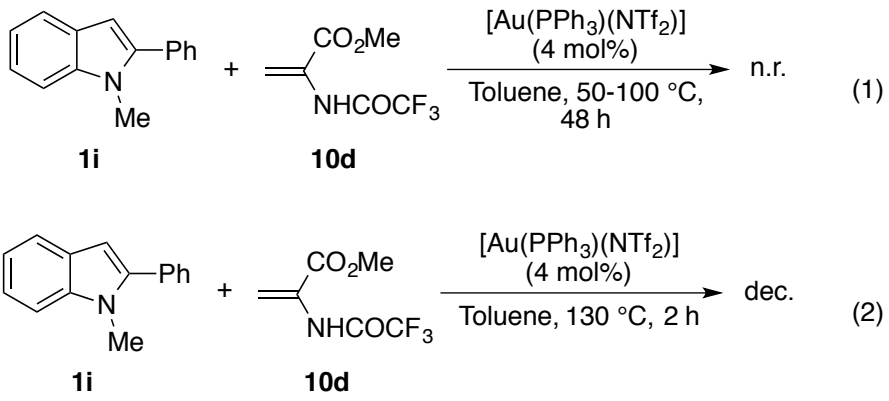
The acetamido moiety of **10a** was substituted with a halogen atoms such as bromine or iodine. However, reaction of acrylates **10b,c** failed leaving starting indole **1i** unreacted. The reactivity of bromo-derivative was tested in the presence of cationic gold(I) generated *in situ*, at 130 °C (microwaves heating) but product **22** was never observed (Scheme 4.15, Eq. 1).

Furthermore, **10c** was reacted in the presence of [Au(PPh$_3$)(NTf$_2$)] at 50 °C but iodo-derivative revealed to be unstable even at this lower temperature (Scheme 4.15, Eq. 2).



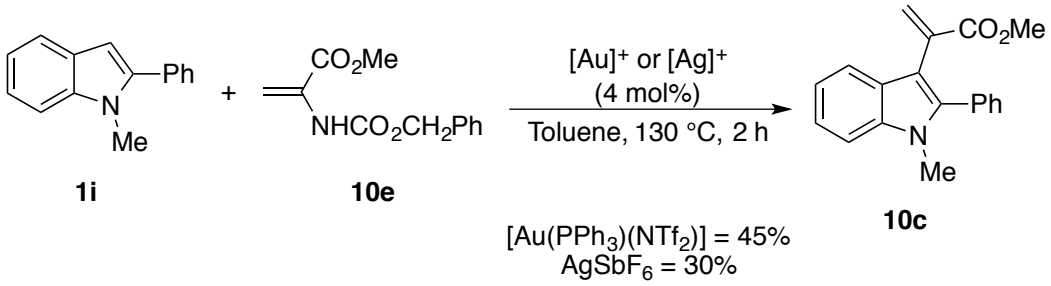
Scheme 4.15

Further modifications on the acetamido moiety were then studied. Thus, **10d** and **10e** were tested under various conditions. A first reaction using methyl trifluoroacetamidoacrylate **10d** was conducted at 50 °C. However no product was observed and both indole **10a** and **10d** remained unreacted even increasing the temperature up to 100 °C during 48 h (Scheme 4.16, Eq. 1). Reaction under standard conditions was neither effective nor led to decomposition of acrylate derivative after 2 h (Scheme 4.16, eq. 2).



Scheme 4.16

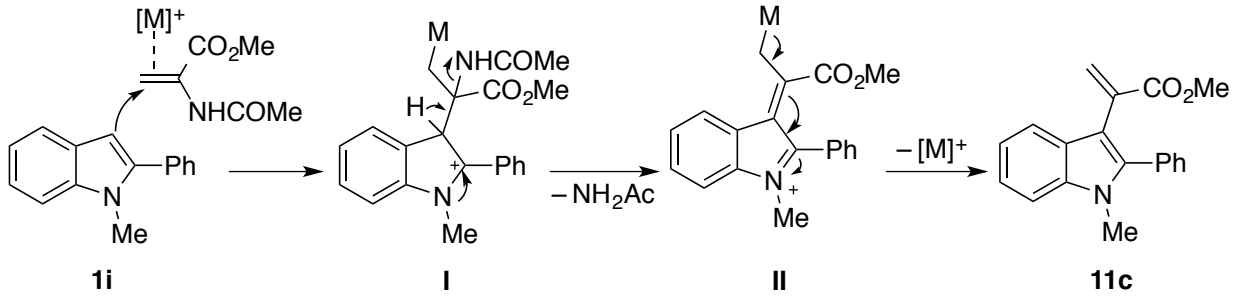
Benzyloxycarbonyl acrylate derivative **10e** was also tested under standard reaction conditions using both $[Au(PPh_3)(NTf_2)]$ and $AgSbF_6$ as catalysts. In this case product **11c** was obtained albeit in lower yield than when using **10a** (Scheme 4.17).



Scheme 4.17

4.3.2.3 Proposed reaction mechanism

A plausible mechanism that could account for formation of the products is shown in Scheme 4.18. Coordination of the catalyst to the C–C double bond of **10a** likely enhances its electrophilicity and facilitate the addition of the indole to give intermediate **I**. Then, a fast thermal and proton assisted elimination of acetamide might afford intermediate **II**. The intermediacy of conjugated structures like **II** has been reported for the reaction of indoles with carbonyl compounds.[188] Finally, a metal elimination with a concomitant rearomatization would account for the formation of the acrylate derivative **11c** and the turnover.[189]



Scheme 4.18

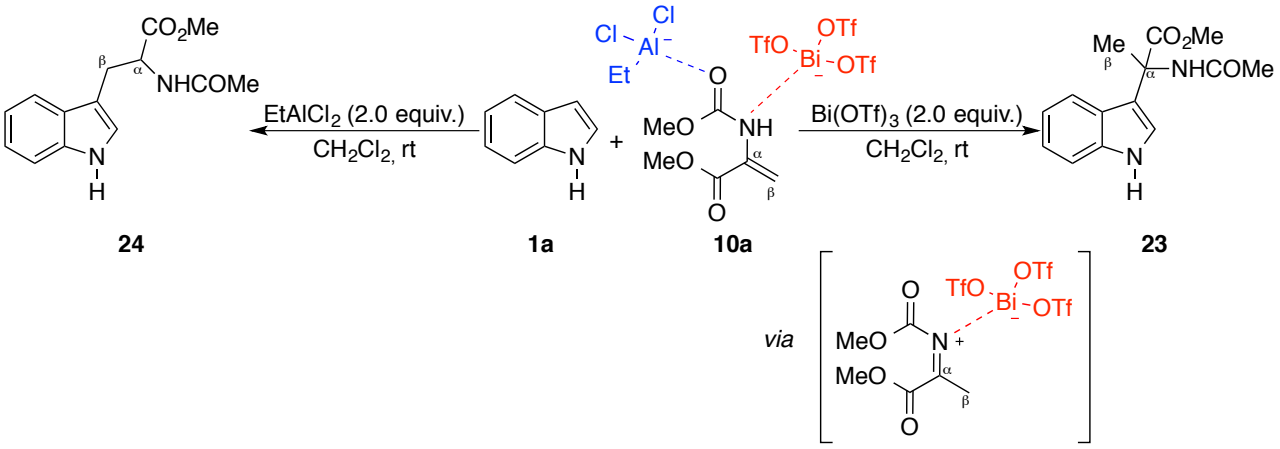
Alternatively, a Lewis acid σ-activation by coordination of the catalyst to the carbonyl oxygen or amide nitrogen of **10a** has been invoked and confirmed by ^{1}H-NMR experiments, to explain the α versus β selectivity observed in the addition of indoles to dehydroalanine by Piersanti and coworkers.[13, 190] In fact, when indole (**1a**) was treated with stoichiometric amounts of Lewis acids, its reaction on the α- or β-carbon of **10a** was strictly dependent on the soft or hard nature of the Lewis species, as shown in Scheme 4.19. Thus, when $Bi(OTf)_3$, a soft Lewis acid, was employed, coordination of the metal to the nitrogen of the amide group led to the formation of a *N*-acylamine intermediate with subsequent nucleophilic attack of the indole on the α position of **10a**. On the other side, hard Lewis acid $EtAlCl_2$ coordinates to the carbonyl group affording the corresponding tryptophan derivative **24** by reaction of indole C–3 on the β carbon of the acrylate.

