Universidad de Oviedo
Universidá d'Uviéu
University of Oviedo

Departamento de Química Orgánica e Inorgánica

Programa de Doctorado*: Síntesis y Reactividad Química*

GENERATION OF HIGHLY REACTIVE INTERMEDIATES UNDER TRANSITION METAL-FREE CONDITIONS: SYNTHESIS OF FUNCTIONALIZED HETEROCYCLIC AND METALLOCENE DERIVATIVES

Silvia González Pelayo

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RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español/Otro Idioma: GENERACIÓN DE INTERMEDIOS ALTAMENTE REACTIVOS EN AUSENCIA DE METALES DE TRANSICIÓN: SÍNTESIS DE HETEROCICLOS FUNCIONALIZADOS Y DERIVADOS DE METALOCENOS.	Inglés: GENERATION OF HIGHLY REACTIVE INTERMEDIATES UNDER TRANSITION METAL-FREE CONDITIONS: SYNTHESIS OF FUNCTIONALIZED HETEROCYCLIC AND METALLOCENE DERIVATIVES

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RESUMEN (en español)

El objetivo principal de la síntesis orgánica es preparar sustancias con relevancia científica y propiedades útiles de manera eficiente y selectiva. En este contexto, una de las metodologías más poderosas para la preparación de compuestos químicos en síntesis orgánica es la catálisis por metales de transición. Se han desarrollado transformaciones poderosas utilizando metales preciosos. Sin embargo, los catalizadores de metales de transición presentan varias desventajas. En este sentido, el desarrollo de nuevos métodos sintéticos que utilicen otros tipos de catalizadores o alternativas libres de metales es uno de los principales objetivos para la academia y la industria. Por ello, se introdujo el termino de 'Química Verde' para mostrar cómo los químicos pueden diseñar medicamentos y otros productos de una manera más sostenible.

En la presente Tesis doctoral se describe la generación de intermedios altamente reactivos y su captura para la síntesis de derivados heterocíclicos y metalocenos funcionalizados. Para ello, se ha desarrolado una eficiente funcionalización de enlaces de silicio-hidrógeno libre de metal mediada por microondas de eninonas y silanos fácilmente disponibles. Una completa economia atómica y la fácil ejecución son características destacadas del método descrito. Este proceso transcurre a traves de intermedios 2-furilcarbenos, que serán atrapados por silanos. Además, estos intermedios podrían ser atrapados de igual forma con alcoholes, azoles y sulfonamidas.
Por otro lado, se describe la síntesis de derivados de azoles funcionalizados mediante la generación asistida por microondas de intermedios de quinone methide (QM) usando agua como disolvente.

Por otro lado, debido a la gran cantidad de aplicaciones exhibidas por derivados de ferroceno funcionalizados, también se investigó nuevas metodologías para la funcionalización de derivados de ferroceno.

Primero, se dearrolló una síntesis de ferrocenilfenoles atrapando intermedios de o-QM y p-QM con ferroceno. Se llevaron a cabo unos análisis biológicos mostrando cierta citotoxididad de algunos de los compuestos preparados frente a líneas celulares de cáncer de ovario y pulmón. Más recientemente, se realizó un un estudio sobre la reactividad del ferroceno con anillos de tres miembros tensionados. Primero, se desarrolló un método para la preparación de derivados de ferrocenos funcionalizados que contienen un resto malonato basado en la apertura del anillo regioselectivo de los ciclopropanos dador-aceptor.

Finalmente, se ideó una síntesis conveniente de derivados de metaloceno

aminofuncionalizados basada en la apertura de anillo regioselectiva de las N-sulfonil aziridinas. Tanto el ferroceno como el ruteneno resultaron ser sustratos adecuados para esta reacción de apertura de anillo. Estos nuevos derivados de metaloceno aminofuncionalizados podrían transformarse en análogos de metaloceno tetrahidroisoquinolina. Se ha demostrado además, que las reacciones multicomponente entre ferroceno, aziridinas y formaldehído son un metodo rápido y eficiente para acceder a estos análogos de metaloceno de tetrahidroisoquinolina.

RESUMEN (en Inglés)

The main goal of organic synthesis is to prepare substances with scientific relevance and useful properties in an efficient and selective manner. In this context, one of the most powerful methodologies for the preparation of high valued chemical compounds in organic synthesis is catalysis by transition metals. Powerful transformations have been developed using precious metals. However, transition metal catalysts present several disadvantages. In this regard, the development of new synthetic methods using widely-metal catalyst or metal-free alternatives is a highly desirable goal for academy and industry. Therefore, 'Green Chemistry' was introduced to show how chemists could design drugs and other products in a more sustainable way.

This Ph.D dissertation describes the generation of highly reactive intermediates and their capture for the synthesis of functionalized heterocyclic and metallocene derivatives.

Thus, we have developed an efficient microwave-mediated metal-free silicon-hydrogen bond functionalization of readily available enynones and silanes. Complete atom efficiency and easy execution are salient features of the developed protocol. This process is proposed to proceed through 2-furyl carbene intermediates, which would be trapped by the silane. These reactive intermediates can also be captured with alcohols, azoles and sulphonamides.

We reported a highly efficient synthesis of functionalized azole derivatives by microwave-assisted generation of quinone methide intermediates (QM) under aqueous conditions.

On the other hand, because of the wealth of applications exhibited by functionalized ferrocene derivatives in fields such as catalysis or medical sciences, we have also investigated new methodologies for the functionalization of ferrocene derivatives.

First, we developed an efficient synthesis ferrocenyl phenols by trapping *o*-QM and *p*-QM intermediates with ferrocene. Preliminary biological evaluation of the products available by these methodologies revealed significant cytotoxicity against ovarian and lung cancer cell lines.

More recently, we embarked on a study about the reactivity of ferrocene towards strained three membered rings. First, we developed a straightforward method for the preparation of functionalized ferrocenes derivatives containing a malonate moiety based on the regioselective ring opening of donor-acceptor cyclopropanes.

Finally, we have devised a convenient synthesis of aminofunctionalized metallocene derivatives based on the regioselective ring-opening of *N*-sulfonyl aziridines. Both ferrocene and ruthenocene proved to be suitable substrates for this ring-opening reaction. These new aminofunctionalized metallocene derivatives could be transformed into metallocene analogues of the tetrahydroisoquinoline motif. A three-component reactions between ferrocene, aziridines and formaldehyde have also demonstrated to represent a rapid and efficient means to access these tetrahydroisoquinoline metallocene analogues.

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

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General Introduction

Defined as "the art and science of constructing substances, natural or designed, whose primary element is carbon",[1] the Organic Synthesis is at the very heart of Organic Chemistry. In fact, Organic Synthesis is of paramount importance because through it man can create new molecules with a wide range of applications with an impact on our well-being.

Although humans had used transformations of matter as a means to prepare food, medicines and diverse tools since ancient times, the beginning of the Organic Synthesis is usually associated with the synthesis of urea by the German chemist Friedrich Wöhler in 1828. This serendipitous discovery demonstrated for the first time that man could prepare organic compounds in the laboratory. Soon after its occurrence, the advent of organic synthesis gave birth first to the dye industry and then to the pharmaceutical industry with the synthesis and commercialization of mauve (or mauveine) and acetylsalicylic acid (aspirin), respectively.

These initial events, together with the improvement of analytical techniques and instrumentation and developments in structural theory that led to a better understanding of the nature of the chemical bond and chemical reactivity, gave momentum to the advancement of Organic Synthesis and its applications in several fields.

In particular, the last 60 years witnessed impressive advances in the development of new synthetic methodologies, which propelled the Organic Synthesis to higher levels of utility and efficiency. These new methods facilitated discovery research, product development and manufacturing of pharmaceuticals and other fine chemicals that benefited society. As a result of these advances, the Organic Synthesis has had a tremendous impact on science and technology. Among the most prominent fields that benefited from applications of Organic Synthesis are those of medicine, chemical biology, molecular recognition and supramolecular chemistry, materials science and nanotechnology.

In parallel with this flourishing development of Organic Synthesis, the concept of sustainability emerged in the last years of the last century as a means to reduce the environmental and health impact of chemical activities. Since then, these concerns and the rules developed to address them, usually referred as Green Chemistry, have had an important impact on the Organic Synthesis and, nowadays, there is growing agreement within the scientific community on the need for developing more sustainable synthetic methods.

For example, sustainability has been highlighted as a global key-issue in the resolution adopted by the general assembly of the United Nations "Transforming our world: the 2030 Agenda for Sustainable Development".[2] Likewise, the European Chemical Society (EuChemS)

[1] K. C. Nicolau, *Tetrahedron* **2003**, *59*, 6683-6738.

[2] https://sustainabledevelopment.un.org/post2015/transformingourworld

in a document published in 2011 entitled "Chemistry: Developing solutions in a changing world" clearly establishes the key role of the Organic Synthesis in the sustainable development and identifies some challenges to which it must confront in order to play this central role. For example, this document stated that: "The challenge for chemists is to find new methods using widely-available metal catalysts, or even metal-free alternatives, to maintain access to the key drugs and other products currently made using precious metals."

In the last years, our research group has incorporated these global concerns. Thus, our research has mainly focused on the development of new catalytic transformations. As already pointed out by Anastas,[3] catalysis is ideally suited to deliver sustainable solutions for the demands of modern society. In line with the above mentioned recommendations from EuChemS, one of our most successful approaches has been the use of catalysts based on affordable metals as a replacement for those still widely used catalysts based on precious metals, which exhibit several drawbacks such as limited availability, high price, and toxicity. Thus, since 2012, our laboratory has pursued the development of new synthetic methodologies based on the use of easily available zinc salts as catalysts.

In this regard, the initial goal of this work has been the development of new efficient and sustainable synthetic methods. Consequently, in the first chapter of this PhD work, we will report our efforts on the preparation of relevant heterocyclic compounds under metal-free conditions. The use of water as solvent for the generation and trapping of highly reactive intermediates is also described.

The second chapter of this PhD work has focused on the development of new methodologies for the preparation of functionalized ferrocene derivatives. Our recent interest in ferrocene chemistry relies on the number of important applications displayed by functionalized ferrocene derivatives in fields like catalysis, material science or medicinal chemistry.

According to these general objectives, the organization of this PhD work is as follows:

1. **Synthesis of Heterocyclic Compounds through Generation of Highly Reactive Intermediates under Metal-free Conditions**
   - **1.1** Generation of 2-Furyl Carbenes and Reactivity thereof with Silanes: A Metal-free Silicon-Hidrogen Functionalization.
   - **1.2** Generation and Capture by Azoles of *ortho*-Quinone Methide Intermediates under Aqueous Conditions

[3] P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res*. **2002**, *35*, 686-694.

2. **New Approaches to Functionalized Ferrocene Derivatives Based on the Reactivity of Quinone Methide Intermediates and Strained Systems**

   2.1 Synthesis and Preliminary Biological Evaluation of New Ferrocene-Phenol Conjugates

   2.2 Synthesis of Functionalized Ferrocene Derivatives through Regioselective Ring-Opening of Donnor-Acceptor Cyclopropanes

   2.3 Synthesis of new Amino-functionalized Metallocene Derivatives from N-Tosyl Aziridines

Chapter 1: Metal-Free reactions

I.1. General Introduction

Everyone who works in organic synthesis aims for the "ideal" reaction. However, what are the main features of the so called ideal reaction? This is not an obvious question because the requirements for the ideal reaction have evolved over time by responding to contemporary issues.

In 1985, Professor Paul A. Wender from Stanford University in a visionary way defined the ideal synthesis as follows:

> *"ideal syntheses [are] those in which the target molecule is assembled from readily available starting materials in one simple, safe, economical, and efficient operation"*.[4]

Thirty-five years later, Wender´s definition retains its validity. In fact, more recently but following the same line of thought, the Nobel Laureate professor Ei-ichi Negishi from Purdue University defined the ideal synthesis as that fulfilling the following expression: [5]

$$\mathbf{Y(ES)^2}$$

(where Y = high **Y**ielding; E = high **E**fficiency; S = **S**elective; E = **E**conomical and S = **S**afe)

Both Wender and Negishi definitions highlight that along with *classical* parameters in the study of chemical reactivity (yield, efficiency, selectivity), *economical and safety issues* have also to be taken into account in the design of a synthetic sequence. In this regard, the ideal character of a given chemical transformation correlates closely with its sustainability.[6] Assuming that there is no one true "ideal" synthesis, in the following lines I will attempt to discuss some (but only some) of the most remarkable research questions posed regarding the development of more sustainable synthetic methods.

[4] P. A. Wender, R. J. Ternansky, *Tetrahedron Lett.* **1985**, *26*, 2625.
[5] E. Negishi, *Chemistry & Chemical Industry,* **2012**, *66*, 247.
[6] Sustainability is defined as „the ability to be maintained at a steady level without exhausting natural resources or causing severe ecological damage" (Collins Dictionary).

I.1.1. Metal-promoted/catalyzed vs metal-free transformations

There is no doubt that metals, particularly transition metals, have become in the last decades essential tools in organic synthesis. The popularity of metal-mediated reactions is because they are able to achieve bond-forming processes and other transformations that are unattainable by other means. In fact, many metal-catalyzed transformations have been so useful that it is difficult to imagine the organic synthesis without these powerful methodologies. As a representative example, the palladium-catalyzed reaction of boronic acids and halides, the so called Suzuki-Miyaura cross-coupling reaction, has found widespread industrial application in the efficient large-scale production of pharmaceuticals, materials and agrochemicals. However, having said that, it is important to recognize that the use of metals in a synthetic sequence entails also some problems. First, some of the most used metals in organic synthesis are extremely scarce and hence expensive. In fact, a report published in 2011 by the European Association for Chemical and Molecular Sciences (EuCheMs) entitled "Chemistry-Developing solutions in a changing world" establishes that

> *"…However, such metals (precious metals) are used in a wide variety of applications and demand is such that global supplies of many are predicted to reach critical levels or even be exhausted in the next 10-20 years. The challenge for chemists is to find new methods using widely-available metal catalysts, or even metal-free alternatives, to maintain access to the key drugs and other products currently made using precious metals…"*

Moreover, most of these metal are highly toxic and their presence as impurities represents an important issue in the large-scale preparation of compounds for medicinal purposes with an important impact not only on the safety but also on the cost of the final drug. In this regard, it is not surprising that avoiding (or at least reducing) trace metal contamination is becoming more and more important as the standards required by the national drug regulatory agencies are also more and more strict.

For all these reasons, in recent years the development of metal-free synthetic sequences has become very popular and the absence of metals, particularly precious metals, in a synthetic procedure is currently a bonus. However, despite remarkable recent accomplishments, the replacement of precious metal-promoted transformations by metal-free alternatives is in its infancy and this task remains a challenge in contemporary organic synthesis.

I.1.2. The selection of the solvent

With its profound influence on reaction rates and product selectivity, the solvent plays an important role in the design of a synthetic procedure.[7] In this regard, it should be noted that, although interesting, solvent-less chemistry is not generally applicable to the efficient synthesis of most organic products. On the contrary, the solvent is usually the major component in a synthetic operation and as a consequence solvents are responsible for the majority of energy use and waste generation. For this reason, solvent selection represents a complex problem, which requires decision making at early stages of the design of a synthesis to identify the most convenient one. Currently, an important aspect in solvent selection is its environmental impact and it is highly convenient that the selected solvent matches as much as possible the requirements of the "Green Chemistry Principles".[8] Consequently, in recent years significant efforts have been devoted to identify more sustainable solvents.[9] As a result of these efforts, some alternative 'green' solvents have been proposed for the replacement of 'no-green' ones.[10] Several solvent selection guides have been published to the aim to reduce the most hazardous solvents.[11] These guides supply a preliminary study of classical solvents which combine environmental evaluation with the ability of the solvent to promote the reaction. Some of the most useful solvent guides have been elaborated by pharmaceutical companies such as Pfizer, GlaxoSmithKline or Sanofis, demonstrating the importance of this question in the manufacture of pharmacologically active compounds.

Comparing the data collected in the different solvent selection guides, a number of interesting conclusions can be drawn. Although these guides do not always agree, there is a great consensus regarding the greenest solvents with water, *n*-propyl acetate, *i*-propyl acetate, 1-butanol and 2-butanol as the highly preferred ones. Conclusions can also be drawn regarding the least desirable solvents. The following solvents are unequivocally considered as undesirable: chloroform, 1,2-DCE, carbon tetrachloride, NMP, DMF, DMAc, benzene, hexane, 1,4-dioxane, 1,2-DME, diethyl ether, and 2-methoxyethanol.

Although solvent selection guides have become a helpful tool in the effort to enhance the greenness of a synthetic procedure, they usually do not incorporate solvents of a bio-based

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[7] a) E. Buncel, R. Stairs, H. Wilson, in *The Role of the Solvent in Chemical Reactions*; R. G. Compton, S. Davies, J. Evans, Eds.; Oxford University Press: UK, **2003**; b) C. Reichardt, T. Welton, *Solvents and Solvent Effects in Organic Chemistry*, 4th ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2011**.

[8] P. T. Anastas, J. C. Warner, Green Chemistry: theory and practice, Oxford: Oxford University Press, U.K, **1998**.

[9] a) T. Welton, *Proc. R. Soc.London, Ser*. A. **2015**, *471*, 1-26; b) M. C. Bubalo, S. Vidović, I. R. Redovniković, S. Jokić, *J. Chem. Technol. Biotechnol.* **2015**, *90*, 1631−1639.

[10] R. Gani, P. A. Gómez, M. Folic, C. Jiménez-González, Constable DC. Solvents in organic synhtesis: replacement and multi-step reactions systems. *Comput. Chem. Eng.* **2008**, *32*, 2420-2444; W. Leitner, P. G. Jessop, C.-J. Li, P. Wasserscheid, A. Stark, ed. P. T. Anastas, Green Solvents in Handbook of Green Chemistry, Wiley-VCH, Weinheim, **2010**, *4.*

[11] D. Prat, J. Hayler, A. Wells, A survey of solvent selection guides. *Green Chem.* **2014,** *16,* 4546-4551.

origin. However, these solvents are extremely convenient because of their renewable character. Presently, 2-methyltetrahydrofuran is the only prevalent example of a bio-based solvent included in solvent selection guides.