---

[188] R. A. Jones, *Comprehensive Heterocyclic Chemistry*, (Eds.:A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, vol. 4. pp 205-242.

[189] A mechanism involving a heterocyclic Csp_2-H activation step was disregarded; see: a) T. de Haro, C. Nevado, *Synthesis* **2011**, 2530-2539; b) P. Lu, T. C. Boorman, A. M. Slawin, I. Larrosa, *J. Am. Chem. Soc.* **2010**, *132*, 5580-5581; c) S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 2742-2744; d) I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* **2010**, *132*, 8858-8859; d) A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 971-975.

[190] A. Avenoza, J. H. Busto, N. Canal, J. M. Peregrina, M. Perez- Fernandez, *Org. Lett.* **2005**, *7*, 3597-3600.



Scheme 4.19

This hypothesis was evaluated by ^{1}H-NMR analysis of an equimolecular mixture of dehydroaminoacid **10a** and the catalyst (both cationic gold(I) and silver) in benzene-d_6 The NMR spectra did not show any significant chemical shift variation or broadening in the signals with respect to pure **10a**. These observations suggest that an electrophilic *N*-acylimine **III** intermediate is unlikely (Figure 4.3).

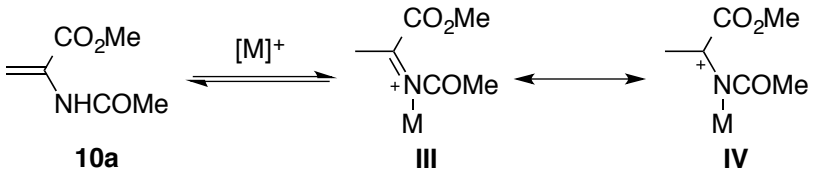
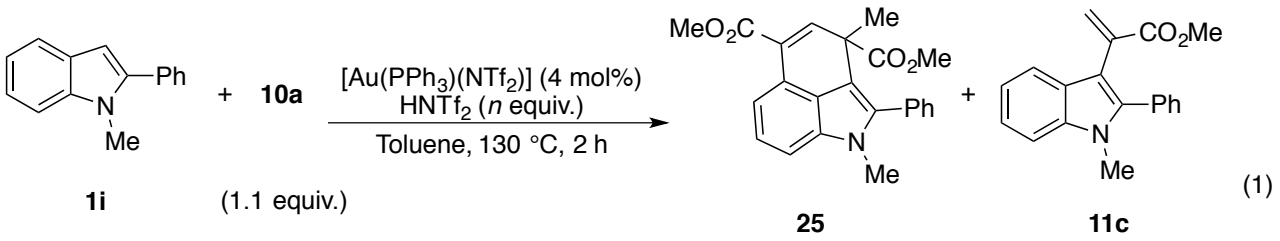


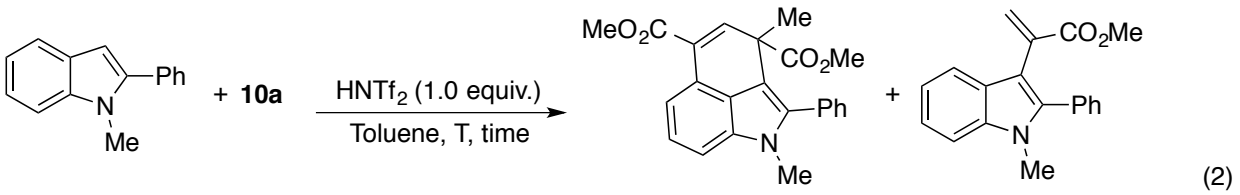
Figure 4.3

Moreover, considering that the reaction medium is somewhat acidic, protonation of the acetamido moiety prior to elimination cannot be excluded. In order to shed light on this fact, control experiments were accomplished. Thus, the reaction was tested in the presence of cationic gold(I) catalyst and 0.1-1 equivalent of $HNTf_2$ (Scheme 4.20, Eq. 1). In addition, **1i** and **10a** were also treated with 1 equivalent of $HNTf_2$ in toluene at 130 °C as well as at rt in the absence of catalyst (Scheme 4.20, Eq. 2).[191]

[191] Triflimide was always chosen as an acidic promoter in order to avoid modification in the counterion structure.



	25	11c
0.1 equiv.:	–	83%
1.0 equiv.:	62%	–



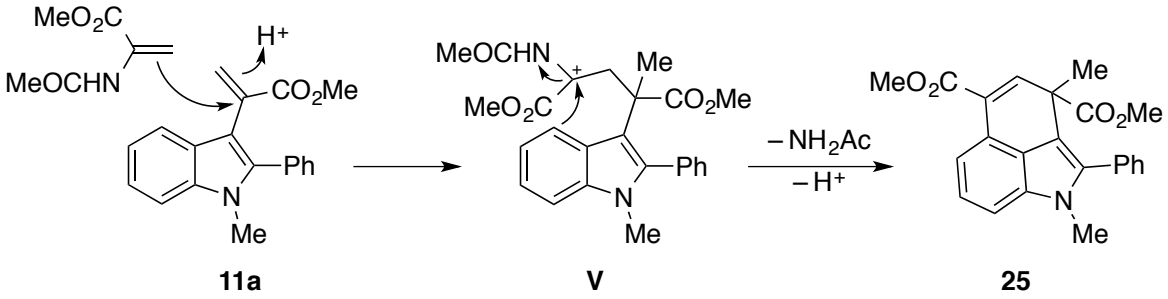
	25	11c
130 °C, 2 h:	33%	9%
rt, 48 h:	–	26%

Scheme 4.20

As illustrated, the use of $HNTf_2$ as a cocatalyst (10 mol%) did not alter the reaction outcome. This result suggests that the elimination of the acetamido moiety from intermediate **I** does not benefit from the presence of an excess of acid. Interestingly, when $HNTf_2$ was used in stoichiometric amounts either in the presence or absence of the gold catalyst at a reaction temperature of 130 ºC an interesting new reaction outcome was observed, while at ambient temperature low yield formation of the expected product was obtained (Scheme 4.20, Eq. 2). The structure of the new compound **25** is interesting as shows an uncommon tricyclic 1,3-dihydrobenzo[*cd*]indole core. Compound **25** was originated by the selective coupling of one molecule of indole and two molecules of the dehydroaminoacid **10a**, whose acetamido groups were lost. The structure of **25** was established by NMR studies.[192]

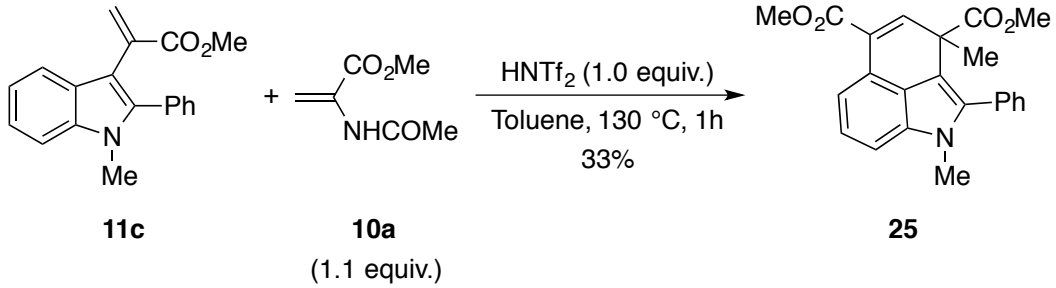
Accordingly to the obtained results, a mechanism involving pure protic catalysis for the formation of **11c** can be reasonably rule out. Moreover, a mechanistic rationale for the formation of **25** likely involved proton-catalyzed addition of a second molecule of **10a** on **11c** followed by electrophilic aromatic substitution at position C–4 of the indole and loss of acetamide (Scheme 4.21).

[192] See experimental part for complete NMR analysis



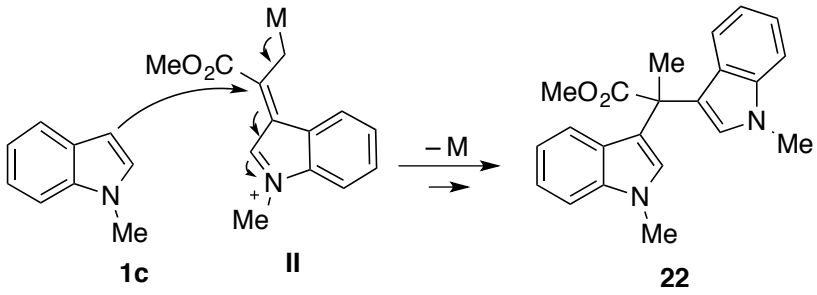
Scheme 4.21

This hypothesis was supported also by experimental evidences. In fact, reaction of **11c** with 1.1 equivalents of acetamidoacrylate 10a in the presence of stoichiometric amounts of $HNTf_2$ yielded **25** although in low yield (Scheme 4.22).



Scheme 4.22

The reaction mechanism reported in Scheme 4.18 also accounts for the behavior of 2-unsubstituted indole **1c**, which led to the formation of compounds **22** (see Table 4.3). The formation of **22** from **1c** may likely take place through conjugate addition of a second molecule of indole to an intermediate like **II**. An analogous behavior is not allowed for 2-substituted indole, as the elimination pathway is probably favored by steric hindrance and by the high reaction temperature involved (Scheme 4.23).



Scheme 4.23

4.4 Experimental data

4.4.1 Preface

4.4.1.1 General methods

All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere.

4.4.1.2 Reagents

This study was carried out using indoles **1h-l, p-r** which are known compounds, prepared following the procedures described in literature.[14-17] Indoles **1b,c** are commercially available and used without any further purification.

N-Acetylacrylammide methyl ester **10a** is commercially available product while **10c-e** were prepared according to the procedures reported in literature.[19-21]

AgOTf, $AgSbF_6$, $AuCl_3$ and $[Au(PPh_3)Cl]$ were purchased from commercial suppliers and used as received, the rest of the gold catalysts were prepared according to literature procedures.[193]

4.4.1.3 Solvents

Some solvents, used for reactions sensitive to oxygen and hydrolysis, were distilled and stored in a protected atmosphere of nitrogen, according to the following standard operations:

Dichloromethane: distilled on $CaCl_2$ and placed on 4Å sieves into a recycling appliance.

Toluene: distilled on metallic sodium and placed on 4Å sieves into a recycling appliance.

The other anhydrous solvents employed are available commercially.

[193] a) N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133-4136; b) L. Ricard, F. Gagosz, *Organometallics*, **2007**, *26*, 4704-4707.

4.4.1.4 Chromatography/purification of compounds

The chromatographic column separations were conducted by flash technique, using silica gel *Merck Grade 9385 60Å* (230-400 mesh).
For thin-layer chromatography (TLC), silica gel 60778-25EA *FLUKA* thin-layer plates were employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 365 nm), by basic solution of $KMnO_4$ (3.0 g $KMnO_4$, 20.0 g K_2CO_3 and 0.3 g KOH in 300 mL of H_2O) or with iodine vapours.

4.4.1.5 NMR spectroscopy

^{1}H NMR analysis were performed with a Varian-Gemini 200 or with Bruker 300, 500 Avance spectrometers at room temperature, respectively at 200, 300, or 500 MHz. The coupling constants (*J*) are expressed in Hertz (Hz), the chemical shifts (δ) in ppm. The multiplicities of the proton spectra were described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), dq (double quartet), dt (double triplet), td (triple doublet), ddd (double double doublet).

^{13}C NMR analyses were performed with the same instruments at 50.3, 75.45 and 125.75 MHz; APT sequences were used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms.

^{19}F NMR analyses were carried out with Bruker 300 Avance spectrometer at 282.4 MHz.

Two-dimensional NMR techniques (COSY, NOESY, HSQC, HMBC) were performed to assign the structure of **25**.

4.4.1.6 IR spectroscopy

Infrared spectra were recorded with *Perkin Elmer FT-IR 16 PC* spectrometer, using discs of NaCl for liquid samples and KBr tablets for solid samples. The absorbance is expressed in wavenumbers (cm^{-1}) with values between 4000 and 400 cm^{-1}.

4.4.1.7 Mass spectrometry

Low resolution MS spectra were recorded with a Fisons MD 800 spectrometer with electron impact source and a Thermo-Finnigan LCQ-advantage AP electrospray/ion trap equipped instrument, using a syringe pump device to directly inject sample solutions. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown in brackets.

4.4.1.8 Melting points

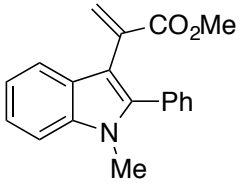
The melting points of the solid products were measured in capillary tube with the device *Stuart Scientific SMP3*.

4.4.2 Experimental data

4.4.2.1 General procedure for the synthesis of α-indoloacrylates **11a,c-n**

To a solution of the catalyst (4 mol%) in anhydrous toluene (5 mL) in a screw cap tube indoles **1** (0.50 mmo, 1.0 equiv.) and 2- α-acetamidoacrylate **2a** (0.55 mmol, 1.1 equiv.) were added at room temperature. The solution was stirred at 130 °C for the time indicated in Table 4.2 then the solvent was removed at reduced pressure. The crude mixture was subjected to flash column chromatography (SiO_2, hexane/ethyl acetate 95:5 to 8:2) to yield the corresponding α-indoloacrylates **11** (for yields see Table 4.2).

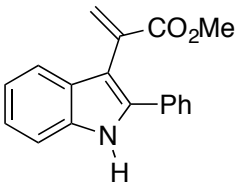
Methyl 2-(1-methyl-2-phenyl-1*H*-indol-3-yl)acrylate (11c)



Yellow solid, m.p.: 76.5-78 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.62-7.67 (m, 1H), 7.15-7.51 (m, 8H), 6.40 (d, *J* = 1.8 Hz, 1H), 5.86 (d, *J* = 1.8 Hz, 1H), 3.71 (s, 3H), 3.39 (s, 3H) ppm. **^{13}C-NMR** (50.4 MHz, $CDCl_3$): δ = 168.4 (C), 139.4 (C), 137.4, 135.0 (C), 132.1 (C), 130.7 (CH), 128.6 (CH_2), 128.4 (CH), 127.3 (CH), 127.2 (CH), 122.5 (CH), 120.6 (CH), 119.6 (CH), 110.8 (CH), 110.0 (CH), 51.9 (CH_3), 31.3 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 2945, 1715, 1273, 1233, 737 cm^{-1}. **MS-(ESI+):** *m/z* (%) = 292 $[M]^+$ (100); 314 $[M + Na]^+$ (20); $C_{19}H_{17}NO_2$ (291.34): calcd C 78.33, H 5.88, N 4.81; found C 78.37, H 5.92, N 4.78.