In the last few years, several non-conventional solvents have been extensively investigated as green alternatives. Among others, ionic liquids, deep eutectic solvents, supercritical fluids or fluorinated solvents have acquired some popularity as reaction media.[12]

I.1.3. Quantitative assessment of the greenness of a synthetic procedure

To accomplishment the green chemistry in the organic synthesis is necessary to modify and design new synthesis pathways and start using green substrates and green reaction conditions. In this concern several environmental, technological and economic parameters have been developed to evaluate the environmental impact of the chemical procedures. The objective of this parameters is to measure how green is a whole synthesis or its specific steps.

Atom Economy measures how many of the atoms present in the starting materials form part of the final product expressed as a percentage[13]. Atom economy is one of the most widely used metrics for measuring the "greenness" of a process or synthesis, however is only for individual steps and does not consider components, which do not appear in the stoichiometric equation.

$$\%Atom\ economy\ =\ \frac{\text{Molecular weight of desired product(s)}}{\text{Sum of all the molecular wight of all reagents}} * 100$$

Environmental Factor (E-factor) is the ratio of the amount of waste generated by the process compared with the amount oh product obtain.[14] To obtain the *ideal* E-Factor all materials used in a process should be contained in the final product. This is the first metric which includes all the chemicals used in the reactions such as solvents and can be applied to a multi-step process.

$$E - Factor\ =\ \frac{\text{Amount of waste produced in the process/Kg}}{\text{Amount of the desired product(s) producec n the process/Kg}}$$

[12] F. M. Kerton, in *Alternative Solvents for Green Chemistry,* RSC, **2009**, ch . 2, p. 23.
[13] B. M. Trost, *Science,* **1991**, *254*, 1471; B. M. Trost, *Angew, Chem. Int. Ed. Engl.,* **1995**, *34,* 259.
[14] R. A. Sheldon, *Chem. Commun.,* **2008**, 3352-3365.

Reactions Mass Efficiency (RME) is ratio of the mass of the isolated product to the total mass of all the reactants, as percentage and was introduce to take yield into account.[15] Reaction yield, atom economy and stoichiometric factor taking into account the excess of reagents, are included in calculation of RME.

$$RME = \frac{1}{1 + \mathrm{E_m}^{16}}$$

Effective Mass Yield (EMY) is the percentage of the mass product relative to the mass of all non-benign materials used in its synthesis.[17] It does differentiate types of waste and does not include environmentally benign compounds.

$$\%EMY = \frac{\text{Actual mass of desired product(s)}}{\text{mass of non} - \text{benign reagents}} * 100$$

I.1.4. Concluding Remark

Inspired by some of the principles discussed above, in the first part of this PhD work the main goal has been the development of new synthetic procedures for the synthesis of functionalized heterocyclic compounds under metal-free conditions. As stated before, water is considered a very convenient solvent in most selection guides and the use of water as solvent has been also considered.

[15] J. Andraos, M. Sayed, *J. Chem. Ed*. **2007**, *84*, 1004-1010.

[16] Where Em is the E-Factor based on mass

[17] D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem*. **2002**, *4*, 521–527.

Part A: Catching elusive 2-Furyl Carbenes with Silanes: A metal-free microwave-assited silicon-hydrogen bond functionalization

A.1 General introduction

Carbenes are a neutral divalent carbon species containing two electrons that are not shared with other atoms.[18] Depending on how these two electrons are located, there are two electronic states: singlet where two electrons are spin-paired in sp^2 orbital and triplet when the two unshared electrons occupy separate orbitals in parallel spins (Figure 1).[19]

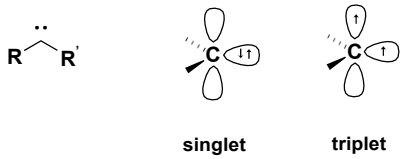
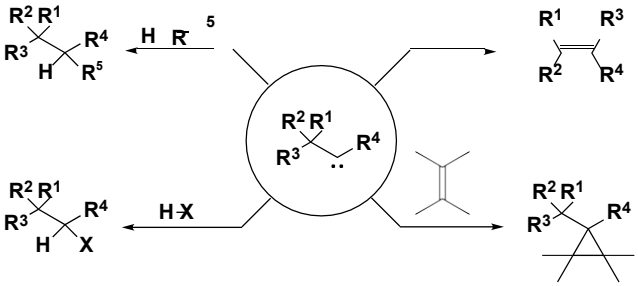


Figure 1: Structure of carbene intermediates: singlet and triplet carbenes.

Carbenes are very reactive intermediates that exhibit a very rich chemistry. For this reason, they have found a wealthy of applications in organic synthesis. Classical reactions carbenes are additions to unsaturated substrates, insertion to C-C and C-heteroatom bond and rearrangements.[20]



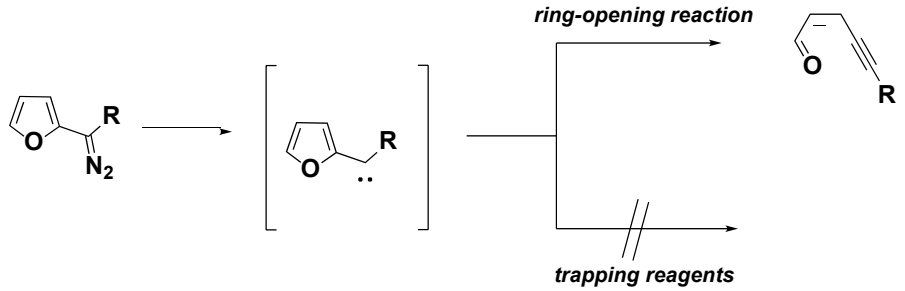
Scheme 1: Reactivity of carbenes.

[18] For comprehensive reviews on the chemistry of heteroarylcarbenes, see: a) R. S. Sheridan, *Chem. Rev.* **2013**, *113*, 7179-7208; b) L. D. Shirtcliff, S. P. McClintock, M. M. Haley, *Chem. Soc. Rev.*, **2008**, 37, 343-364.

[19] a) H. Tomioka, *In Reactive Intermediate Chemistry;* R. A. Moss, M. S Platz, M. Jones, jr, Eds, *Wiley-Interscience: Hoboken, NJ* ,**2004**, p 375; b) G. Bertran, *In reactive intermediate chemistry,* R. A. Moss, M. S Platz, M. Jones, jr, Eds, *Wiley-Interscience: Hoboken, NJ,* **2004**, p 329.

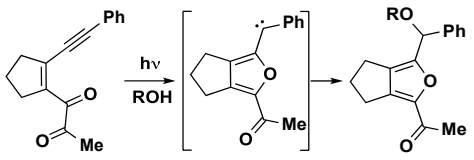
[20] A. Nickon, *Acc. Chem. Res.* **1993**, *26*, 84-89.

2-Furyl carbenes are a class of particularly interesting intermediates. These species can be generated from diazocompounds or 2-furyldiazirines (Scheme 2). [21] However, these intermediates undergo an easy ring-opening reaction with formation of an enynone derivative. This fact has hampered the use of these intermediates in organic synthesis through capture in the presence of potential trapping reagents.



Scheme 2: Generation of 2-furyl carbenes and ring-opening reaction to enynone.

To the best of our knowledge, only one isolated example of trapping of furyl carbenes with protic solvents has been reported. In 1995, Saito and co-workers developed the first example with good yields of trapping 2-furyl carbene intermediates in presence of protic solvents (Scheme 3).[22] They unitentionally found that irradiation in presence of water or alcohols of this enynone could give the ring-closure to furyl product. They proposed that the reaction proceeds through the intermediate 2-furyl carbene.



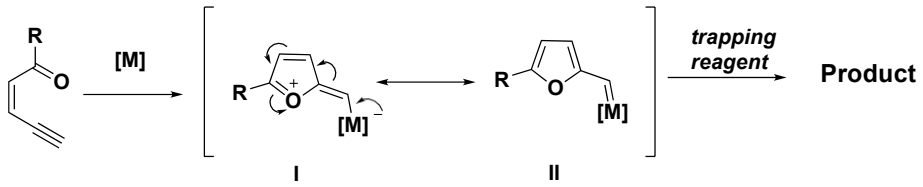
Scheme 3: First example of trapping 2-furyl carbenes with high-good yields.

[21] For reviews on the generation and synthetic applications of 2-furyl carbene complexes, see: a) K. Miki, S. Uemura, K. Ohe, *Chem. Lett.* **2005**, *34,* 1068-1072; b) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449; c) J. Ma, L. Zhang, S. Zhu, *Curr. Org. Chem.* **2016**, *20*, 102-118; d) G. Mass, *Angew. Chem. Int. Ed.* **2009**, *48*, 8186.

[22] a) Nakatani, S. Maekawa, K. Tanabe and I. Saito, *J. Am. Chem. Soc.* **1995**, *117*, 10635-10644; b) K. Nakatani, K. Aduchi, K. Tanabe and I. Saito, *J. Am. Chem. Soc.* **1999**, *121*, 8221-8228; c) K. Nakatani, K. Tanabe and I. Saito, *Tetrahedron Lett.* **1997**, *38*, 1207-1210. For reviews on enynones as carbene sources, see: a) K. Miki, S. Uemura, K. Ohe, *Chem. Lett.* **2005**, *34*, 1068-1073; b) H. Kusama, Iwasawa, *Chem. Lett.* **2006**, *35*, 1082-1087, c) K. Ohe, K. Miki, *J. Synth. Org. Chem.,* Jpn. **2009**, *67*, 1161-1171.

However, this methodology present important limitations as a multi step synthesis of starting material, protic solvents are needed to trapping the carbene and very poor selectivity. Interestingly, under the developed reaction conditions alkenes and silanes failed to afford the insertion products.

To overcome the limitations in developing synthetic applications of 2-furyl carbene, in the last years several efficient alternatives using enynones in the presence of transition metal complexes as catalysts have been developed.[23] These reactions are proposed to proceed through furyl metal carbene complexes (Scheme 4).[24] The formation of these intermediates involves initial coordination of alkyne to the metal (Cr, Au, Cu, Rh, Ru, Pt, Pd). Subsequent intramolecular nucleophilic attack to the activated alkyne would afford intermediate **I** can be also described in its carbene form II. Moreover, starting from enynones as precursors of carbenes avoids the use of diazocompounds as precursors of its.[25]



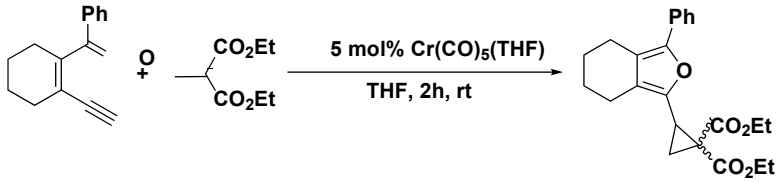
Scheme 4: Generation of 2-furyl carbenes from alkynes with transitions metals.

[23] a) J. R. Fulton, V. K. Aggarwal, J. de Vicente, *Eur. J. Org. Chem.* **1995**, 1479-1492; b) W. Xiong, C. Qi, H. He, L. Ouyang, M. Zhang, H. Jiang, *Angew. Chem. Int. Ed.* **2015**, *54*, 3084-3087; c) V. K. Aggarval, J. de Vicente, R. V. Bonnert, *Org. Lett.* **2001***, 3,* 2785-2788; d) J. Barluenga, C. Valdes, *Angew. Chem. Int. E.* **2011***, 50*, 7486-7500; e) J. Barluenga, M. Tomas-Gamasa, F. Aznar, C. Valdes, *Eur. J. Org. Chem.* **2011***, 8*, 1520-1526; f) J. Barluenga, M. Tomas-Gamasa, F. Aznar, C. Valdes, *Adv. Synth. Catal.* **2010***, 352*, 3235-3240.

[24] L. Chen, K. Chen, S. Zhu, *Chem. Rev.* **2018**, *4*, 1-55.

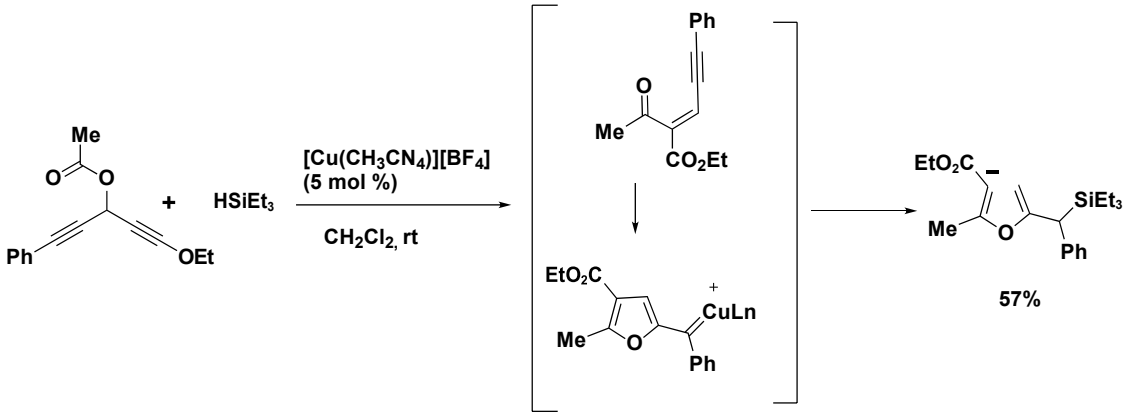
[25] Use of diazocompounds as precursors of carbenes has important limitations due its toxicity, the explosive hazard and a number of side reactions as diazodimerizations an azine formation.

For instance, in 2002 Prof. Ohe and Uemura developed a Cr-catalyzed cyclopropanation of alkenes via 2-furylcarbene complexes using $Cr(CO)_5(THF)$ as catalyst.[26] This Cr-carbenoid intermediate was trapped by several alkenes in goo to excellent yields (Scheme 5).



Scheme 5: Cr-catalyzed cyclopropanation.

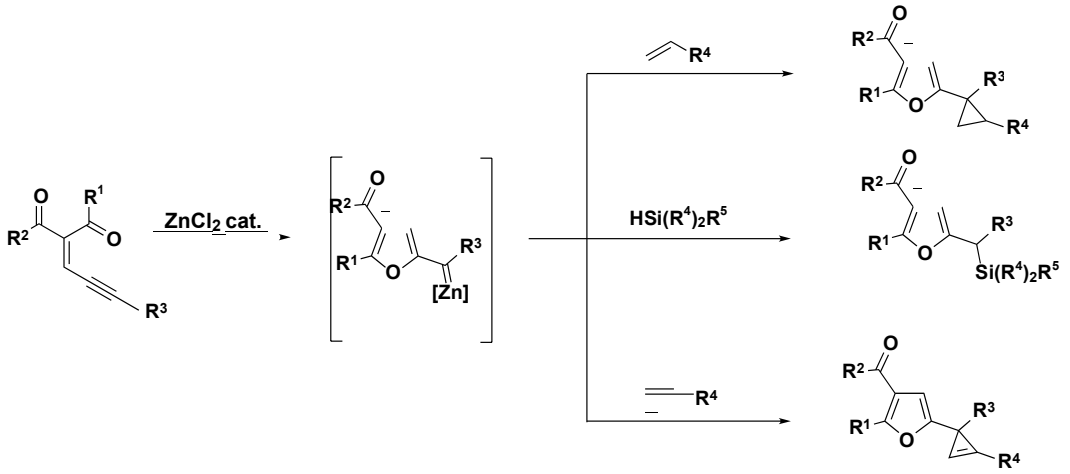
In 2008, Prof. Barluenga and co-workers described a regioselective Cu-catalyzed synthesis of substituted furans form bis-propargilic esters. The process initiates by 1,2 alcoxy migration giving rise to 2-furyl copper carbene. The generation of this 2-furyl copper carbene allows the formation of C-X (X = Si) bond formation.[27]



Scheme 6: Cu(I)-catalyzed synthesis of furane derivateves.

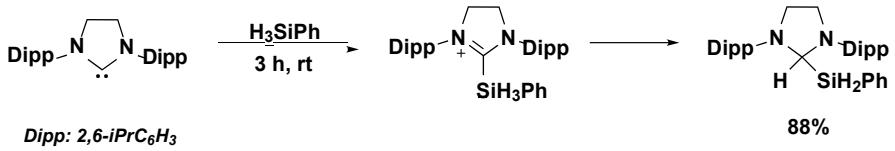
More recently, our group has reported some zinc-catalyzed transformations of enynones with generation of zinc carbene intermediates.[28] Specifically, these intermediates could be trapping with alkenes and silanes to give cyclopropanation and Si-H bond respectively, via 2-furyl Fischer-type zinc-(II). More recently the synthesis of cyclopropenes by trapping with alkynes has been also developed (Scheme 7).[29]

[26] K. Miki, F. Nishino, K. Ohe, S. Uemura, *J. Am. Chem. Soc.* **2002**, *124*, 5260-5261.
[27] J. Barluenga, L Riesgo, R. Vicente, L. A. López, M. Tomas, *J. Am. Chem. Soc.* **2008,** *130*, 13528-13529.
[28] a) M. J. González, L. A. López, R. Vicente, *Tetrahedron Lett.* **2015**, *56*, 1600-1608; b) R. Vicente, J. González, L. Riesgo, J. González, L. A. López, *Angew. Chem. Int. Ed.*, **2012**, *51*, 8063-8067.
[29] M. J. González, R. Vicente, L. A. López, *Org. Lett.* **2014**, *16*, 5780-5783.



Scheme 7: Zinc-catalyzed cyclopropanation, Si-H activation and cyclopropenation.

Moreover, in 2010 Bertand and co-workers reported the first examples of the activation of Si-H bonds with stable singlet carbenes (scheme 8).[30] They proposed that the activation involves the Lewis acid character of the silane and the initial formation of Lewis acid-based adducts followed by a migration occurs from the Si atom group to the carbene center.



Scheme 8: Activation of Si-H bond with stable singlet carbenes.

Despite these advances using metal catalysts and considering the importance of the development of a more sustainable chemistry, we realized that the development of metal-free alternatives would be highly convenient. Regarding these results and inspired by the recent work of Bertrand previously mentioned, we wondered whether a metal-free cross-coupling reaction between available enynones in presence of silanes could be accomplished by formation of 2-furyl carbene intermediates.

[30] G. D. Frey, J. D. Masuda, B. Donnadieu and G. Bertrand, *Angew. Chem. Int. Ed.*, **2010**, *49*, 944-9447.