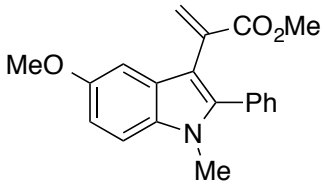
Methyl 2-(2-phenyl-1*H*-indol-3-yl)acrylate (11a)



White solid, m.p.: 66-68 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.40 (bs, 1H), 7.16-7.62 (m, 9H), 6.58 (d, *J* = 1.8 Hz, 1H), 6.00 (d, *J* = 1.8 Hz, 1H), 3.42 (s, 3H) ppm. **^{13}C-NMR** (50.4 MHz, $CDCl_3$): δ = 168.2 (C), 136.2 (C), 136.0 (C), 135.0 (C), 133.2 (C), 129.0 (CH_2), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 122.9 (CH), 120.8 (CH), 119.6 (CH), 120.8 (CH), 111.3 (CH), 110.2 (CH), 52.0 (CH_3) ppm. **IR** (NaCl): $\tilde{\nu}$ = 3059, 2949, 1715, 1604, 1455, 744 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 278 $[M]^+$ (100); $C_{18}H_{15}NO_2$ (277.32): calcd C 77.96, H 5.45, N 5.05; found C 77.93, H 5.42, N 5.02.

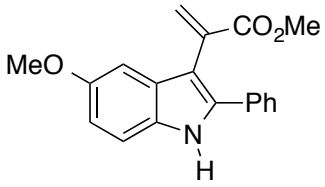
Methyl 2-(5-methoxy-1-methyl-2-phenyl-1*H*-indol-3-yl)acrylate (11d)



White solid, m.p.: 78.5-80 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.26-7.47 (m, 6H), 7.07 (d, *J* = 2.6 Hz, 1H), 6.95 (dd, *J* = 2.2, *J* = 8.8 Hz, 1H), 6.39 (d, *J* = 1.8 Hz, 1H), 5.83 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 3.37 (s, 3H, CH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 168.4 (C), 155.1 (C), 139.9 (C), 135.2 (C), 132.8 (C), 132.2 (C), 130.6 (CH), 128.6 (CH_2), 128.3 (CH), 127.5 (C), 127.0 (CH), 112.6 (CH), 110.7 (CH), 110.4 (C), 101.6 (CH), 56.3 (CH_3), 51.8 (CH_3), 31.3 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 1728, 1485, 1205, 1101, 811, 776 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 322 $[M]^+$ (25); 344 $[M + Na]^+$ (100); $C_{20}H_{19}NO_3$ (321.37): calcd C 74.75, H 5.96, N 4.36; found C 74.68, H 6.04, N 4.41.

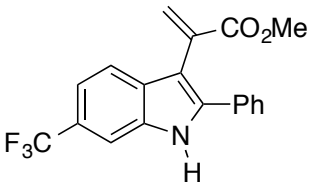
Methyl 2-(5-methoxy-2-phenyl-1*H*-indol-3-yl)acrylate (11e)



White solid, m.p.: 141.8-143.1 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.50 (bs, 1H), 7.17-7.44 (m, 6H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.87 (dd, *J* = 2.6, *J* = 8.8 Hz, 1H), 6.58 (d, *J* = 1.8 Hz, 1H), 5.99 (d, *J* = 1.8 Hz, 1H), 3.86 (s, 3H, CH_3), 3.42 (s, 3H, CH_3) ppm. **^{13}C-NMR** (50.4 MHz, $CDCl_3$): δ = 168.4 (C), 155.0 (C), 137.0 (C), 135.2 (C), 131.2 (C), 131.2 (C), 129.2 (C) 129.0 (CH_2), 128.2 (CH), 128.0 (CH), 127.6 (CH), 113.1 (CH), 112.2 (CH), 109.9 (C), 101.3 (CH), 56.2, (CH_3), 52.1 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3387, 1700, 1484, 1216 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 248 $[M - CO_2Me]^+$ (40); 308 $[M]^+$ (100); 330 $[M + Na]^+$ (90); Anal. for $C_{19}H_{17}NO_3$ (307.34): calcd C 74.25, H 5.58, N 4.56; found C 74.31, H 5.51, N 4.49.

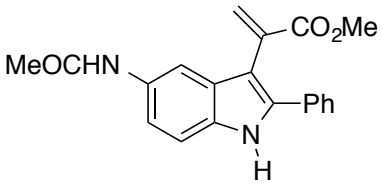
Methyl 2-(2-phenyl-6-(trifluoromethyl)-1*H*-indol-3-yl)acrylate (11f)



White solid, m.p.: 193-195 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.57 (bs, 1H), 7.26-7.67 (m, 8H), 6.62 (d, *J* = 1.8 Hz, 1H), 5.98 (d, *J* = 1.8 Hz, 1H), 3.46 (s, 3H, CH_3) ppm. **^{13}C-NMR** (75 MHz, acetone-d_6): δ = 167.3 (C), 139.5 (C), 135.5 (C), 135.3 (C), 132.8 (C), 131.4 (C), 129.1 (CH_2), 128.7 (CH), 128.4 (CH), 128.2 (CH), 125.9 (q, J_{C-F} = 271 Hz, C), 123.8 (q, J_{C-F} = 32 Hz, C), 120.0 (C), 116.7 (q, J_{C-H} = 4 Hz, CH), 110.2 (C), 109.2 (q, J_{C-F} = 4 Hz, CH), 51.5 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3304, 1702, 1338, 1100 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 346 $[M]^+$ (100); 368 $[M + Na]^+$ (25); $C_{19}H_{14}F_3NO_2$ (345.32): calcd C 66.09, H 4.09, N 4.06; found C 66.13, H 4.12, N 4.10.

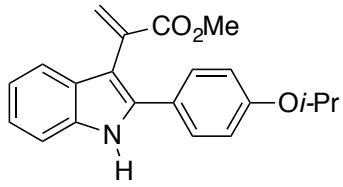
Methyl 2-(5-acetamido-2-phenyl-1*H*-indol-3-yl)acrylate (11g)



White solid, m.p.: 227-229 °C.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 11.54 (bs, 1H), 9.79 (bs, 1H), 7.78 (s, 1H), 7.32-7.49 (m, 7H), 6.40 (d, *J* = 1.5 Hz, 1H), 5.87 (d, *J* = 1.5 Hz, 1H), 2.98 (s, 3H), 2.02 (s, 3H) ppm. **^{13}C-NMR** (50.4 MHz, DMSO-d_6): δ = 168.3 (C), 168.0 (C), 137.1 (C), 135.9 (C), 133.3 (C), 133.2 (C), 133.1 (C), 129.3 (CH_2), 128.6 (CH), 128.3 (CH), 128.0 (CH), 127.7 (C), 116.3 (CH), 112.0 (CH), 109.5 (CH), 109.3 (C), 52.3 (CH_3), 42.8 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3386, 1713, 1673, 1563, 1322 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 335 [M]$^+$ (10); 357 [M + Na]$^+$ (100); Anal. for $C_{20}H_{18}N_2O_3$ (334.37): calcd C 71.84, H 5.43, N 8.38; found C 71.67, H 5.38, N 8.37.

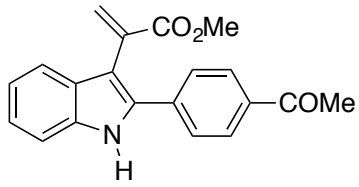
Methyl 2-(2-(4-isopropoxyphenyl)-1*H*-indol-3-yl)acrylate (11h)



White solid, m.p.: 80-82 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.42 (bs, 1H), 7.59-7.62 (m, 1H), 7.38 (d, *J* = 8.7, 2H), 7.18-7.35 (m, 3H), 6.90 (d, *J* = 8.7, 2H), 6.58 (d, *J* = 1.7, 1H), 6.01 (d, *J* = 1.7, 1H), 4.58 (sept, *J* = 6.0 Hz, 1H), 3.49 (s, 3H), 1.38 (d, *J* = 6.0 Hz, 6H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 168.7 (C), 158.1 (C), 136.5 (C), 136.1 (C), 135.4 (C), 129.2 (CH_2), 129.0 (C), 128.3 (CH), 125.6 (C), 122.7 (CH), 120.8 (CH), 119.4 (CH), 116.5 (CH), 111.4 (CH), 109.5 (C), 70.4 (CH), 52.3 (CH_3), 22.4 (2 x CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3354, 2976, 1714, 1609, 1456, 1249 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 336 [M]$^+$ (50); 358 [M + Na]$^+$ (100); $C_{21}H_{21}NO_3$ (335.40): calcd C 75.20, H 6.31, N 4.18; found C 75.26, H 6.24, N 4.05.

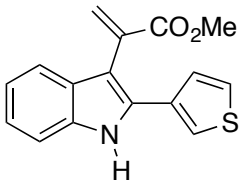
Methyl 2-(2-(3-acetylphenyl)-1*H*-indol-3-yl)acrylate (11i)



White solid, m.p.: 195.2-196 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.81 (bs, 1H), 8.09-8.10 (m, 1H), 7.83-7.88 (m, 1H), 7.56-7.70 (m, 2H), 7.13-7.47 (m, 4H), 6.62 (d, *J* = 1.8 Hz, 1H), 6.01 (d, *J* = 1.8 Hz, 1H), 3.47 (s, 3H), 2.59 (s, 3H) ppm. **^{13}C-NMR** (50.4 MHz, $CDCl_3$): δ = 198.1 (C), 168.0 (C), 137.7 (C), 136.2 (C), 134.8 (C), 134.7 (C), 133.6 (C), 132.2 (CH), 129.3 (CH), 129.2 (CH_2), 128.7 (C), 127.7 (CH), 127.2 (CH), 123.3 (CH), 120.9 (CH), 119.6 (CH), 111.5 (CH), 110.8 (C), 52.2 (CH_3), 26.8 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3335, 1707, 1690, 1292, 739 cm^{-1}. **MS-(ESI+):** *m/z* (%) = 318 [M]$^-$ (100); $C_{20}H_{17}NO_3$ (319.35): calcd C 75.22, H 5.37, N 4.39; found C 75.14, H 5.31, N 4.44.

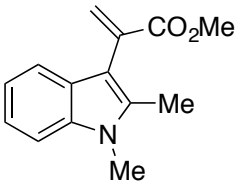
Methyl 2-(2-(thiophen-3-yl)-1*H*-indol-3-yl)acrylate (11l)



White solid, m.p.: 166.7-167.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.44 (bs, 1H), 7.57-7.60 (m, 1H), 7.18-7.35 (m, 6H), 6.65 (d, *J* = 1.8 Hz, 1H), 6.02 (d, *J* = 1.8 Hz, 1H), 3.57 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 168.5 (C), 135.9 (C), 135.1 (C), 134.0 (C), 131.9 (C), 129.2 (CH_2), 128.9 (C), 126.9 (CH), 126.7 (CH), 123.1 (CH), 122.5 (CH), 120.9 (CH), 119.5 (CH), 111.4 (CH), 110.2 (C), 52.4 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 3364, 1713, 1289, 1168, 741 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 284 $[M]^+$ (100); 306 $[M + Na]^+$ (50); $C_{16}H_{13}NO_2S$ (283.34): calcd C 67.82, H 4.62, N 4.94; found C 67.94, H 4.56, N 4.87.

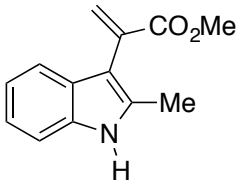
Methyl 2-(1,2-dimethyl-1*H*-indol-3-yl)acrylate (11m)



White solid, m.p.: 88.5-90.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.46-7.48 (m, 1H), 7.28- 7.32 (m, 1H), 7.18-7.24 (m, 1H), 7.10-7.16 (m, 1H), 6.60 (d, *J* = 2.0 Hz, 1H), 5.83 (d, *J* = 2.0 Hz, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 2.39 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 168.6 (C), 136.9 (C), 135.4 (C), 135.0 (C), 128.1 (CH_{22}), 127.5 (C), 121.5 (CH), 120.1 (CH), 119.1 (CH), 109.6 (C), 109.2 (CH), 52.5 (CH_3), 30.0 (CH_3), 11.7 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 2951, 1710, 1470, 1287, 1143, 1104, 759 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 229 $[M]^+$ (60); 252 $[M + Na]^+$ (100); $C_{14}H_{15}NO_2$ (229.27): calcd C 73.34, H 6.59, N 6.11; found C 73.42, H 6.57, N 6.09.

Methyl 2-(2-methyl-1*H*-indol-3-yl)acrylate (11n)



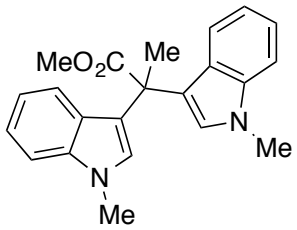
White solid, m.p.: 93.1-94 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.98 (bs, 1H), 7.41-7.44 (m, 1H), 7.23-7.40 (m, 1H), 7.05-7.18 (m, 2H), 6.56 (d, *J* = 1.8 Hz, 1H), 5.81 (d, *J* = 1.8 Hz, 1H), 3.82 (s, 3H), 2.36 (s, 3H) ppm. **^{13}C-NMR** (50.4 MHz, $CDCl_3$): δ = 168.4 (C), 135.3 (C), 134.6 (C), 133.5 (C), 128.2 (C), 127.8 (CH_2), 121.6 (CH), 120.2 (CH), 119.0 (CH), 110.6 (CH), 109.9 (C), 52.4 (CH_3), 12.7 (CH_3) ppm. **IR** (KBr tablets): $\tilde{\nu}$ = 3327, 1699, 1290, 1169, 751 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 216 $[M]^+$ (100); 238 $[M + Na]^+$ (20); $C_{13}H_{13}NO_2$ (215.25): calcd C 72.54, H 6.09, N 6.51; found C 72.51, H 6.00, N 6.43.

4.4.2.2 Gold- or silver-catalyzed synthesis of **22**

To a solution of the catalyst (2 mol%) in anhydrous toluene (5 mL) in a screw cap tube indole **1c** (100 mg, 0.76 mmol) and 2- α-acetamidoacrylate **2a** (120 mg, 0.84 mmol) were added at room temperature. The solution was stirred at temperature and for the time indicated in Table 4.3 then the solvent was removed at reduced pressure. The crude mixture was subjected to flash column chromatography (SiO_2, hexane/ethyl acetate 95:5) to yield **22** (for yields see Table 4.2).