A.2 Results and Discussion

A.2.1 Screening and scope of reaction conditions

Easily available enynone **1a**[31] and triethylsilane **2a** were selected as model substrates under a variety of reaction conditions (Table 1). First, we found that heating under standard oil-bath at 90 ^{o}C for 48 hours 1a and an excess of the silane (6 equiv) gave the furan derivative **3a** in 20% yield after chromatographic purification (entry 1). Notably, when we performed the reaction under microwave heating at 140 ^{o}C for four hours **3a** was obtained in 84% isolated yield (entry 2). Next, we investigated the reaction with different amounts of silane (entries 3-7). Gratifyingly, using 3 equiv. of the silane component we obtained the best result, affording the furane derivative **3a** in 91% isolated yield (entry 3).

The use of stoichiometric amount of silane gave the product in a good yield but did not improve previous result (entry 4).

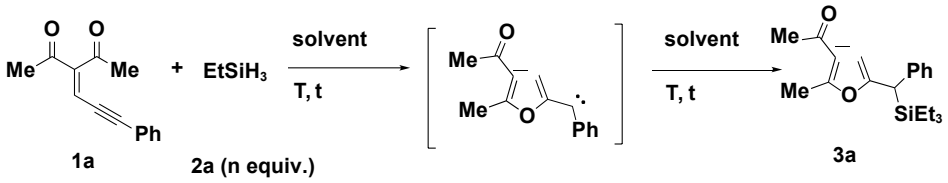
Other solvents and temperature conditions did not improve the yield of **3a**. However, we found that the reaction also proceeded in the absence of solvent with an excess of triethylsilane (entry 7) in 77% yield. Finally, under oil-bath condition heating at 140 ^{o}C, the reaction required extended reaction time to afford a comparable yield (entries 5-6). Yield of **3a** under this metal-free reaction is equivalent to that reported in our previous zinc-catalyzed reaction.[32]

Moreover, inductively coupled plasma mass spectrometry (ICP-MS) analyses ruled out the involvement of metal species arising from contamination of reactants and/or solvent.

[31] Enynone **3a** was prepared through a Knoevenagel condensation between the 2,4 pentanedione and 3-phenyl-2-propynal.

[32] Yield reported in the literature for the Zn-catalized reaction of **3a** 90%. See reference 11, b.

Table 1: Screening of reaction conditions.



entry	n	solvent	T (°C)	t (h)	Yield (%)
1	6	toluene	90	48	20
2	6	toluene	140 (MW)	4	84
3	***3***	***toluene***	***140 (MW)***	***4***	***91***
4	1.5	toluene	140 (MW)	4	71
5	3	toluene	140	4	30
6	3	toluene	140	12	80
7	30	-	100	22	77

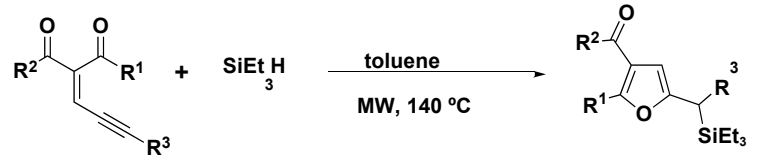
The structure of **3a** was deduced by NMR techniques, being the spectroscope data in agreement with those previously described in the literature.

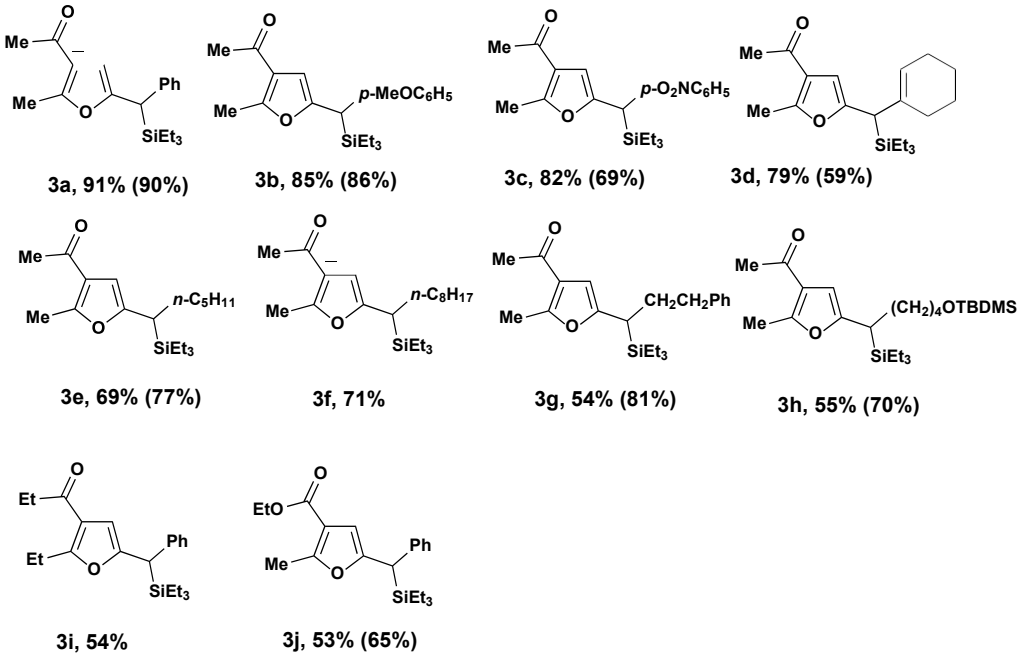
With optimal conditions in hand, we investigated the scope of this new metal-free silicon-hydrogen bond functionalization between a range of enynones and silane derivatives. Initially we studied the effect of the substituents in the enynone component. Electron-rich (enynone **1b**; R^1 = R^2 = Me, R^3 = *p*-$MeOC_6H_4$, entry 2) and -poor (enynone **1c**; R^1 = R^2 = Me, R^3 = *p*-$O_2NC_6H_4$) aromatic groups at the acetylenic position (R^3) were found to be well tolerated in this transformation providing furan derivatives **3b** and **3c** in good isolated yields (85 and 82%, respectively). Substrate bearing an alkenyl group (enynone **1d**; R^3 = cyclohexenyl, entry 4) posed no problems giving rise to furan derivative **3d** in 79% isolated yield.

Enynones with alkyl chains installed at the acetylenic position (**1e**-**g)** were also suitable substrates for this transformation affording the corresponding furan derivatives **3e**-**g** in moderate isolated yields (69% and 54%). In the same way, a protected alcohol in the alkyl chain (enynone **1h**; R^3 = $(CH_2)_4OTBDMS$, 55%) was also well tolerated.

Enynones **1i** (R^1 = R^2 = Et, R^3 = Ph) and **1j** (R^1 = Me, R^2 = OEt, R^3 = Ph) were also tested and afforded the expected furan derivatives **3i** and **3j** in moderate isolated yields (54% and 53 %).

Table 2: Scope of the reaction of eninones **1** and triethylsilane**.**





3a, 91% (90%) **3b, 85% (86%)** **3c, 82% (69%)** **3d, 79% (59%)**

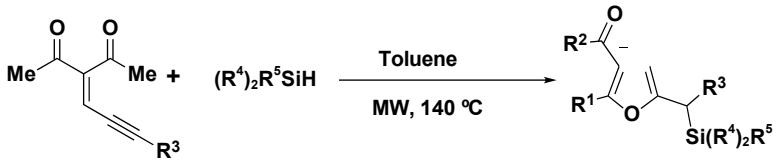
3e, 69% (77%) **3f, 71%** **3g, 54% (81%)** **3h, 55% (70%)**

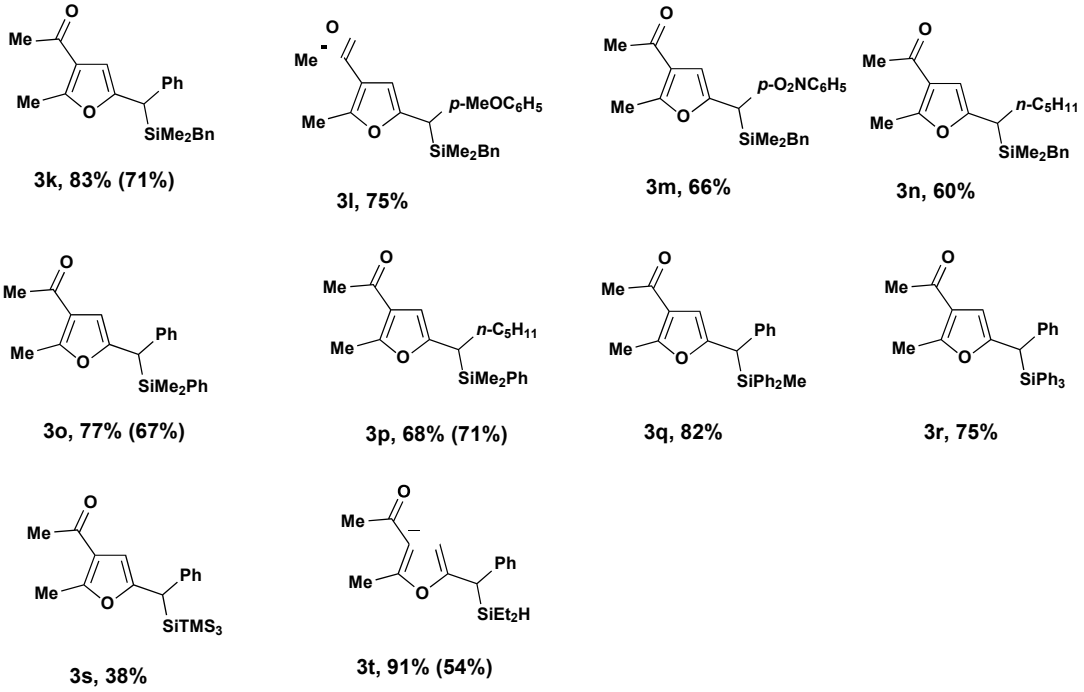
3i, 54% **3j, 53% (65%)**

Reaction conditions: 1 (0.2 mmol), 2 (0.6 mmol, 3 equiv.), toluene (0.1M), 140 ^{o}C (microwave heating). Yield of isolated product after column chromatography. The values in parenthesis correspond to the yields reported in the literature for the zinc-catalyzed reaction.

Next, we extended the scope to silanes with other substituents (table 3). Benzyldimethylsilane and phenyldimethylsilane readily reacted with enynones **1** delivering the corresponding furan derivatives **3k**-**p** in good yields (83% and 71%). Similarly, diphenylmethylsilane (**2d**) and triphenylsilane (**2e**) providing the corresponding functionalized furan derivatives **3q** and **3r** in 82 and 75% yield respectively. To our delight, highly sterically encumbered trisubstituted tris(trimethylsilyl)silane was able to participate in this transformation in a reasonable yield (38%). Finally, the reaction of enynone **1a** and diethylsilane posed no problems delivering the corresponding furan derivative **3t** in excellent isolated yield (91%). In contrast, phenylsilane and triethoxysilane were not suitable reagents under our reaction conditions.

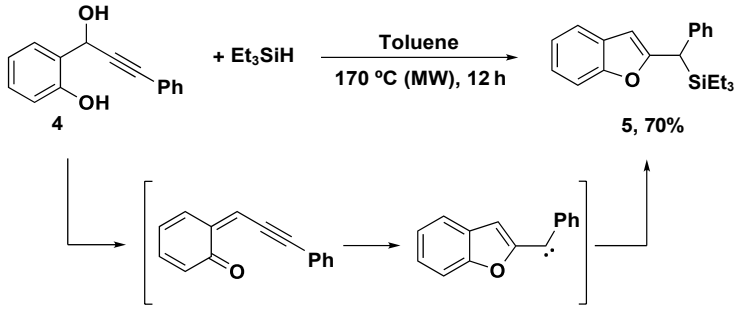
Table 3: Scope of the reaction of enynones and different silanes**.**





Reaction conditions: 1 (0.2 mmol), 2 (0.6 mmol, 3 equiv.), toluene (0.1M), 140 °C (microwave heating). Yield of isolated product after column chromatography. The values in parenthesis correspond to the yields reported in the literature for the zinc-catalyzed reaction

Next, to further expand the scope we extend the study to the generation of benzofuran carbene, using alkynyl-substituted o-hydroxy-benzyl alcohol as starting material and triethylsilane **2a**. Under MW conditions, quinone methide intermediate was generated by dehydration followed by cyclization and trapping of the resulting benzofuryl carbene in 70 % yield (scheme 9).



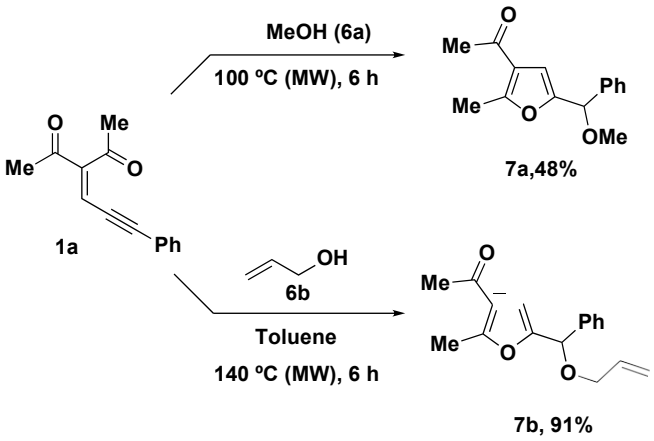
Scheme 9: Microwave-mediated metal-free synthesis of benzofuran derivative **5.**

A.2.2 Metal-free heteroatom-hydrogen bond functionalization

Preliminary studies were conducted to assess the potential of this metal-free methodology for the functionalization of oxygen-hydrogen and nitrogen-hydrogen bonds.

First, we found that the reaction of enynone **1a** with methanol (**6a**) as the trapping reagent under standard afforded only traces of the corresponding ether **7a**. However, the use of methanol as solvent at 100 ^{o}C provided a significant improvement of the yield (48 %).

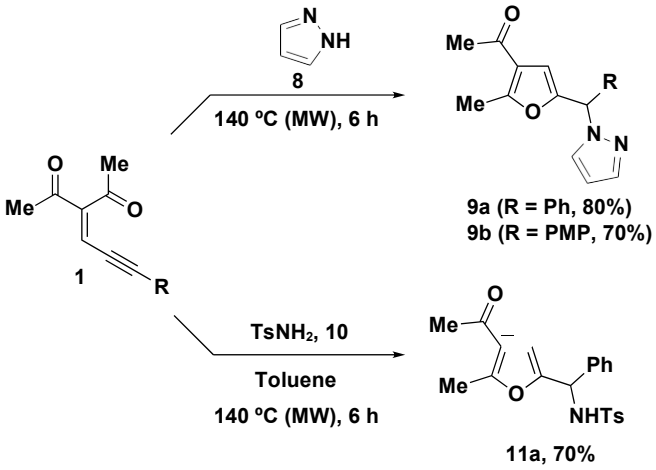
On the other hand, reaction of enynone **1a** with allylic alcohol (**6b**, 3 equivalents) in toluene at 140 ^{o}C proceeded with complete chemoselectivity delivering furyl ether derivative **7b** in excellent isolated yield (91%). Significantly, under these reaction conditions neither cyclopropanation of the olefinic moiety nor insertion into the allylic carbon-hydrogen bonds were observed.



Scheme 10: Microwave assisted O-H functionalization.

Finally, we also briefly examined the feasibility of a hydrogen-nitrogen bond functionalization and we found that reaction of enynones **1a** (R = Ph) and **1b** (R = *p*-$MeOC_6H_4$) with an excess of pyrazole (**8**) in toluene at 140 ^{o}C led to the formation of furyl- and pyrazolyl-containing triarylmethane derivatives **9a**,**b** in good isolated yields (Scheme 5).

Extension of this protocol to 4-toluenesulfonamide (**10**) produced the functionalized furan derivative **11a** in 70% isolated yield.



Scheme 11: Microwave assisted N-H functionalization.

Unfortunately, cyclopropanation reactions with alkenes as styrene, tetramethyl ethylene and indene under standard metal-free conditions did not afford the desired product ciclopropane and the starting materials were recovered.

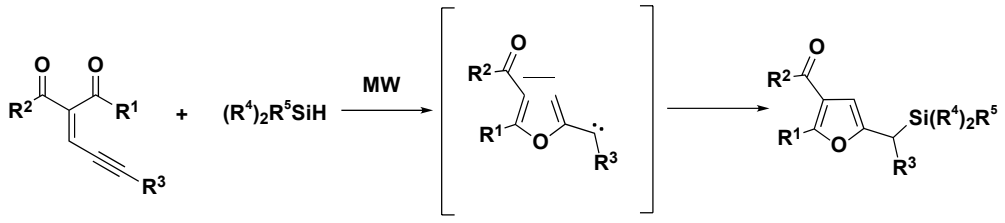
A.3 Conclusions

- We have reported an efficient microwave mediated metal-free silicon-hydrogen bond functionalization of readily available enynones and silanes with synthetically useful yields. Complete atom efficiency and easy execution are salient features of the developed protocol.

- This process proceeds through a trapping of 2-furyl carbene intermediate, which would be trapped by the silane. Prior to our study, these intermediates proved to be particularly elusive.

We developed preliminary studies for the generation and trapping of these 2-furyl carbenes with other heteroatoms. Metal-free oxygen-hydrogen and nitrogen-hydrogen bond functionalization of representative alcohols, azoles and sulfonamieds are provided.

Graphical Summary



Catching Elusive 2-Furyl Carbenes with Silanes: A Metal-Free Microwave-Assisted Silicon-Hydrogen Bond Functionalization

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Abstract: An efficient, metal-free, silicon–hydrogen bond functionalization based on the microwave-assisted reaction of readily available enynones and silanes is reported. This process seemingly proceeds through a 2-furyl carbene species, a particularly elusive intermediate. Preliminary studies on the metal-free oxygen–hydrogen and nitrogen–hydrogen bond functionalization of representative alcohols, azoles and sulfonamides are also provided.