Methyl 2,2-bis(1-methyl-1*H*-indol-3-yl)propanoate (22)



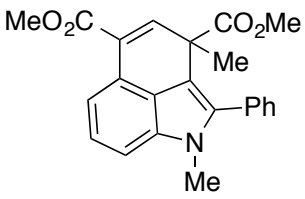
White solid, m.p.: 160-161 °C.
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.49-7.54 (m, 2H), 7.20-7.33 (m, 6H), 7.01-7.06 (m, 2H), 6.84 (s, 2H), 3.72 (s, 6H), 3.67 (s, 3H), 2.12 (s, 3H) ppm. **^{13}C-NMR** (50.4 MHz, $CDCl_3$): δ = 176.3 (C), 137.9 (C), 127.8 (CH), 126.8 (C), 121.6 (CH), 119.1 (CH), 118.0 (C), 109.5 (CH), 46.5 (C), 52.4 (CH_3), 32.9 (CH_3), 26.6 (CH_3) ppm. **IR** (KBr): ν ~ = 2945, 1715, 1273, 1233, 737 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 369 $[M + Na]^+$ (100); $C_{22}H_{22}N_2O_2$ (346.42): calcd,C 76.28, H 6.40, N 8.09; found C 76,34, H 6.32, N 8.02.

4.4.2.3 Acid or gold/acid-catalyzed synthesis of **25**

To a solution of the catalyst (4 mol%) in anhydrous toluene (5 mL) in screw cap tube, indole **1i** (50 mg, 0.24 mmol), 2-acetamidoacrilate **2a** (38 mg, 0.27 mmol) and $HNTf_2$ (67.5 mg, 0.24 mmol) were added. The solution was stirred at 130 °C for 2 hours then the solvent was removed at reduced pressure. The crude mixture was subjected to flash column chromatography (SiO_2, hexane/ethyl acetate 95:5) to yield compound 2**5** (28 mg, 62%).

In alternative to a solution of indole **1i** (50 mg, 0.24 mmol) and 2-acetamidoacrilate **2a** (38 mg, 0.27 mmol) in anhydrous toluene (3 mL) in a screw cap tube, $HNTf_2$ (67.5 mg, 0.24 mmol) was added. The solution was stirred at 130 °C for 2 hours then the solvent was removed at reduced pressure. The crude mixture was subjected to flash column chromatography (SiO_2, hexane/ethyl acetate 95:5) to yiel **11c** (6 mg, 9%) and 2**5** (18 mg, 40%).

Dimethyl 1,3-dimethyl-2-phenyl-1,3-dihydrobenzo[*cd*]indole-3,5-dicarboxylate (25)



Yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.80 (m, 1H), 7.51-7.44 (m, 3H), 7.33 (dd, *J* = 6.4 Hz, 2.8, 2H), 7.23 (m, 2H), 6.82 (s, 1H), 3.92 (s, 3H), 3.61 (s, 3H), 3.53 (s, 3H), 1.48 (s, 3H) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 174.0 (C), 167.2 (C), 142.3 (CH), 136.8 (C), 134.4 (C), 132.3 (C), 131.0 (CH), 129.1 (CH), 128.6 (CH), 128.2 (C), 124.7 (C), 123.3 (CH), 122.6 (C), 116.8 (CH), 116.6 (C), 110.2 (CH), 52.9 (CH_3), 52.2 (CH_3), 47.5 (C), 30.1 (CH_3), 27.4 (CH_3) ppm. **IR** (KBr): $\tilde{\nu}$ = 2948, 1731, 1712, 1459, 1259, 1226, 755 cm^{-1}. **MS-(ESI+)**: *m/z* (%) = 398 $[M + Na]^+$ (100);

$C_{23}H_{21}NO_4$ (375.42): calcd C 73.58, H 5.64, N 3.73; found C 73.45, H 5.69, N 3.68.

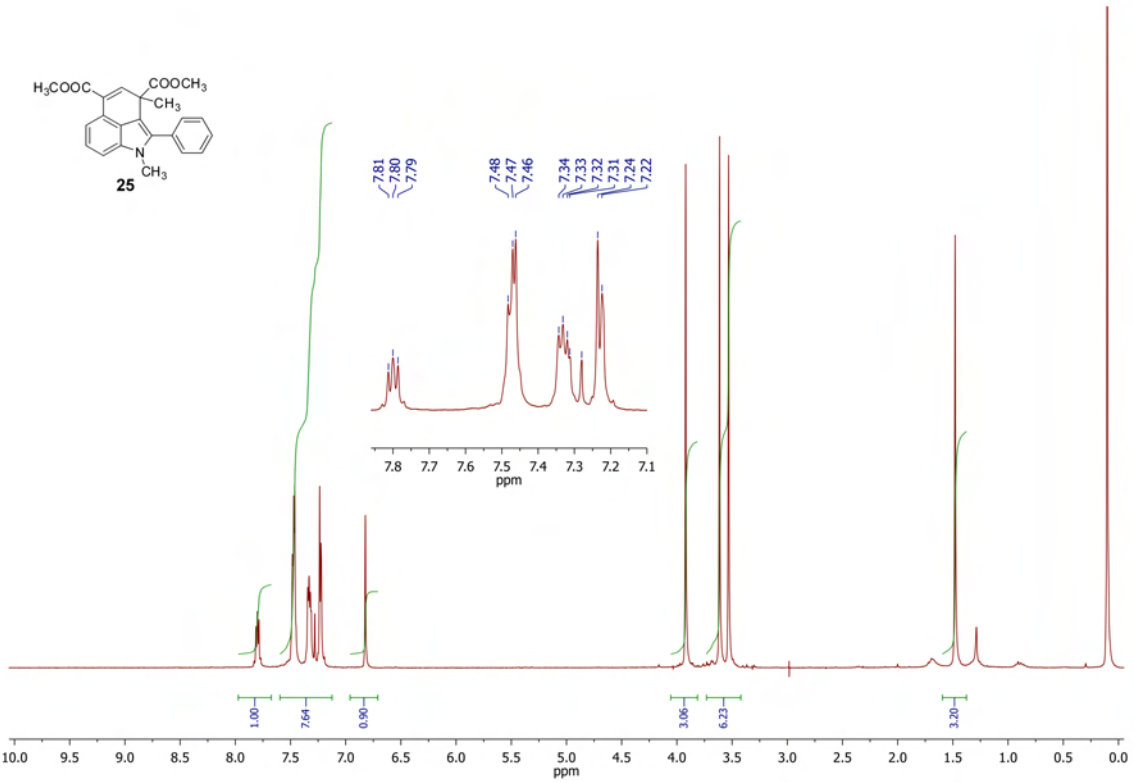


Figure 4.4

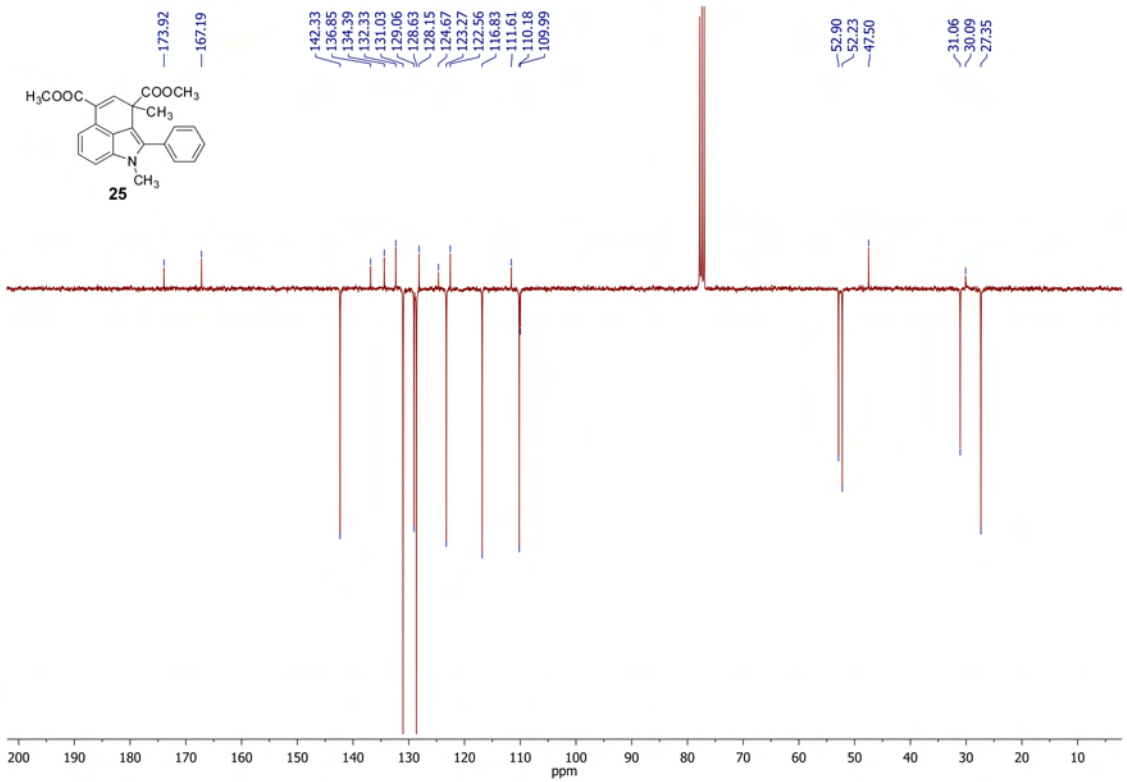


Figure 4.5

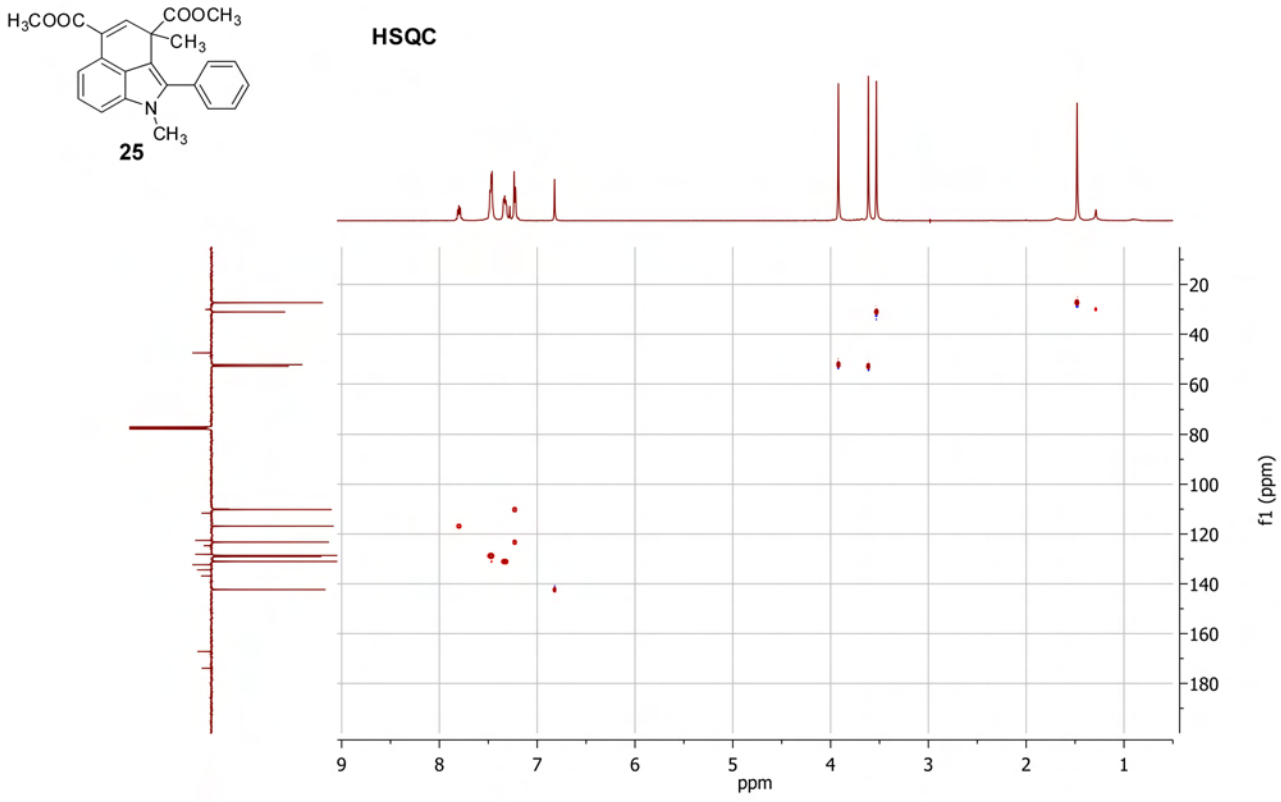


Figure 4.6

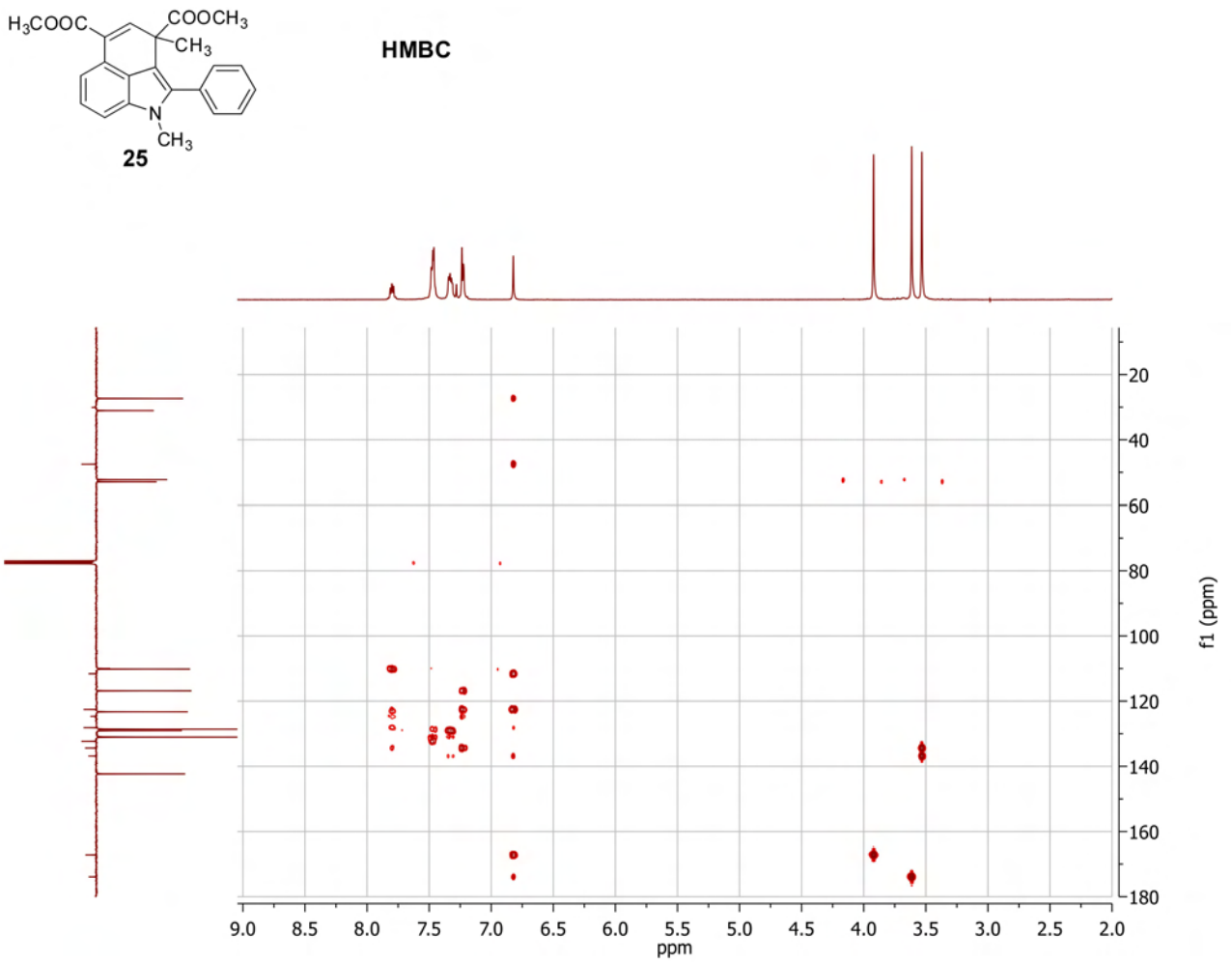

H3COOC
COOCH3
CH3
N
CH3
25
HMBC
20
40
60
80
100
120
140
160
180
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

Figure 4.7

Conclusions

According to the results presented in this work through chapters 2-4, the following main conclusions can be drawn:

Chapter 2.

- A facile access to a relevant scaffold such as [*c*]-carbo- and furoannulated tetrahydrocarbazoles has been described. This approach is based on a Lewis acid catalyzed formal [4+2]-cycloaddition of 2-vinylindoles with cyclic enones. Although the results are preliminary and could be improved, this strategy presents higher efficiency and more versatility than other previously reported based on the construction of the [c]-ring through manipulations of preformed 3,4-disubstituted carbazole derivatives.
- The formal [4+2]-cycloaddition of 2-vinylindoles and simplier enones can be catalyzed by gold complexes. These catalysts showed similar or superior efficiency, including the diastereomeric excesses, when compared with classical Lewis acids, but can be used under more convenient reaction conditions, including low catalyst loadings or ambient temperature.

Chapter 3.

- A modular approach to synthesis of substituted tetrahydrocarbazole derivatives through a gold-catalyzed intermolecular [4+2]-cycloaddition of 2-vinylindoles and N-allenamides has been developed. An appropriate selection of the reaction conditions enabled the selective preparation of different tetrahydrocarbazoles, including a new multicomponent reaction (two molecules of the allene and one of the vinylindole).
- This approach is applicable to the functionalization of other heteroarenes as 3-vinylindoles or 2-vinylbenzofurans.

Chapter 4.

- A novel reaction pathway was identified in the reaction of 2-vinylindoles with dehydroaminoacids in the presence of gold or silver catalysts. This new reaction comprises the coupling of the two molecules to selectively afford α-indolylacrylate derivatives, which are a relevant class of compounds.
- This new reaction outcome involves a regioselectivity that is complementary to the one previously observed in related gold-catalyzed hydroarylations reactions which afforded β-indolylacrylate derivatives.

De acuerdo con los resultados presentados en los capítulos 2-4 de esta Memoria, se pueden extraer las siguientes conclusiones:

Capítulo 2.

- Se ha descrito una nueva forma de preparación de moléculas con los esqueletos tetrahidrobenzo[*c*]carbazol o tetrahidrofuro[3,4-*c*]carbazole, que aparecen en familias de productos naturales poco convencionales. Esta aproximación sintética se base en una reacción de cicloadición formal [4+2] entre 2-vinilindoles y enonas cíclicas. Aunque los resultados son preliminaries y pueden mejorarse, esta estrategia es más eficiente y versátil que otras previamente descritas basadas en la manipulación del esqueleto de la molecula previamente formada.
- La cicloadición formal [4+2] de 2-vinilindoles y enonas sencillas puede llevarse a cabo utilizando complejos de oro como catalizador. Estos complejos han mostrado eficiencia o mejor, incluso en los valores de exceso diastereoisomérico, cuando se compara con la actividad de otros catalizadores ácidos de Lewis. El uso de catalizadores de oro permite una disminución de la carga de catalizador y llevar a cabo la reacción a temperatura ambiente.