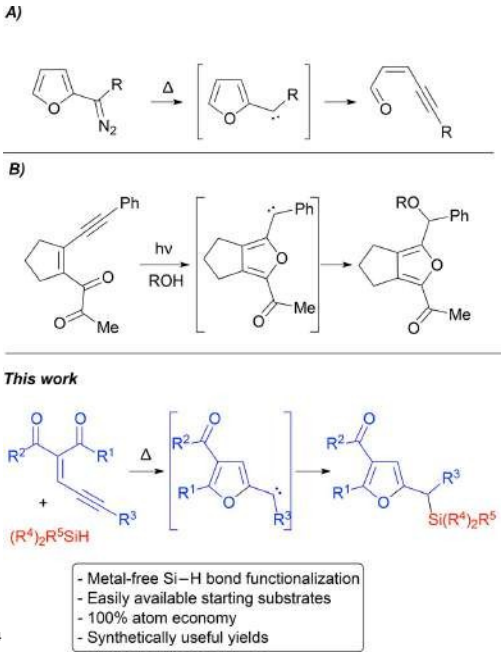
Keywords: carbenes; furans; metal-free coinditions; microwave-assisted reaction; silanes

2-Furyl carbenes are elusive intermediates and, for this reason, they have traditionally been regarded as synthetically useless intermediates.[1] As a result, a ple- thora of transition metal-based alternatives have been reported in the last years.[2]

Generated from 2-furyl diazo compounds or 2-furyldiazirine derivatives, these intermediates undergo a rapid ring-opening reaction to give enynones, which precludes their capture when generated in the presence of potential trapping reagents (Scheme 1, *A*).[3]

In a different approach, in 1995, Saito et al. managed the photochemical generation and subsequent intermolecular trapping by protic solvents of 2-furyl carbene intermediates arising from enynes featuring a conjugated *a*-diketone moiety (Scheme 1, *B*).[4] The *a*-diketone structural motif was found to be crucial for the success of the cyclization step since substrates lacking the additional carbonyl group located adjacent to that one involved in the cyclization did not afford any product resulting from the trapping of the postulated carbene intermediate. Although this contribution represents the first high-yield trapping reaction of 2-furyl carbene intermediates, the need of a multistep sequence for the synthesis of the starting enynones and the exclusive use of protic solvents (water and alcohols) as trapping reagents impose significant limitations on the synthetic applicability of this methodology. In particular, silanes and alkenes were found to be completely unsuccessful trapping reagents.

Clearly, the development of readily available precursors for the generation of 2-furyl carbenes susceptible of being intercepted by suitable trapping re- agents would be particularly appealing.



Due to our recent interest in the silicon–hydrogen bond functionalization[5] and inspired by a recent work of Bertrand and co-workers on the activation of Si–H bonds with stable singlet carbenes,[6] we decided to test the thermal behaviour of readily available enynones in the presence of silanes. As a result, in this communication we report a facile, metal-free, silicon–hydrogen bond functionalization based on the trapping of 2-furyl carbene intermediates.[7] Preliminary studies on the functionalization of other heteroatom–hydrogen bonds are also disclosed.

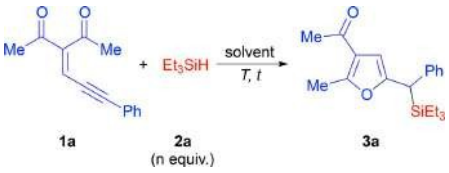
On the outset we studied the reaction of enynone 1a with triethylsilane 2a under a variety of reaction conditions (Table 1). First, we found that heating a mixture of 1a and 2a (6 equiv.) in toluene at 90 8C for 48 hours afforded the furan derivative 3a in 20% yield after chromatographic purification (Table 1, entry 1). Gratifyingly, when the reaction was per- formed under microwave heating at 140 8C an im- proved yield was achieved (84% isolated yield, Table 1, entry 2). Next, we tried to reduce the amount of the silane component. Although the reaction worked well with a nearly stoichiometric amount of the silane component (Table 1, entry 4), the use of 3 equiv. proved optimal in terms of yield (quantitative by NMR; 91% isolated yield; Table 1, entry 3). The reaction could also be performed under standard oil- bath conditions, although these conditions required an extended reaction time to afford a comparable yield (Table 1, entries5 and 6). The reaction also proceeded in the absence of solvent but in this case an excess of triethylsilane was required (Table 1, entry 7).

Inductively coupled plasma mass spectrometry (ICP-MS) analyses ruled out the involvement of metal species arising from contamination of reactants and/or solvent.

These results represent a proof of concept demonstration of the feasibility of using enynones as 2-furyl carbene precursors for the metal-free silicon–hydrogen bond functionalization.

With the optimized reaction conditions in hand (microwave heating at 140 8C in toluene, 3 equiv. of silane), the substrate scope of this metal-free silicon– hydrogen bond functionalization was assessed using a range of enynones and silane derivatives (Table 2). Regarding the enynone component, both electron- rich (enynone 1b; R^1 = R^2 = Me, R^3 = *p*-$MeOC_6H_4$) and electron-poor (enynone 1c; R^1 = R^2 = Me, R^3 = *p*-$O_2NC_6H_4$) aromatic groups at the acetylenic position (R^3) were found to be well tolerated in this transfor-

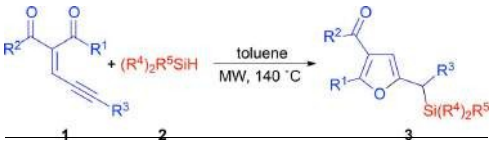
Table 1. Optimization of the reaction conditions: summary.[a]



Entry	n	Solvent	*T* [8C]	*t* [h]	Yield [%][b]
1	6	toluene	90	48	20
2	6	toluene	140 (MW)	4	84
3	*3*	*toluene*	*140 (MW)*	*4*	*91*[c]
4	1.5	toluene	140 (MW)	4	71
5	3	toluene	140	4	30[d]
6	3	toluene	140	12	80
7	30	–	100	22	77

[a] Unless otherwise stated, these exploratory experiments were performed on a 0.2 mmol scale.
[b] Isolated yields unless otherwise specified.
[c] 99% yield by NMR (dibromomethane as internal standard).
[d] Crude yield by NMR (dibromomethane as internal standard).

Table 2. Microwave-assisted reaction of enynones 1 and silanes 2: scope.[a]



R^1, R^2, R^3	R^4, R^5	3, Yield[b]
Me, Me, Ph	Et, Et	3a, 91% (90)[5a]
Me, Me, *p*-$MeOC_6H_4$	Et, Et	3b, 85% (86)[5a]
Me, Me, *p*-$O_2NC_6H_4$	Et, Et	3c, 82% (69)[5a]
Me, Me, 1-cyclohexenyl	Et, Et	3d, 79% (59)[5a]
Me, Me, *n*-C_5H_{11}	Et, Et	3e, 69% (77)[5a]
Me, Me, *n*-C_8H_{17}	Et, Et	3f, 71%
Me, Me, CH_2CH_2Ph	Et, Et	3g, 54% (81)[5b]
Me, Me, $(CH_2)_4OTBS$	Et, Et	3h, 55% (70)[5b]
Et, Et, Ph	Et, Et	3i, 54%
Me, OEt, Ph	Et, Et	3j, 53% (65)[5b]
Me, Me, Ph	Me, Bn	3k, 83% (71)[5b]
Me, Me, *p*-$MeOC_6H_4$	Me, Bn	3l, 75%
Me, Me, *p*-$O_2NC_6H_4$	Me, Bn	3m, 66%
Me, Me, *n*-C_5H_{11}	Me, Bn	3n, 60%
Me, Me, Ph	Me, Ph	3o, 77% (67)[5b]
Me, Me, *n*-C_5H_{11}	Me, Ph	3p, 71% (68)[5a]
Me, Me, Ph	Ph, Me	3q, 82%[c]
Me, Me, Ph	Ph, Ph	3r, 75%[c]
Me, Me, Ph	TMS, TMS	3s, 38%[c]
Me, Me, Ph	Et, H	3t, 91%[c] (54)[5b]

[a] *Reaction conditions:* 1 (0.2 mmol), 2 (0.6 mmol, 3 equiv.), toluene (0.1 M), 140 8C (microwave heating).
[b] Yield of isolated product after column chromatography. The values in parenthesis correspond to the yields reported in the literature for the zinc-catalyzed reaction.[5]
[c] Reaction run with 6 equivalents of silane.

mation providing furan derivatives 3b and 3c in good isolated yields (85 and 82%, respectively).

Similarly, a substrate bearing an alkenyl group at this position (enynone 1d; R^3 = cyclohexenyl) posed no problems giving rise to furan derivative 3d in 79% isolated yield.

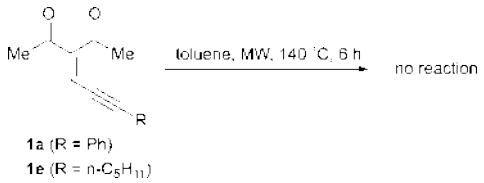
Enynones 1e–g with alkyl chains installed at the acetylenic position were also suitable substrates for this transformation affording the corresponding furan derivatives 3e–g in moderate isolated yields. A protected alcohol in the alkyl chain [enynone 1h; R^3 = $(CH_2)_4OTBS$] was also well tolerated.

Some modifications on the structure of the enynone component were also realized. Thus, enynones 1i (R^1 = R^2 = Et, R^3 = Ph) and 1j (R^1 = Me, R^2 = OEt, R^3 =Ph) behaved similarly and afforded the expected furan derivatives 3i and 3j in moderate isolated yields. Next, the scope of this metal-free silicon–hydrogen bond functionalization was expanded to other silanes. Indeed, benzyldimethylsilane (2b) and phenyldimethylsilane (2c) readily reacted with enynones 1 delivering the corresponding furan derivatives 3k–p in good yields. Diphenylmethylsilane (2d) and triphenylsilane (2e) also proved to be suitable silane counterparts in this microwave-mediated transformation providing the corresponding functionalized furan derivatives 3q and 3r in 82 and 75% yields, respectively. Even a highly sterically encumbered trisubstituted silane, namely tris(trimethylsilyl)silane (2f), was able to participate in this transformation although with a significant decrease in the yield. Finally, the reaction of enynone 1a and diethylsilane (2g) posed no problems delivering the corresponding furan derivative 3t in excellent isolated yield. In contrast, phenylsilane and triethoxysilane were not suitable reagents under our reaction conditions.

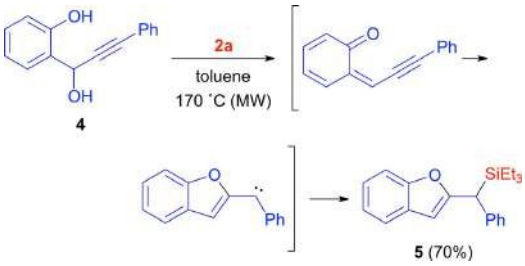
As shown in Table 2, in most cases the yields of this metal-free reaction are equivalent or superior to those reported in our previous zinc-catalyzed reaction.[5]

Next, we conducted some control experiments in absence of silane aimed at gaining insight into the structure of the intermediate involved in this transformation. Thus, when solutions of enynones 1a (R^1 = R^2 = Me, R^3 = Ph) and 1e (R^1 = R^2 = Me, R^3 = *n*-C_5H_{11}) in toluene were heated under microwave irradiation at 140 °C for 6 h, neither a dimerization product nor (in the case of enynone 1e) a vinylfuran derivative resulting from a 1,2-H shift were observed, with the majority of mass balance being unreacted enynone (Scheme 2). These observations are in full agreement with those previously reported by Shechter and coworkers in the generation of 2-furyl carbenes by vacuum pyrolyses of some tosylhydrazone sodium salts.[8]

To further demonstrate the synthetic utility of this metal-free cyclization/silicon–hydrogen bond functionalization sequence, we decided to extend the study to the generation of the benzofused analogue intermediate, namely a benzofuran carbene intermediate. In this regard, we envisioned alkynyl-substituted *o*-hydroxybenzyl alcohol 4 as a suitable starting substrate. We surmised that initial microwave-assisted thermal dehydration to furnish the corresponding *o*-quinone methide,[9] followed by cyclization and trapping of the resulting benzofuryl carbene could represent a convenient metal-free approach to silyl-substituted benzofuran derivatives. In fact, the formation of benzofuran derivative 5 in 70% isolated yield after heating a mixture of alkynyl-substituted *o*-hydroxybenzyl alcohol 4 and triethylsilane (2a) in toluene at 170 °C clearly demonstrated the feasibility of this methodology (Scheme 3).



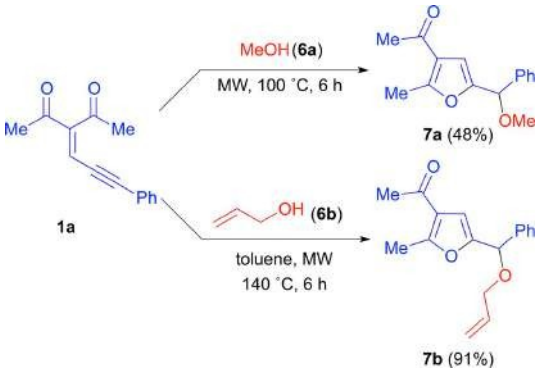
Scheme 2. Control experiments performed in the absence of silane reagent.



Scheme 3. Microwave-mediated, metal-free synthesis of benzofuran derivative 5.

Having established the feasibility of using enynones 1 as 2-furyl carbene precursors, preliminary studies were also conducted to assess the potential of this metal-free methodology for the functionalization of oxygen–hydrogen bonds (Scheme 4).[10]

Initially, we found that the reaction of enynone 1a with methanol (6a) as the trapping reagent under the conditions developed for the silicon–hydrogen bond functionalization (3 equivalents of methanol, toluene as solvent, microwave heating at 140 °C for 6 hours), afforded only traces of the corresponding ether 7a. Pleasingly, the use of methanol as solvent at 100 °C provided a significant improvement of the yield. On

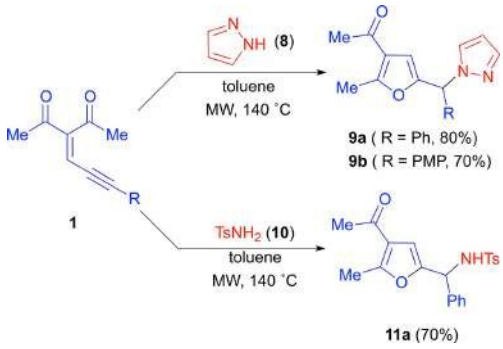


Scheme 4. Microwave-assisted O–H bond functionalization.

the other hand, reaction of enynone 1a with allylic alcohol (6b, 3 equivalents) in toluene at 140 8C proceed- ed with complete chemoselectivity delivering furyl ether derivative 7b in excellent isolated yield (91%). Significantly, under these reaction conditions neither cyclopropanation of the olefinic moiety nor insertion into the allylic carbon–hydrogen bonds were ob- served.

Finally, we also briefly examined the feasibility of a hydrogen–nitrogen bond functionalization. After some optimization, we found that reaction of enynones 1a (R= Ph) and 1b (R= *p*-MeOC$_6$H$_4$) with an excess of pyrazole (8) in toluene at 140 8C led to the formation of furyl- and pyrazolyl-containing triarylmethane derivatives 9a and 9b in good isolated yields (Scheme 5). Extension of this protocol to 4-toluenesulfonamide (10) produced the functionalized furan derivative 11a in 70% isolated yield.

In short, we have described the microwave-mediat- ed, metal- and additive-free reaction of readily available enynones and silanes to afford functionalized furylsilanes. This non-diazo silicon–hydrogen bond func- tionalization is believed to proceed by means of a 2- furyl carbene intermediate, which in turn would be trapped by the silane. It is worthy of note that, with a few notable exceptions, these intermediates have largely defied trapping. Notable aspects of our protocol are: (i) availability of the starting materials, (ii) easy execution, (iii) complete atom efficiency, and (iv) synthetically useful yields. Preliminary results demon- strated that this protocol could be used for the gener- ation and trapping of other heteroaryl carbenes as well as for the functionalization of other heteroatom– hydrogen bonds. In our opinion, these preliminary findings could open up new pathways for the develop- ment of new metal-free methodologies, an attractive field in contemporary organic synthesis. In particular, our group is actively pursuing the development of new strategies for the metal-free C–C bond forma- tion, a traditional domain of metal-based methodolo- gies.



Scheme 5. Microwave-assisted N–H bond functionalization.

Experimental Section

Representative Procedure (3a)

A 2–5-mL microwave vial was charged with the enynone 1a (42.4 mg, 0.2 mmol), triethylsilane 2a (69.8 mg, 0.6 mmol, 3.0 equiv.), toluene (2 mL) and a stirring bar. The vessel was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at 140 8C for 4 hours in a Biotage Initiator microwave apparatus. The solvent was removed under reduced pressure. ^{1}H NMR (dibromome- thane as internal standard) revealed the formation of furan derivative 3a in quantitative yield. Purification by flash chromatography (SiO_2, hexane:EtOAc= 10:1) furnished 3a as a pale yellow oil; yield: 59.8 mg (91%). ^{1}H NMR: (400 MHz, $CDCl_3$): d= 0.61 (q, *J* = 8.0 Hz, 6H), 0.88 (t, *J* = 8.0 Hz, 9H), 2.37 (s, 3 H), 2.58 (s, 3 H), 3.63 (s, 1H), 6.23 (s, 1H), 7.14–7.22 (m, 3H), 7.26–7.30 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): d= 2.9 (CH_2), 7.2 (CH_3), 14.5 (CH_3), 29.1 (CH_3), 35.2 (CH), 105.6 (CH), 122.2 (C), 125.3 (CH), 127.9 (CH), 128.4 (CH), 140.3 (C), 154.8 (C), 156.6 (C), 194.3 (C); HR-MS (EI): *m/z* = 328.1858, calculated for $[C_{20}H_{28}O_2Si]^+$ (M^+): 328.1859.

Acknowledgements

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References

[1] For comprehensive reviews on the chemistry of heteroaryl carbenes, see: a) R. S. Sheridan, *Chem. Rev.* 2013, *113*, 7179; b) L. D. Shirtcliff, S. P. McClintock, M. M. Haley, *Chem. Soc. Rev.* 2008, *37*, 343.

[2] For reviews on the generation and synthetic applications of 2-furyl carbene complexes, see: a) K. Miki, S. Uemura, K. Ohe, *Chem. Lett.* 2005, *34*, 1068; b) A. F ̂rstner, P. W. Davies, *Angew. Chem.* 2007, *119*, 3478 ; *Angew. Chem. Int. Ed.* 2007, *46*, 3410; c) J. Ma, L. Zhang, S. Zhu, *Curr. Org. Chem.* 2016, *20*, 102. For se- lected examples, see: d) K. Miki, F. Nishino, K. Ohe, S. Uemura, *J. Am. Chem. Soc.* 2002, *124*, 5260 ; e) K. Miki, Y. Washitake, K. Ohe, S. Uemura, *Angew. Chem.* 2004, *116*, 1893 ; *Angew. Chem. Int. Ed.* 2004, *43*, 1857;
f) H. Cao, H. Zhan, J. Cen, J. Lin, Y. Lin, Q. Zhu, M. Fu, H. Jiang, *Org. Lett.* 2013, *15*, 1080 ; g) Y. Yu, S. Yi,
C. Zhu, W. Hu, B. Gao, Y. Chen, W. Wu, H. Jiang, *Org. Lett.* 2016, *18*, 400; h) Y. Xia, S. Qu, Q. Xiao, Z.-X. Wang, P. Qu, L. Chen, Z. Liu, L. Tian, Z. Huang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* 2013, *135*, 13502.

[3] a) R. V. Hoffman, H. Shechter, *J. Am. Chem. Soc.* 1971, *93*, 5940 ; b) R. V. Hoffman, G. G. Orphanides, H. Shechter, *J. Am. Chem. Soc.* 1978, *100*, 7927. For the generation and trapping of 2-furyl chlorocarbene, see:
c) T. Khasanova, R. S. Sheridan, *J. Am. Chem. Soc.* 1998, *120*, 233. For a computational study on this rear- rangement, see: d) D. M. Birney, *J. Am. Chem. Soc.* 2000, *120*, 10917.

[4] a) K. Nakatani, S. Maekawa, K. Tanabe, I. Saito, *J. Am. Chem. Soc.* 1995, *117*, 10635; b) K. Nakatani, K. Aduchi, K. Tanabe, I. Saito, *J. Am. Chem. Soc.* 1999, *121*, 8221; c) K. Nakatani, K. Tanabe, I. Saito, *Tetrahe- dron Lett.* 1997, *38*, 1207.

[5] a) R. Vicente, J. Gonzµlez, L. Riesgo, J. Gonzµlez,
L. A. LÛpez, *Angew. Chem.* 2012, *124*, 8187; *Angew. Chem. Int. Ed.* 2012, *51*, 8063 ; b) S. Mata, L. A. LÛpez,
R. Vicente, *Chem. Eur. J.* 2015, *21*, 8998.

[6] a) G. D. Frey, J. D. Masuda, B. Donnadieu, G. Bertrand, *Angew. Chem.* 2010, *122*, 9634; *Angew. Chem. Int. Ed.* 2010, *49*, 9444. For a recent related example, see : b) C. Mohopatra, P. P. Samuel, B. Li, B. Niepçtter, C. J. Sch ̂rmann, R. Herbst-Irmer, D. Stalke, B. Maity, D. Koley, H. W. Roesky, *Inorg. Chem.* 2016, *55*, 1953. For selected examples involving insertion of dichlorocar- bene into the Si–H bond, see: c) D. Seyferth, J. M. Bur- litch, *J. Am. Chem. Soc.* 1963, *85*, 2667; d) D. Seyferth,
R. Damrauer, J. Y.-P. Mui, T. F. Jula, *J. Am. Chem. Soc.* 1968, *90*, 2944; e) Y. Goldberg, H. Alper, *Organometal- lics* 1995, *14*, 804 ; W. Liu, I. D. Sharp, T. D. Tilley, *Langmuir* 2014, *30*, 172.

[7] For recent organocatalytic transformations of conjugated ene-yne ketones, see: a) J. S. Clark, A. Boyer, A. Aimon, P. E. Garcìa, D. M. Lindsay, A. D. F. Syming- ton, Y. Danoy, *Angew. Chem.* 2012, *124*, 12294; *Angew. Chem. Int. Ed.* 2012, *51*, 12128; b) J. S. Clark, F. Romiti,
K. F. Hogg, M. H. S. A. Hamid, S. C. Richter, A. Boyer, J. C. Redman, L. J. Farrugia, *Angew. Chem.* 2015, *127*, 5836; *Angew. Chem. Int. Ed.* 2015, *54*, 5744.

[8] For example, pyrolysis of 1-diazo-1-(2-furyl)ethane at 275 ßC resulted in the formation of *cis*- and *trans*-2-hexen-4-ynals (36% overall yield). In this transformation 2-vinylfuran was also formed in a yield as low as 3.6%. A similar result was reported for the pyrolysis of 1-diazo-1-(2-furyl)propane. See ref.[3a] for details.

[9] For reviews on the synthetic applications of *o*-quinone methides, see: a) M. S. Singh, A. Nagaraju, N. Anand,
S. Chowdhury, *RSC Adv.* 2014, *4*, 55924; b) R. W. Van De Water, T. R. R. Pettus, *Tetrahedron* 2002, *58*, 5367;
c) P. Wan, B. Barker, L. Diao, M. Fischer, Y. Shi, C. Yang, *Can. J. Chem.* 1996, *74*, 465.

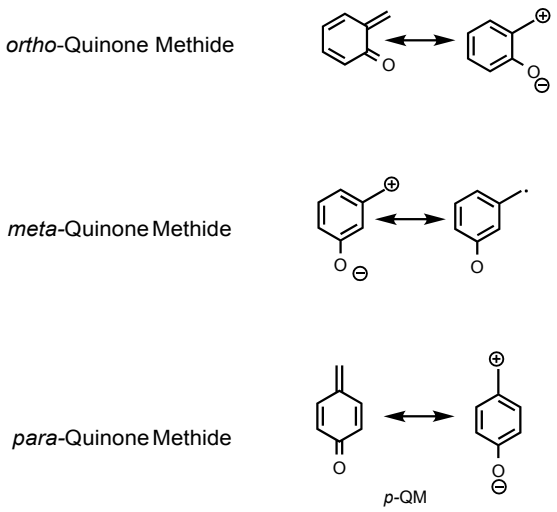
[10] For the synthesis of ethers by metal-free coupling of tosylhydrazones and alcohols or phenols, see: J. Barluen- ga, M. Tomµs-Gamasa, F. Aznar, C. Valdÿs, *Angew. Chem.* 2010, *122*, 5113; *Angew. Chem. Int. Ed.* 2010, *49*, 4993.

Part B: Microwave-assisted generation and capture by azoles of quinone methide intermediates under aqueous conditions

B.1. Quinone Metide Intermediates: General aspects

Quinone methides (QMs) are highly reactive intermediates that have attracted special interest in organic synthesis, material chemistry and biochemistry.[33]

These intermediates exist in three isomeric forms: *ortho*, *metha* and *para* quinone methides. *ortho*-QM and *para*-QM are resonance hybrid of neutral molecules and the zwitterionic form that makes an important contribution to the overall molecular structure (Scheme 1). In contrast, *meta*-QMs are an unstable triplet diradical of two canonical forms, one of which is zwitterionic form.



Scheme 1: Isomeric forms of quinone methides.

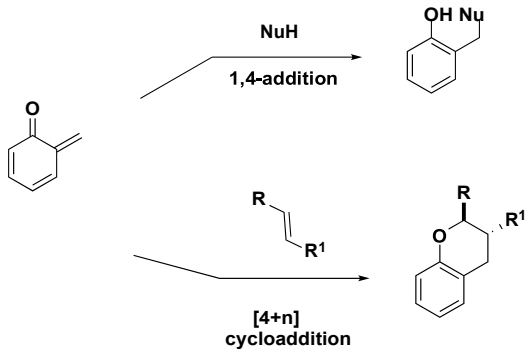
Ortho- and *para*- quinone methides are highly polarized compounds and have been used in several fields such as medicinal chemistry, asymmetric synthesis and synthesis of natural products.[34]

[33] a) D. V. Osipov, V. A. Osyanin, Y. N. Klimochkin, *Russ. Chem. Rev.* **2017**, *86*, 625–687; b) A. A. Jaworski, K. A. Scheidt, *J. Org. Chem.* **2016**, *81*, 10145-10153; c) M. S. Singh, A. Nagaraju, N. Anand, S. Chowdhury, *RSC Adv.* **2014**, *4*, 55924-55959; d) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu, T. R. R. Pettus, *Acc. Chem. Res.* **2014**, *47*, 3655–3664; e) N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160-9173; f) R. W. van de Watter, T. R. R. Pettus, *Tetrahedron.* **2002**, *58*, 5367-5405; g) B. S. Ferreira, C. F. Silvia, C. A. Pinto, T. G. D. Gonzaga, F. V. Ferreira, *J. Heterocyclic Chem*. **2009**, *46,* 1180-1189; h) H. Amoru, J. L. Bras, *Acc. Chem. Res.* **2002**, *35*, 501-510.

[34] T P Pathak, M S Sigman, *J. Org. Chem*. **2011,** *79,* 9210-9215.

B.1.1. Reactivity of Quinone Methides

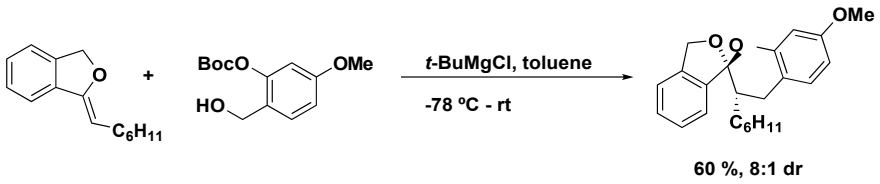
The reactivity of QMs mimics that of α,β-unsaturated ketones and, as a result, they react easily with nucleophiles to provide corresponding 1,4-addition products.[35] Additionally, o-QMs react extremely facile with electron rich dienophiles to give [4+2][36] and other [4+*n*] cycloaddition reactions.[37]



Scheme 2: Reactivity profiles of *ortho*-quinone methide intermediates.

A number of natural products as well as biologically active heterocycles have been accessed utilizing *in situ* generated *o*-QMs.

For instance, *o*-QMs react with a variety of dienophiles via [4+n] cycloaddition. As illustrative example, Pettus and co-workers reported the synthesis of a variety of chromans spiroketals through [4+2] cycloaddition of enol ethers with *o*-QMs.[38] This methodology allows the synthesis of a wide number of unusual chroman spiroketals (scheme 3).



Scheme 3: Synthesis of chroman spiroketals.

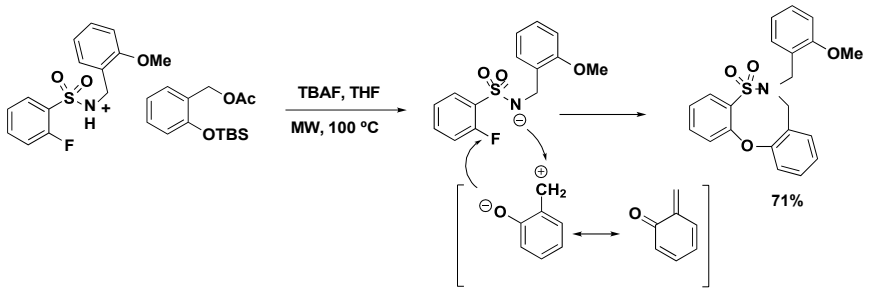
[35] For a recent contribution on the catalytic asymmetric substitution of *ortho*-hydroxybenzyl alcohols with enamines, see: M.-M. Xu, H.-Q. Wang, Y. Wan, J. Yan, S. Zhang, S.-L. Wang, F. Shi, *Org. Chem. Front.* **2017**, *4*, 358-368; for the 1,4-addition reaction of deoxycytidine to *ortho*-quinone methide intermediates, see: M. P. McCrane, E. E. Weinert, Y. Lin, E. P. Mazzola, Y.-F. Lam, P. F. Scholl, S. E. Rokita, *Org. Lett.* **2011**, *13*, 1186-1189.

[36] L. Xu, F. Liu, L.-W. Xu, Z. Gao, Y.-M. Zhao, *Org. Lett.* **2016**, *18*, 3698-3701.

[37] For [4+1] cycloaddition reactions, see: a) N. Meisinger, L. Roiser, U. Monk-owius, M. Himmelsbach, R. Robiette, M. Wasser, *Chem. Eur. J.* **2017**, *23*, 5137–5142 and references cited therein; for a recent [4+3] cycloaddition reaction of *ortho*-quinone methide intermediates, see: G.-J. Mei, Z.-Q. Zhu, J.-J. Zhao, C.-Y. Bian, J. Chen, R.-W. Chen, F. Shi, *Chem. Commun.*

[38] J Veljkovic', L Uzelac, K Molcanov, K Mlinaric'-Majerski,M Kralj, P Wan, N Basaric, **2012,** *J. Org. Chem*. *77,* 4596-4610.

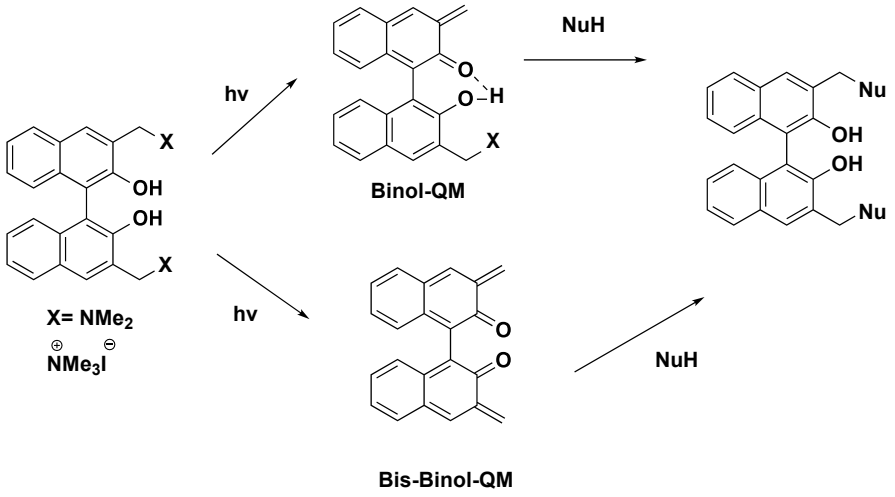
In 2010, Handson and co-workers reported the first example of hetero [4+4] cycloadditions via *in situ* generation of *o*-QM intermediates.[39] Starting from fluorobenzenesulfonamides, *o*-QM was generated under microwave conditions, to afford 5,2,1-dibenzooxathiazocine-2,2-dioxide scaffolds.



Scheme 4: Synthesis of 5,2,1-dibenzooxathiazocine-2,2-dioxides by hetero [4+4] cyclization.

Moreover, recently, different laboratories have been working on the interactions of QM to generate an efficient cross-linking and target-promoted alkylation of DNA [40] by photochemical and fluoride-induced activation.

Freccero and co-workers reported the photo-induced generation of new binol quinone methide, which undergoes addition of free nucleophiles.[41]



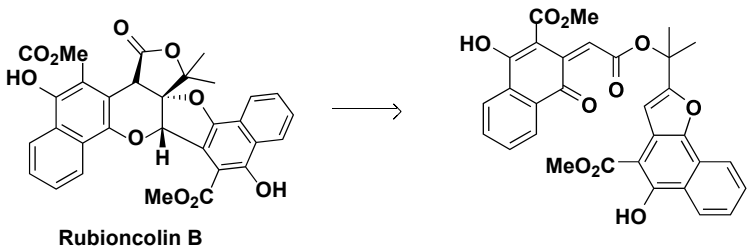
Scheme 5: Generation and reactivity of Binol-QMs.

[39] T. B. Samarakoon, M. Y. Hur, R. D. Kurtz and P. R. Hanson, Org. Lett, **2010**, *12*, 2182-2185.

[40] For a study of the substituent effect on the reactivity of *ortho*-quinone methide intermediates with biological nucleophiles, see: E. E. Weinert, R. Dondi, S. Colloredo-Melz, K. N. Frank- enfield, C. H. Mitchell, M. Freccero, S. E. Rokita, *J. Am. Chem. Soc.* **2006**, *128*, 11940-11947.

[41] S. N. Richter, S. Maggi, S. C. Mels, M. Palumbo, M. Freccero, *J. Am. Chem. Soc.* **2004**, *126*, 13973-13979.

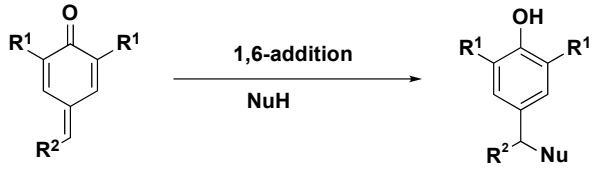
It should also be noted that recently *o*-QM intermediates have become increasingly important in total synthesis. For example, in 2008 Trauner and co-workers reported the synthesis of Rubioncolin B through an intramolecular Diels-Alder reaction of an *o*-QM intermediate.[42]



Scheme 6: *o*-QM intramolecular Diels-Alder approach to Rubioncolin B.

On the other hand, *p*-Quinone methide intermediates have been proposed as key intermediates in biosynthesis, enzyme inhibition, and in the biosynthesis and subsequent chemistry of lignin.[43] Surprisingly, the reactivity of *p*-QMs has received less attention than that of the *ortho* isomers.

Despite of the high reactivity of *p*-QM intermediates, it has been possible the generation of 2,6-disubstituted stable *p*-QMs that allows the study of its reactivity. There are examples of *p*-QMs in intramolecular cyclization reactions and with several nucleophiles as pyrrole, thiol and boranes in 1,6- conjugate addition.[44]



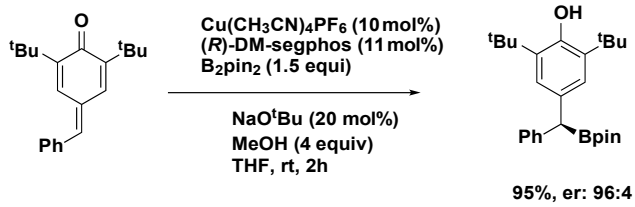
Scheme 7: 1,6-cycloadditions to p-Quinone methides.

[42] J. P. Lumb, K. C. Choong, D. Trauner, *J. Am. Chem. Soc.* **2008**, *130*, 9230-9231.

[43] a) O. R. Gottlieb, *Fortsch. Chem. Org. Naturst*. **1978**, *35*, 1; b) K. L. Rinehart; T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Keifer, F. Sun, L. H. Li, D. G Martin, *J. Org. Chem*. **1990**, *55*, 4512-4515; c) M. G. Peter, *Angew. Chem. Int. Ed. Engl*. **1989**, *28*, 555-557; d) M. Sugumaran, *Bioorg. Chem*. **1987**, *15*, 194-211; e) G. J. Leary, *Wood Sci. Technol.* **1980***, 14*, 21-34.