Capítulo 3.

- Se ha desarrollado una nueva aproximación a derivados de tetrahidrocarbazoles mediante una cicloadición formal [4+2] de 2-vinilindoles and N-alenamides catalizada por complejos de oro. La selección adecuada de las condiciones de reacción permite la preparación de manera totalmente selective de varios derivados de tetrahidrocarbazol, incluyendo una nueva reacción multicomponente (dos moléculas de aleno y una de 2-vinilindole).
- Esta reacción es applicable a la funcionalización de heteroarenos análogos como los 3-vinilindoles o 2-vinilbenzofuranos.

Capítulo 4.

- Se ha descubierto un patron de reactividad en el proceso de acoplamiento de 2-vinilindoles y dehidroaminoácidos catalizado por complejos de oro o plata. Esta nueva reacción permite la preparación selective de derivados de α-indolilacrilatos, una familia de compuestos escasamente estudiada.
- El resultado de esta reacción es interesante, ya que la regioquímica obtenida es complementaria a la observada en la reacción análoga de hidroarilación de alquinos con indoles, que conduce a la formación del correspondiente β-indolilacrilato.

In accordo con i risultati presentati in questo lavoro nei capitoli 2-4 si possono dedurre le seguenti conclusioni:

Capitolo 2:

- Descrizione di una nuova metodologia per la preparazione di molecole aventi come nucleo principale il nucleo tetraidrocarbenzo[c]carbazolico o tetraidrofuro[3,4-c]carbazolico. Entrambe queste classi di composti appartengono alla famiglia dei prodotti naturali difficilmente ottenibili per via sintetica. I risultati descritti si sono ottenuti tramite una reazione di cicloaddizione formale [4+2] con 2-vinilindoli ed enoni ciclici. Nonostante i risultati siano preliminari e possano migliorare, questa strategia risulta più efficiente e versatile delle altre finora descritte.
- La cicloaddizione formale [4+2] dei 2-vinilindoli ed enoni semplici può essere catalizzata tramite complessi di oro. Questi catalizzatori hanno dimostrato uguale o maggiore efficienza rispetto agli acidi di Lewis classici, sia in termini di rese che in termine di diasteroselezione. L'uso dei catalizzatori di oro consente inoltre di condurre le reazioni in condizioni più blande, a temperatura ambiente e con minor percentuale di catalizzatore.

Capitolo 3:

- E' stato sviluppato un approccio modulare per la sintesi di derivati tetraidrocarbazolici attraverso una cicloaddizione [4+2] formale di 2-vinilindoli e *N*-allenammidi catalizzata da complessi di oro. Una adeguata selezione delle condizioni di reazione consente la preparazione in maniera totalmente selettiva di vari derivati di tetraidrocarbazolici, includendo una nuova reazione multicomponente (due molecole di allene ed una di 2-vinilindolo).
- Questa reazione è applicabile alla funzionalizzazione di eteroareni analoghi come 3-vinilindoli o 2-vinilbenzofurani.

Capitolo 4:

- E' stato scoperto un nuovo profilo di reattività per la reazione tra 2-vinilindoli e deidroaminoacidi, catalizzato da complessi di oro e argento. Questa nuova reazione permette la preparazione selettiva di derivati α-indololacrilici, una famiglia di composti scarsamente studiata.
- Il risultato di questa reazione è interessante, in quanto la regioselettività ottenuta è complemetare a quella osservata nella reazione analoga di idroarilazione di alchini con indoli, la quale conduce alla formazione del corrispondente β-indololacrilato.