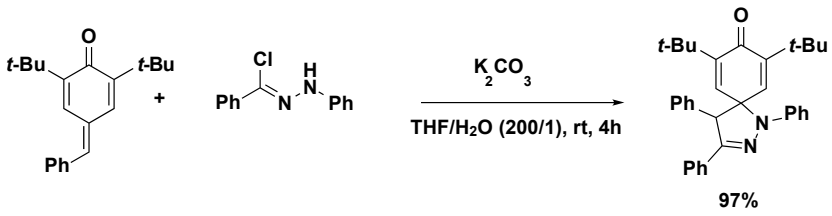
[44] For reviews on the chemistry ofp-QMs: a) H.-u. Wagner, R. Gompper in *The chemistry of the Quinonoid Compounds,* vol. 2, Willey, New York, 1974, chap 18, pp. 1145-1178; b) M. M. Toteva, J. P. Richard, *Adv. Phys. Org. Chem.* **2011***, 45*, 39-91; c) Xiao-Li Jiang, Shu-Fang Wu, Jin-Rong Wang, Han Lu,* Guang-Jian Mei* andFeng Shi; *Org. Biomol. Chem*. **2018**, *16,* 8395-8402.

o-QM have been widely used in asymmetric synthesis, however only few examples of enantioselective additions to *p*-QM have been reported.[45] In 2015, Tortosa and co-workers developed a synthesis of dibenzylic boronates through the enantioselective 1,6-addition of a chiral copper(I) boryl complex to a *p*-QM.[46]



Scheme 8: Copper-catalyzed borilative aromatization of p-QM.

In addition, [3 + 2] cycloadition of *p*-QMs have also been explored.[47] For instance, Su and co-workers reported a new methodology to synthetize spiropyrazoline-cyclohexadienones through [3 +2] cycloadition of *p*-QMs with nitriles under mild conditions with high regioselectivity and excellent yields.[48]

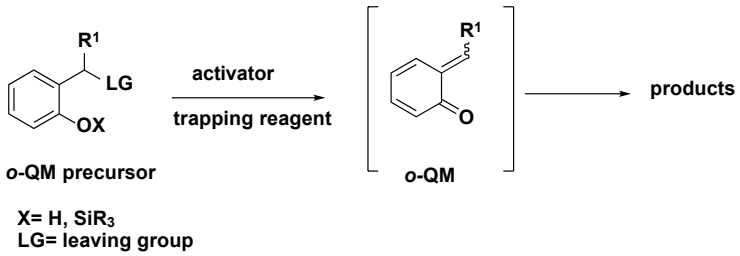


Scheme 9: [3+2] cycloaddition of *p*-QMs with nitrile imines.

[45] Y. Luo, I. D. Roy, A. G. E. Madec, H. W. Lam, *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 4186-4190.
[46] C. Jarava-Barrera, A. Parra, A. López, F. Cruz-Acosta, D. Collado-Sanz, D. J. Cardenas, M. Tortosa. *Acs. Catal.* **2016**, *6*, 442-446.
[47] a) R. Pan, L. Hu, C. Han, A. Lin, H. Yao, *Org. Lett.* **2018**, *20*, 1974-1977; b) X.-Z. Han, Y.-H. Deng, K.-J. Gan, X. Yan, K.-Y. Yu, F.-X. Wang, C.-A. Fan. *Org. Lett.* **2017,***19*,1752−1755; b) X.-X. Zhang, J.-Y. Du, Y.-H. Deng, W.-D. Chu, X. Yan, K.-Y. Yu, C.-A. Fan, *J. Org. Chem.* **2016**, *81*, 2598-2606; c) Z. Yuan, W. Wei, A. Lin, H Yao, *Org. Lett.* **2016**,*18*, 3370-3373.
[48] Y. Su, Y. Zhao, B. Chang, X. Zhao, R. Zhang, X. Liu, D. Huang, K.-h. Wang, C. Huo, Y. Hu, *J. Org. Chem.* **2019**, *84*, 6719-6728.

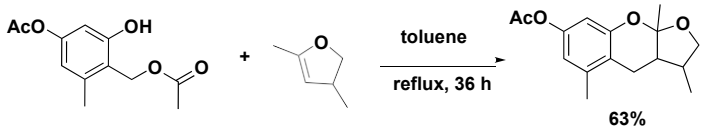
B.1.2 Generation of Quinone Methide

As, mentioned in the previous section, QMs are highly reactive species, which have attracted attention in different areas of chemistry. As a result, a plethora of methods for the generation *in-situ* have been developed. Most existing methods rely on acid-, base- or as fluoride-mediated elimination reactions of substrates substituted at the benzylic position with good leaving groups.[49]



Scheme 10: General methodologies for the generation in situ of quinone methides intermediates.

Among the thermal conditions to generate *o*-QMs, the use of different basic reagents is the most commonly used providing excellent steresoselectivity and good yields. Acid conditions are less studied because of the low compatibility of acids with dienophiles and the greater ionic character. As example, Baldwin and co-workers reported a synthesis for the natural product (±)-Alboatrin generating *o*-QM from *o*-methyleneacetoxy. This reaction occurs through a hetero Diels-Alder reaction.[50]

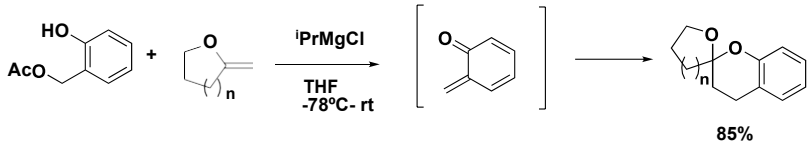


Scheme 11: Synthesis of (±) Alboatrin.

One example of the generation of *o*-QM using basic conditions was reported by Chistropher D. Bray using o-hydroxybenzyl acetate as starting material, iPrMgCl and exo-enol ethers to obtain mono-benzannelated spiroketals in a hetero Diels-Alder reaction.[51]

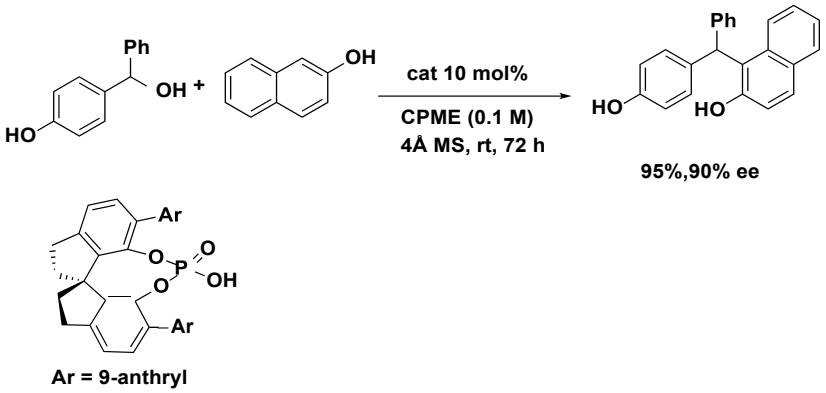
[49] T. B. Samarakoon, M. Y. Hur, R. D. Kurtz, P. R. Hanson, *Org. Lett.* **2010**, *12*, 2182-2185; b) acid-catalyzed elimination: S. Saha, C. Schneider, *Org. Lett.* **2015**, *17*, 648-651; c) base-promoted elimination: C. D. Bray, *Org. Biomol. Chem.* **2008**, *6*, 2815-2819.
[50] R. Rodriguez, R. M. Adlington, J. E. Moses, A. Cowley, J. E. Baldwin, *J. Org. Lett.* **2004**, *6*, 3167-3169.
[51] C. D. Bray, *Org. Biomol. Chem*. **2008**, 6, 2815-2819.

This methodology could be applicable to the synthesis of natural products (berkeclic acid, chaetoquadrin A).



Scheme 12: Generation of o-QM using o-hydroxybenzyl acetate and iPrMgCl.

As an example of generation of quinone methides in acid conditions, Sun and co-workers reported a new methodology to generate *in-situ p*-QMs catalyzed by chiral phosporic acids. This method allows preparing a range of useful triarylmethanes from stable *para*-hydroxybenzyl alcohols with excellent efficiency and enantioselectivity.[52]



Scheme 13: Chiral phosphoric acid catalyzed asymmetric addition of naphthols to *p*-QMs.

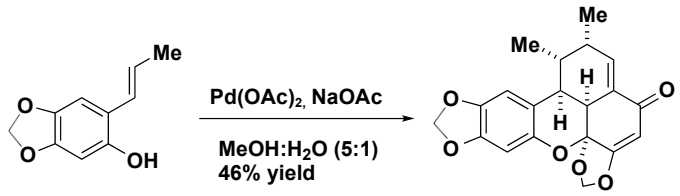
Other methodologies for the in-situ generation of *o*-QM include oxidation [53] or isomerization[54] reactions of appropriate starting materials. In the last few years transition-metal-mediates procedures have also emerged as powerful alternatives for the generation of *o*-QM.

[52] a) Y. F. Wong, Z. Wang, J. Sun, *Org. Biomol. Chem*. **2016**, *14*, 5751-5754. b) Z. Wang, Y. F. Wong, J. Sun, *Angew. Chem., Int. Ed.* **2015**, *54*, 13711−13714.

[53] For a representative example, see: L. M. Bishop, M. Winkler, K. N. Houk, R. G. Bergman, D. Trauner, *Chem. Eur. J.* **2008**, *14*, 5405-5408.

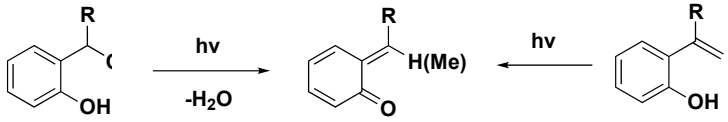
[54] For the generation of *ortho*-quinone methides through Pd-catalyzed isomerization of vinylphenols, see: M. J. Schultz, M. S. Sigman, *J. Am. Chem. Soc.* **2006**; *128*, 1460-1461.

In 1971 Chapman and co-workers reported the synthesis of the natural product carpanone via formation of *o*-QM from vinylphenol and dimerization using $Pd(OAc)_2$.[55]



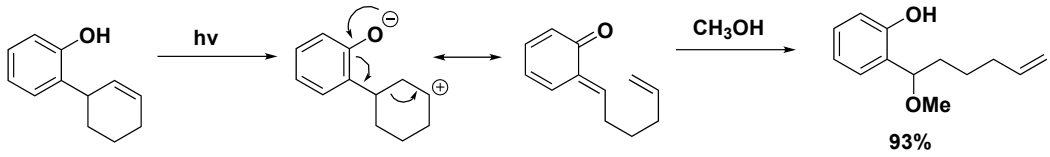
Scheme 14: Pd-catalyzed total synthesis of carpanone.

On the other hand, the use of photochemical energy is also common to generate *o*-QM, generally using light to remove the water from ortho-hydorxybenzyl alcohols or intramolecular proton transfer in ortho-hydroxystyrenes.[56]



Scheme 15: Generation of *o*-QM by photochemical energy.

As example of photochemical generation of o-QM intermediate, group of Miranda reported the formation of QM via C-C fragmentation of a zwitterion form by excited state intramolecular proton transfer.[57]



Scheme 16: Generation of *o*-QM via C-C fragmentation of zwitterions.

In summary, the use of QMs as highly reactive intermediates has enabled new pathways in different areas of chemistry and especially in biochemistry. Most of these current methodologies require the use of some activator for the generation of these synthetically useful intermediates.

[55] O. L Chapman, M. R. Engel, J. P. Springer, J. C. Clardy; *J. Am. Chem. Soc*. **1971**, *93*, 6696-6698.
[56] M. S. Singh, A. Nagaraju, N. Anand, S. Chowdhury; *RSC Adv.* **2014**, *4*, 5924-55959.
[57] J. Delgado, A. Espinos, M. C. Jimenez, M. A. Miranda, *Chem. Commun.* **2002**, 2636-2637.

B.2. General Objectives

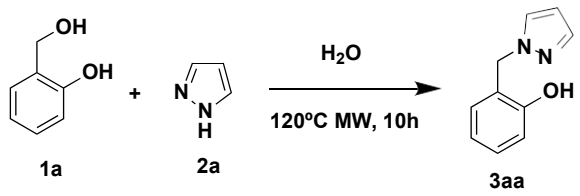
As stated in the introduction, QM intermediates have become increasingly important intermediates in organic synthesis. As a result, our main goal in this chapter has been the generation of these valuable intermediates under environmentally benign conditions. In this study, we have used pyrazole derivatives as trapping reagents because this heterocyclic nucleus is present in several biologically revelant compounds.[58]

[58] For a recent review on biologically active pyrazole derivatives, see: a) A. Ansari, A. Ali, M. Asif, Shamsuzzaman, *New J. Chem.* **2017**, *41*, 16-41; selected examples of thermal reactions of 2-hydroxybenzyl alcohols with azole derivatives under non-aqueous conditions: b) D. V. Osipov, V. A. Osyanin, L. G. Voskressensky, Y. N. Klimochkin, *Synthesis* **2017**, *49*, 2286-2296; c) V. A. Osyanin, N. E. Sidorina, Y. N. Klimochkin, *Synth. Commun.*

B.3 Results and Discussion

o-Hydroxybenzyl alcohol **1a** was selected as model substrate for the generation of the *o*-quinone methide intermediate. Initially, an excess of commercial pyrazole **2a** was used as trapping reagent. During the screening of reaction conditions, a variety of solvents were tested to promote de formation of the compound **3aa.** Surprisingly, when we carried out the reaction with water as solvent we obtained the highest yield (90%). Furthermore, the excess of the pyrazole could be recover by sublimation, which allows it to be used again and minimizes waste generation.[59]

On the other hand, we found that by microwave heating for 10h we obtained full conversion of starting material, however under conventional oil-bath thermal condition the reaction required more time to reach similar yield.

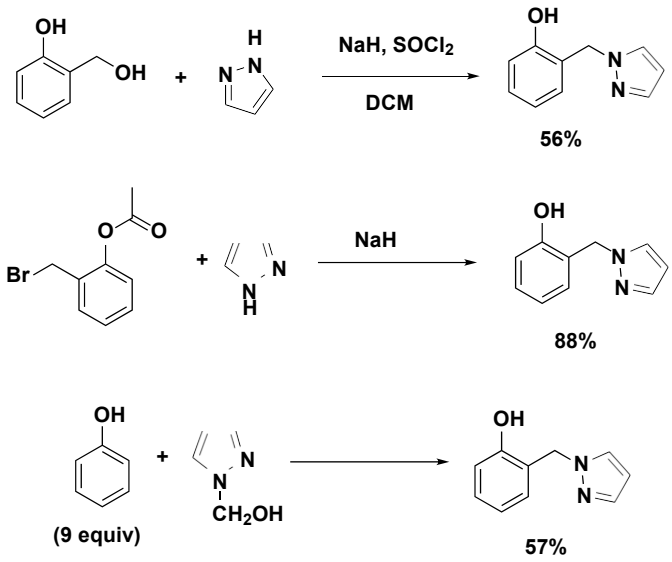


Scheme 1: General conditions for the generation and trapping of *o*-QM intermediate in water.

It is worth noting that compound **3aa**, a valuable intermediate in the synthesis of compounds with antiarrhythmic activity, had previously been obtained in 56% yield after chromatographic purification by reaction between *o*-hydroxybenzyl alcohol and thionyldipyrazole (prepared *in situ* from pyrazole and harmful thionyl chloride) in dichloromethane.[60]

[59] Compound **3aa** was also prepared in 88 % yield from 2-(bromo- methyl)phenyl acetate and pyrazole in the presence of NaH (3 equiv.; a pyrophoric chemical), see: Y. L. Choi, H. Lee, B. T. Kim, K. Choi, J.-N. Heo, *Adv. Synth. Catal.* **2010**, *352*, 2041-2049; in a different approach, compound **3aa** was isolated in 57 % yield by reaction of 1-hydroxymethyl- pyrazole with excess phenol (9 equiv.), see: H. S. Attaryan, V. I. Rstakyan, S. S. Hayotsyan, G. V. Asratyan, *Russ. J. Gen. Chem.* **2012**, *82*, 1319–1321.

[60] M. Ogata, H. Matsumoto, K. Takahashi, S. Shimizu, S. Kida, M. Ueda, S. Kimoto, M. Haruna, *J. Med. Chem.* **1984**, *27*, 1142-1149.



Scheme 2: Different approaches to synthetize compound **3aa.**

The structure of compound **3aa** was confirmed using NMR experiments. As shown in the ^{1}H-NMR spectrum (Figure 1), the singlet at 5.25 ppm corresponds to the benzylic hydrogens. The triplet at 6.27 ppm for 1H is assigned to the hydrogen from the C4-H. The other signals between 6.88 and 7.57 ppm are protons of the pyrazol and from the phenol function. The singlet at 10.32 ppm is assigned to the hydrogen from the hydroxy group.

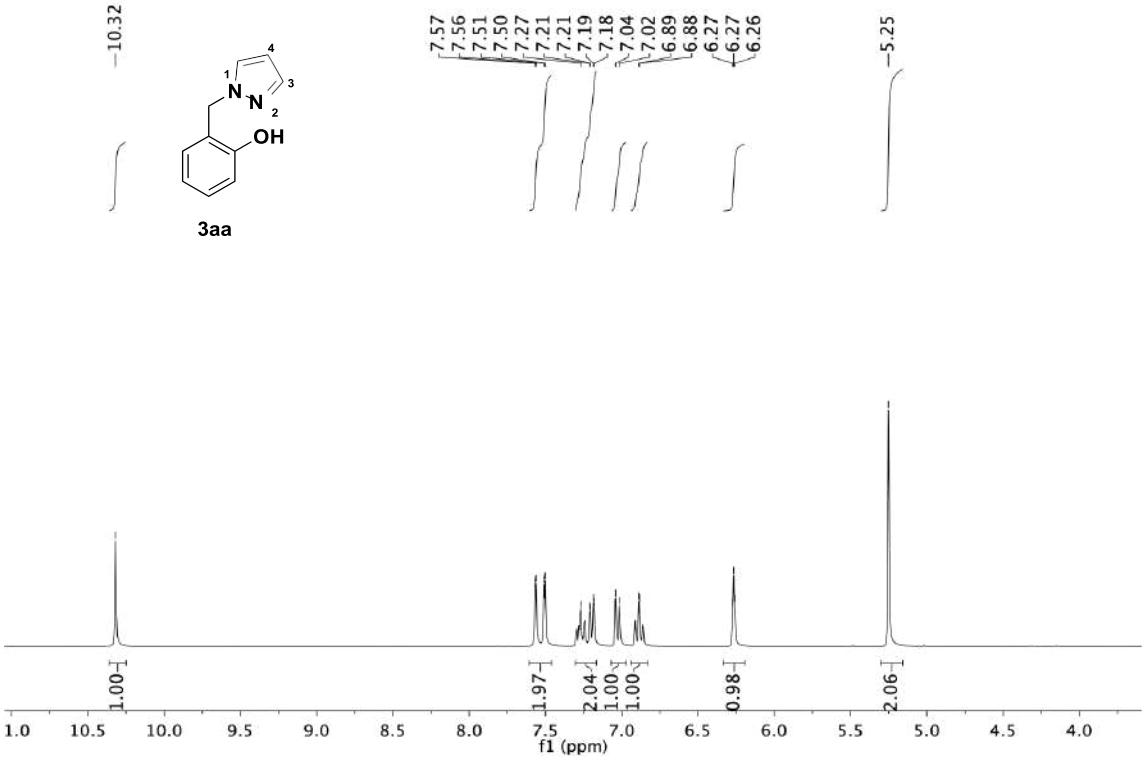


Figure 1: ^{1}H-NMR ($CDCl_3$, 300 MHz) of compound **3aa**.

In the ^{13}C-NMR spectrum (Figure 2), the signal at 53.4 ppm is from the CH_2 benzylic. At lower fields, there are two signals from quaternary carbons at 123.3 ppm and at 156.6 ppm which belongs to carbon with the hydroxy group. The rest of the signals correspond to the others CH carbons.

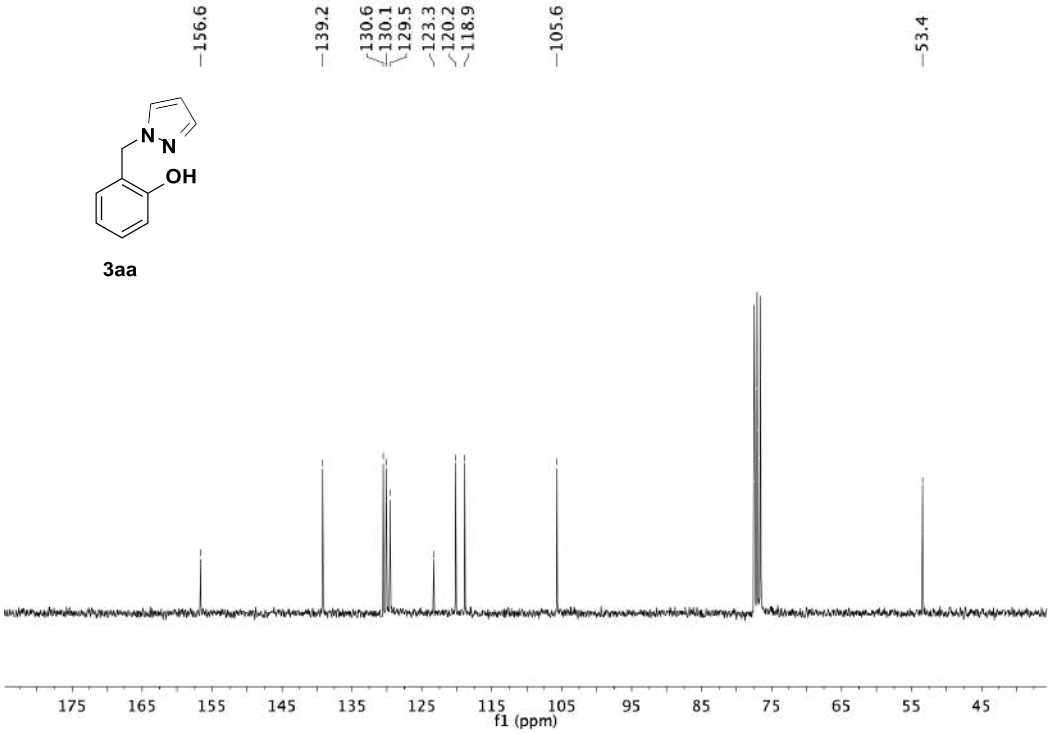


Figure 2: ^{13}C-NMR ($CDCl_3$, 75 MHz) of compound **3aa**.

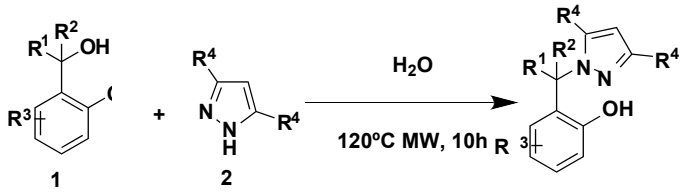
Having established suitable conditions for the synthesis of **3aa**, we turned our attention to the scope of the reaction using a range of substituted *o*-hydroxybenzylalcohols **1**. First, we investigated the reaction of phenyl-substituted *o*-hydroxy-benzyl alcohol **1b** (R^1 = Ph, R^2= R^3= H) with pyrazole **2a** to obtain **3ab** with excellent yield (88%). Likewise, compound **3ab** can also be obtained in good yields and isolated in pure form without the need of chromatography. The use of aryl-substituted substrates (R^1 = tolyl, R^2 = R^3 = H) **3ca-3ea** also afforded the expected products with good yields.

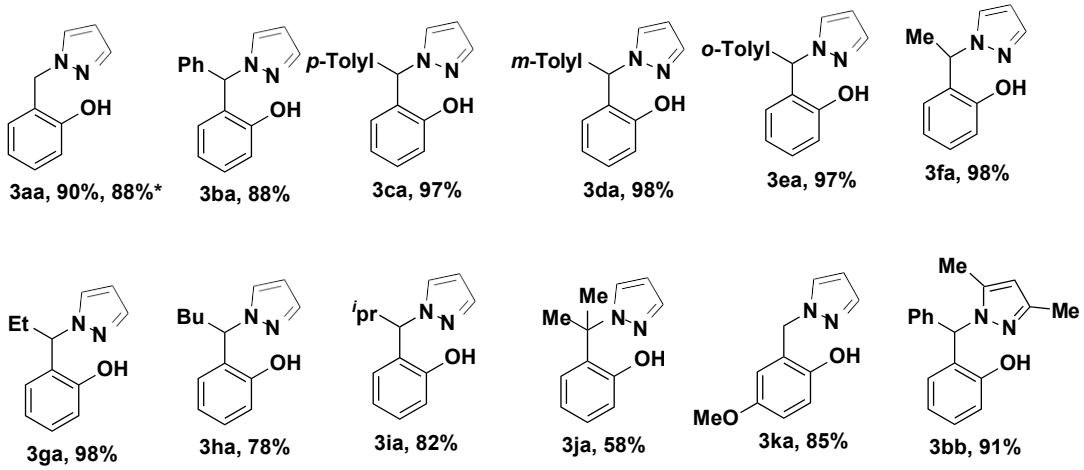
In order to know the effect of the substituents, we extended the study to substrates with alkyl groups at the benzylic position. Interestingly, we found that primary alkyl group and isopropyl group afforded the alkylated pyrazole derivatives **3fa-3ia** in good to excellent yields. However, with two alkyl groups at the benzylic position **1j** the desired product **3ja** was obtained with moderate yields (58%). With additional substitution at the aryl backbone, the expected product **3ka** was obtained in 85%.

We checked the reaction on a 1.0 mmol obtaining the corresponding product **3aa** in similar yield (88%).

Finally, we tried the reaction with substituted 3,5-dimethylpyrazole **2b** with 2-[hydroxy(phenyl)methyl]phenol **1b** and also obtained the compound **3bb** with 91%.

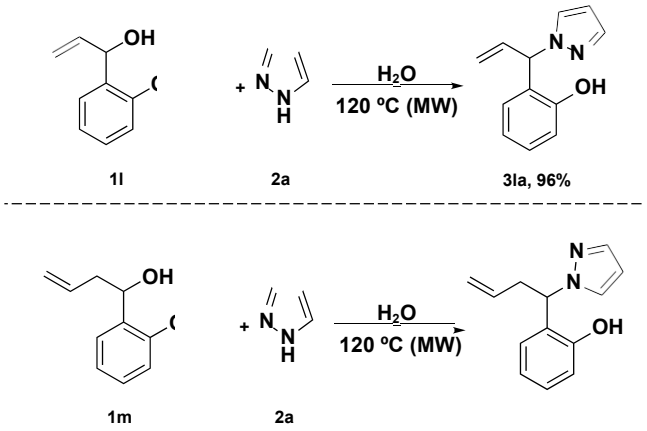
Table 1: Reaction of *o*-hydroxybenzyl alcohols **1** wit pyrazole derivaties **2**





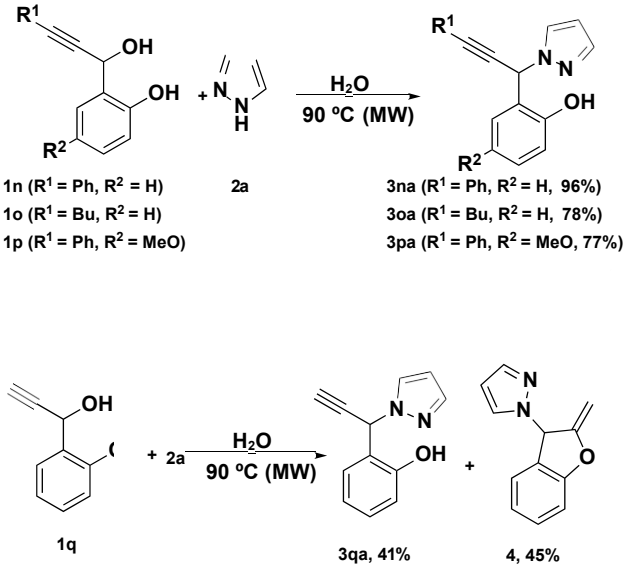
Reaction conditions: **1** (0.2 mmol), **2** (1.2 mmol, 6 equiv .), water (2mL), 120 ^{o}C (microwave heating), 10 h.

To further expand the scope, we extended the study to substrates with alkenyl and alkynyl substituents at the benzylic position. With alkenyl substituents a completely chemoselective transformation took place delivering the expected product in good yields.



Scheme 3: Reaction of alkenyl- substrates with pyrazole in water.

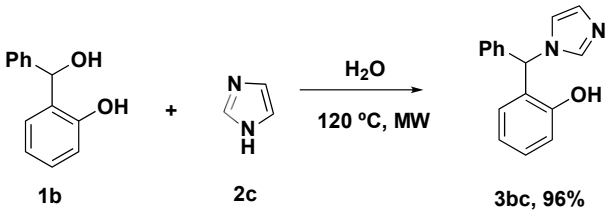
With internal alkynyl group at the benzylic position we carried the reaction at 90 ºC to obtain substrates **3na**-**3pa** with good yields. However, with terminal acetylenic substrate we observed mixture of **3qa** and **4** with moderate yields (41% and 45% respectively). The formation of benzofuran derivative **4** could be explained in terms of a 5-*exo*-*dig* addition of a phenolate oxygen atom to the substituted sp-hybridized carbon atom of **3qa**.[61]



Scheme 4: Reaction of alkynyl-substituted substrates with pyrazole in water.

[61] For related intramolecular additions of phenolate to unactivated double and triple bonds, see: C. M. Evans, A. J. Kirby, *J. Chem. Soc. Perkin Trans. 2* **1984**, 1269-1275.

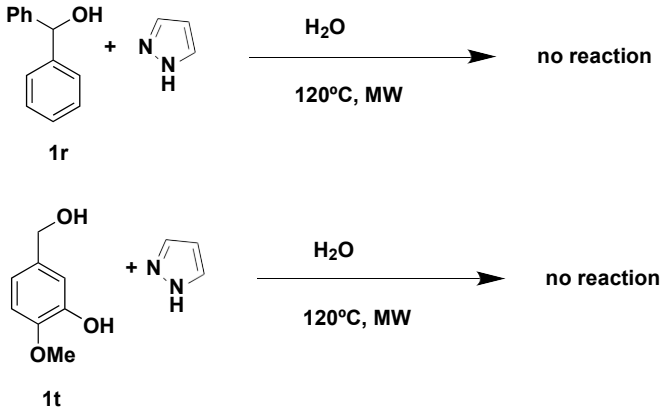
Finally, to further demonstrate the potential of this process, we extended the study to other azole derivatives. Gratifyingly, upon treatment of *o*-hydroxybenzyl alcohol **1b** with imidazole **2c** under the above reaction conditions we obtained the corresponding coupling product **3bc** in nearly quantitative yield.[62]



Scheme 5: Extension to imidazole.

In order to support the participation of *o*-quinone methite intermediate, we tried some control experiments.

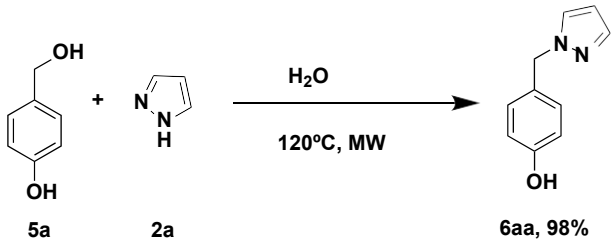
First, the treatment of alcohol **1r** without the hydroxy group at the *orto* position with pyrazole under microwave irradiation at 120 ^{o}C for 10h did not form the alkylation product and the starting material were recovered. We also tried the reaction with the hydroxy group at the *meta* position **1t** and we recovered the starting material.



Scheme 6: Control experiments aimed at demonstrating the participation of quinone methide intermediates.

[62] Under otherwise identical conditions, reactions with indole and pyrrole did not proceed, and the starting materials were recovered unchanged.

However, with the hydroxy group at the *para* position **5a** we could observe the generation of phenol derivative **6aa** with good yield. Taken collectively, these observations support the participation of QMs intermediates being not possible the reaction by direct displacement of hidroxy group.



Scheme 7: Control experiment demonstrating the participation of p-quinone methide intermediate **6aa**.

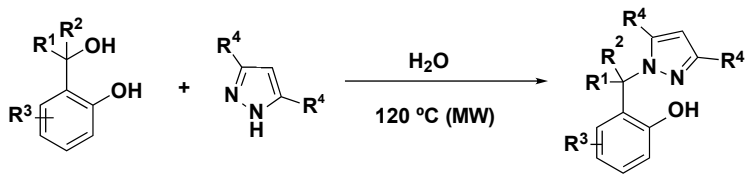
B. 4 General conlcusions

- We have described a new efficient methodology for the generation of *o*-quinone methide intermediates under thermal conditions. Surprisingly, using water as solvent all the transformations generated the corresponding *N*-alkylated azole derivative products with good to excellent yields.

- In contrast to most current methodologies for the generation of these synthetically valuable intermediates, our protocol does not require the use of any activator.

- This protocol does no require chromatographic purification, which makes our protocol particularly well suited for large-scale syntheses.

- Preliminary studies demonstrated that this protocol could also be used for the generation and capture of *para*-quinone methide intermediates.



- Activator-free C-N bond formation
- Good to excellent yields
- No chromatography required
- Reduced waste generation

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Communication

Sustainable Chemistry

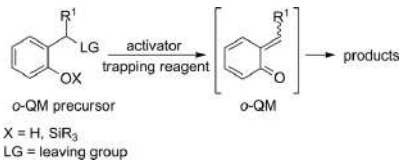
Microwave-Assisted Generation and Capture by Azoles of *ortho*-Quinone Methide Intermediates under Aqueous Conditions

Silvia González-Pelayo[a] and Luis A. López*[a]

Abstract: An efficient activator-free protocol for the coupling of *o*-hydroxybenzyl alcohols and azoles in water has been developed. This C–N bond-formation process is supposed to proceed through an *ortho*-quinone methide intermediate. A broad range of *o*-hydroxybenzyl alcohols that include those with alkenyl and alkynyl functionalities is compatible with this protocol. In most cases, the products are isolated in good to excellent yields without chromatographic purification. Preliminary results demonstrated that this methodology can also be used for the generation and trapping of isomeric *para*-quinone methide intermediates.

Introduction

ortho-Quinone methides (*o*-QMs) are highly reactive intermediates that have found a vast array of applications in organic synthesis and medicinal chemistry.[1] As a result, a plethora of successful approaches have been established for their in-situ generation from suitable substrates. Most existing methods rely on acid-, base- or fluoride-mediated elimination reactions of substrates substituted at the benzylic position with good leaving groups (Scheme 1).[2] Other methodologies for the in-situ generation of *o*-QMs include oxidation[3] or isomerization[4] reactions of appropriate starting materials. Finally, in the last few years transition-metal-mediated procedures have also emerged as powerful alternatives for the generation of *o*-QMs.[5]



Scheme 1. General structure of *ortho*-quinone methide intermediates and elimination methods for their in-situ generation.

The reactivity of *o*-QMs mimics that of □,ß-unsaturated ketones, and – consequently – they react easily with nucleophiles that include those of biological relevance to provide corresponding 1,4-addition products.[6] Additionally, *o*-QMs undergo extremely facile [4+2] cycloaddition reactions with several electron-rich dienophiles[7] and other [4+*n*] cycloaddition reactions.[8] Remarkable levels of stereoselectivity have been accomplished in some of these transformations by using transition-metal catalysts or organocatalysts.[9]

Taking into account the obvious multiple advantages of water as reaction medium in the context of the development of environmentally benign synthetic procedures, we embarked on a study of the feasibility to generate *o*-QMs in water.[10] Herein, we report the realization of this goal; specifically, we describe the microwave-assisted generation of these valuable intermediates and their capture by azoles to lead to synthetically useful *N*-functionalized azole derivatives in good to excellent yields. Interestingly, this process does not require the presence of an activator to proceed. In general, the reactions are very clean and do not require chromatographic purification. The feasibility of this protocol for the generation of isomeric *para*-quinone methides is also advanced.

Results and Discussion

Initial studies focused on the generation of parent *ortho*-quinone methide from *o*-hydroxybenzyl alcohol (**1a**). In these exploratory experiments, we selected pyrazole (**2a**) as a trapping reagent, because this heterocyclic nucleus is present in several biologically relevant compounds.[11] Pleasingly, we found that by microwave heating at 120 °C for 10 h a mixture of **1a** and **2a** (6 equiv.) in water afforded *N*-substituted pyrazole derivative **3aa** in excellent yield (90 %) after extraction with ethyl acetate and removal of excess pyrazole by sublimation under reduced pressure at 60 °C (Scheme 2). The reaction also proceeded under conventional oil-bath thermal conditions. However, under these conditions an extended reaction time was required to reach a comparable yield.

Salient features of this C–N bond-forming transformation include: (a) it does not require the presence of an activator; (b) all the solvents involved in this process (water and ethyl acetate used in the extraction step) are classified as "recommended" in

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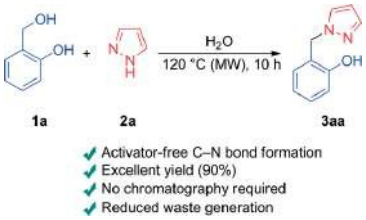
http://personales.uniovi.es/web/sos

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201701183.



Scheme 2. Initial results for the generation and trapping of *ortho*-quinone methide intermediates in water.

terms of greenness evaluation in most common solvent selection guides;[12] (c) the leftover pyrazole could be recovered in pure form almost quantitatively by sublimation, which allows it to be used again and minimizes waste generation; and (d) compound **3aa** was isolated in high purity and excellent yield without chromatographic purification.

It is worth noting that compound **3aa**, a valuable intermediate in the synthesis of compounds with antiarrhythmic activity, had previously been obtained in 56 % yield after chromatographic purification by reaction between *o*-hydroxybenzyl alcohol and thionyldipyrazole (prepared in situ from pyrazole and harmful thionyl chloride) in dichloromethane.[13,14]

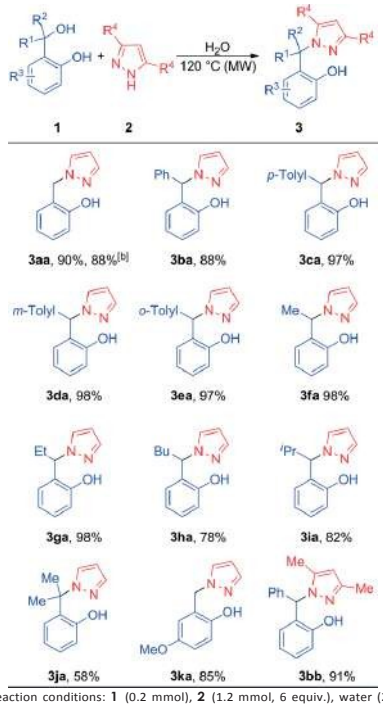
Encouraged by this promising initial result, the substrate scope of this C–N bond-forming process was assessed by using a range of substituted *o*-hydroxybenzyl alcohols **1** (Table 1).

As a result of the relevance of triarylmethanes (TRAMs) in a number of important areas,[15] initially we questioned whether our protocol could be applied to the synthesis of triarylmethane derivatives that contain a pyrazolyl group. For that purpose, we first investigated the reaction of phenyl-substituted *o*-hydroxybenzyl alcohol **1b** (R^1 = Ph, R^2 = R^3 = H) with pyrazole (**2a**) under the above conditions. To our delight, we found that **1b** performed perfectly well and delivered the targeted triarylmethane derivative **3ba** in excellent yield. Aryl-substituted substrates **1c**–**1e** (R^1 = tolyl, R^2 = R^3 = H) were also found to be viable substrates in this transformation. Interestingly, all three isomeric substrates furnished the desired TRAMs **3ca**–**3ea** in nearly quantitative yield regardless of the position of the methyl substituent. As in the model reaction, TRAMs **3ba**–**3ea** could be isolated in pure form without the need of chromatography after standard extraction and sublimation under reduced pressure.

To further expand the scope of this process we extended the study to substrates that bear alkyl groups at the benzylic position. We found that *o*-hydroxybenzyl alcohols **1f**–**1h** that bear a primary alkyl group at the benzylic position are suitable substrates and afford the corresponding phenol derivatives **3fa**–**3ha** in good to excellent yields. Similarly, substrate **1i** that has an isopropyl group at this position (R^1 = isopropyl, R^2 = R^3 = H) posed no problems and afforded the alkylated pyrazole derivative **3ia** in 82 % yield.[16]

Substrate **1j** that has two alkyl groups at the benzylic position (R^1 = R^2 = Me, R^3 = H) was also well suited to this transformation and afforded the desired product **3ja**, albeit in lower yield (58%).

Table 1. Scope of the reaction of *o*-hydroxybenzyl alcohols **1** with pyrazole derivatives **2**.[a]



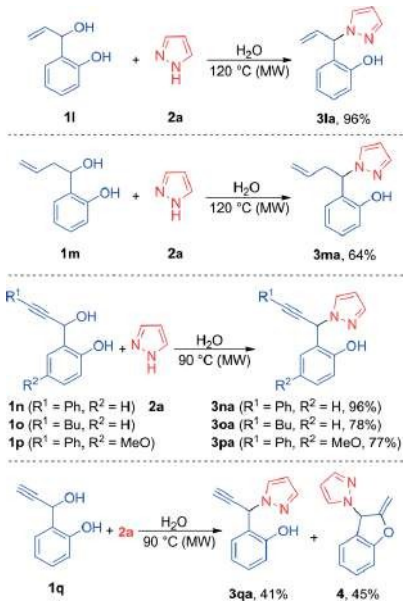
[a] Reaction conditions: **1** (0.2 mmol), **2** (1.2 mmol, 6 equiv.), water (2 mL), 120 °C (microwave heating), 10 h. Unless otherwise stated, all products were isolated by initial extraction with ethyl acetate, subsequent removal of solvent and final sublimation of excess pyrazole under reduced pressure at 60 °C. [b] Reaction performed on a 1.0 mmol scale.

The reaction could be extended to substrate **1k** that has additional substitution at the aryl backbone (R^1 = R^2 = H, R^3 = 4-MeO), and the expected product **3ka** was obtained in 85 % yield.

Finally, substituted pyrazoles are also suitable reagents in this C–N bond-forming process. Reaction of 3,5-dimethylpyrazole (**2b**) with 2-[hydroxy(phenyl)methyl]phenol (**1b**) afforded compound **3bb** in good yield (91 %).

To further expand the scope of this C–N bond-forming reaction and evaluate the feasibility of an eventual cascade process, we extended the study to substrates with additional functionalities at the benzylic position (Scheme 3). First, we found that alkenyl functions do not interfere with the reaction course. Indeed, a completely chemoselective transformation was observed with substrates **1l** and **1m** that have vinyl and allyl groups, respectively. Under the applied reaction conditions, we

did not observe any product that resulted from the participation of the unsaturated moiety.

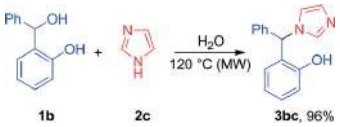


Scheme 3. Reaction of alkenyl- and alkynyl-substituted substrates with pyrazole in water.

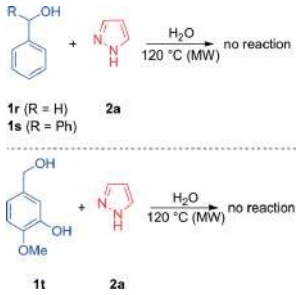
The reactivity of substrates that have alkynyl groups at the benzylic position towards pyrazole (**2a**) was also investigated. We found that treatment of substrates **1n**–**1p** that have an internal alkyne with pyrazole (**2a**) in water at 90 °C led to the formation of the expected pyrazole-containing products. Both aryl and alkyl groups at the alkyne terminus were well tolerated as illustrated by the formation of adducts **3na**–**3pa** in good yields (77–96 %). In contrast, reaction with terminal acetylenic substrate **1q** yielded a chromatographically separable mixture of **3qa** (41 %) and **4** (45 %). The formation of benzofuran derivative **4** could be explained in terms of a 5-*exo*-*dig* addition of a phenolate oxygen atom to the substituted sp-hybridized carbon atom of **3qa**.[17,18]

To demonstrate further the potential of this process, we extended the study to other azole derivatives. Gratifyingly, upon treatment of *o*-hydroxybenzyl alcohol **1b** with imidazole (**2c**) under the above reaction conditions we obtained the corresponding coupling product **3bc** in nearly quantitative yield (Scheme 4).[19]

Next, we conducted some control experiments to gain insight into the mechanism of this reaction (Scheme 5). Thus, when benzyl alcohol (**1r**) and pyrazole (**2a**) were heated in water under microwave irradiation at 120 °C for 10 h no reaction was observed. A similar result was obtained with diphenylmethanol (**1s**). We found that, under otherwise similar conditions, the reaction of pyrazole (**2a**) with phenol derivative **1t** with a hydroxymethyl group at the *meta* position did not proceed, and the starting materials were recovered unchanged. Taken collectively, these observations would rule out a direct displacement of the hydroxy group, which thus supports the participation of an *ortho*-quinone methide intermediate.

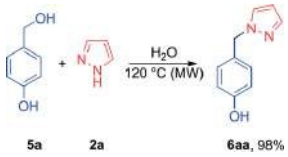


Scheme 4. Extension to imidazole.



Scheme 5. Control experiments aimed to demonstrate participation of *ortho*-quinone methide intermediates.

Although our focus has been on the generation of *ortho*-quinone methide intermediates, it should be noted that isomeric *para* intermediates[20] can also be efficiently generated in water, as illustrated by the formation of phenol derivative **6aa** from *p*-hydroxybenzyl alcohol (**5a**) and pyrazole (**2a**) under above reaction conditions (Scheme 6).[21] The high-yielding preparation of compound **6aa** clearly exemplifies the potential of the reported methodology. Interestingly, the use of toluene as solvent in this transformation under otherwise identical conditions (microwave irradiation at 120 °C for 10 h) failed to provide phenol derivative **6aa** with comparable efficacy, which emphasizes the unique features of water in this process.



Scheme 6. Preliminary study on the extension to *p*-hydroxybenzyl alcohols.

Conclusions

We have demonstrated that *ortho*-quinone methide intermediates can be efficiently generated under thermal conditions in

water. In contrast to most current methodologies for the generation of these synthetically valuable intermediates, our protocol does not require the use of any activator. Once generated, these reactive species can be efficiently and irreversibly trapped by azoles to furnish the corresponding *N*-alkylated azole derivatives in good to excellent yields. In most cases, the isolation of the products does not require chromatographic purification, which makes our protocol particularly well suited for large-scale syntheses. Preliminary studies demonstrated that this protocol could also be implemented for the generation and trapping of *para*-quinone methide intermediates. Further applications of this protocol are currently under investigation by our research group.

Experimental Section

Representative Procedure for 3aa: A 2–5 mL microwave vial was charged with *o*-hydroxybenzyl alcohol (**1a**) (24.8 mg, 0.2 mmol), pyrazole (**2a**) (81.7 mg, 1.2 mmol), H_2O (2 mL), and a triangular stirring bar. The vessel was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction mixture at 120 °C for 10 h in a Biotage Initiator microwave apparatus. Then, the reaction mixture was allowed to reach room temperature and extracted with ethyl acetate (3 × 3 mL). The solvent was removed under reduced pressure (rotary evaporator). Then, the flask was fitted with a cold finger and placed into a preheated 60 °C oil bath and stirred in vacuo. After 30 min, the excess pyrazole was recovered nearly quantitatively and pyrazole derivative **3aa** was isolated as a white solid. Yield 31.4 mg, 90 %. M.p. 123–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.25 (s, 2 H), 6.27 (t, *J* = 2.1 Hz, 1 H), 6.89 (td, *J* = 7.4 and 0.9 Hz, 1 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 7.20 (dd, *J* = 7.5 and 1.4 Hz, 1 H), 7.25 (td, *J* = 7.5 and 1.4 Hz, 1 H), 7.51 (d, *J* = 2.1 Hz, 1 H), 7.56 (d, *J* = 1.7 Hz, 1 H), 10.32 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.4, 105.6, 118.9, 120.2, 123.3, 129.5, 130.1, 130.6, 139.2, 156.6 ppm. HRMS (EI): calcd. for $[C_{10}H_{10}N_2O]^+$ [M$^+$] 174.0788; found 174.0788.

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Keywords: Synthetic methods · Nitrogen heterocycles · Azoles · Quinone methides · C–N bond formation · Microwave chemistry

[1] For selected recent reviews on the chemistry of *o*-QM intermediates, see: a) D. V. Osipov, V. A. Osyanin, Y. N. Klimochkin, *Russ. Chem. Rev.* **2017**, *86*, 625–687; b) A. A. Jaworski, K. A. Scheidt, *J. Org. Chem.* **2016**, *81*, 10145–10153; c) M. S. Singh, A. Nagaraju, N. Anand, S. Chowdhury, *RSC Adv.* **2014**, *4*, 55924–55959; d) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu, T. R. R. Pettus, *Acc. Chem. Res.* **2014**, *47*, 3655–3664; e) N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160–9173; f) R. W. van de Watter, T. R. R. Pettus, *Tetrahedron* **2002**, *58*, 5367–5405.

[2] For selected examples of the generation of *ortho*-quinone methides through elimination reactions, see: a) fluoride-mediated elimination: T. B. Samarakoon, M. Y. Hur, R. D. Kurtz, P. R. Hanson, *Org. Lett.* **2010**, *12*, 2182–2185; b) acid-catalyzed elimination: S. Saha, C. Schneider, *Org. Lett.* **2015**, *17*, 648–651; c) base-promoted elimination: C. D. Bray, *Org. Biomol. Chem.* **2008**, *6*, 2815–2819.

[3] For a representative example, see: L. M. Bishop, M. Winkler, K. N. Houk, R. G. Bergman, D. Trauner, *Chem. Eur. J.* **2008**, *14*, 5405–5408.

[4] For the generation of *ortho*-quinone methides through Pd-catalyzed isomerization of vinylphenols, see: M. J. Schultz, M. S. Sigman, *J. Am. Chem. Soc.* **2006**; *128*, 1460–1461; for additional examples, see ref.[5a]

[5] For a review on applications of *ortho*-quinone methides in transition-metal catalysis, see: a) T. P. Pathak, M. S. Sigman, *J. Org. Chem.* **2011**, *76*, 9210–9215; for a recent contribution that involves proton/metal dual catalysis, see: b) J. Ma, K. Chen, H. Fu, L. Zhang, W. Wu, H. Jiang, S. Zhu, *Org. Lett.* **2016**, *18*, 1322–1325.

[6] For a recent contribution on the catalytic asymmetric substitution of *ortho*-hydroxybenzyl alcohols with enamines, see: M.-M. Xu, H.-Q. Wang, Y. Wan, J. Yan, S. Zhang, S.-L. Wang, F. Shi, *Org. Chem. Front.* **2017**, *4*, 358–368; for the 1,4-addition reaction of deoxycytidine to *ortho*-quinone methide intermediates, see: M. P. McCrane, E. E. Weinert, Y. Lin, E. P. Mazzola, Y.-F. Lam, P. F. Scholl, S. E. Rokita, *Org. Lett.* **2011**, *13*, 1186–1189; for the use of binol quinone methides as DNA alkylating reagents, see: S. N. Richter, S. Maggi, S. C. Mels, M. Palumbo, M. Freccero, *J. Am. Chem. Soc.* **2004**, *126*, 13973–13979; for a study of the substituent effect on the reactivity of *ortho*-quinone methide intermediates with biological nucleophiles, see: E. E. Weinert, R. Dondi, S. Colloredo-Melz, K. N. Frankenfield, C. H. Mitchell, M. Freccero, S. E. Rokita, *J. Am. Chem. Soc.* **2006**, *128*, 11940–11947.

[7] For selected applications of [4+2] cycloaddition reactions of *ortho*-quinone methide intermediates in total synthesis, see: a) J.-P. Lumb, K. C. Choong, D. Trauner, *J. Am. Chem. Soc.* **2008**, *130*, 9230–9231; b) L. Xu, F. Liu, L.-W. Xu, Z. Gao, Y.-M. Zhao, *Org. Lett.* **2016**, *18*, 3698–3701; for additional examples, see ref.[1]

[8] For [4+1] cycloaddition reactions, see: a) N. Meisinger, L. Roiser, U. Monkowius, M. Himmelsbach, R. Robiette, M. Wasser, *Chem. Eur. J.* **2017**, *23*, 5137–5142 and references cited therein; for a recent [4+3] cycloaddition reaction of *ortho*-quinone methide intermediates, see: G.-J. Mei, Z.-Q. Zhu, J.-J. Zhao, C.-Y. Bian, J. Chen, R.-W. Chen, F. Shi, *Chem. Commun.* **2017**, *53*, 2768–2771; for a formal [4+4] cycloaddition reaction, see ref.[2a]

[9] For a review that covers advances in catalytic asymmetric reactions of *ortho*-quinone methides, see: Z. Wang, J. Sun, *Synthesis* **2015**, *47*, 3629–3644; for a review on the applications of quinone methides in asymmetric organocatalysis, see: L. Caruana, M. Fochi, L. Bernardi, *Molecules* **2015**, *20*, 11733–11764; for a catalytic asymmetric oxa-Diels–Alder reaction of *ortho*-quinone methides generated in situ from *ortho*-hydroxybenzyl alcohols, see: J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu, F. Shi, *Angew. Chem. Int. Ed.* **2015**, *54*, 5460–5464; *Angew. Chem.* **2015**, *127*, 5550; for an enantioselective cyclization of *ortho*-hydroxybenzyl alcohols with enaminones, see: J.-J. Zhao, Y.-C. Zhang, M.-M. Xu, M. Tang, F. Shi, *J. Org. Chem.* **2015**, *80*, 10016–1024; for a recent organocatalytic asymmetric intramolecular [4+2] cycloaddition reaction of *ortho*-quinone methide intermediates, see: Y. Xie, B. List, *Angew. Chem. Int. Ed.* **2017**, *56*, 4936–4940; *Angew. Chem.* **2017**, *129*, 5018.

[10] A photochemical generation and reactivity of *ortho*-naphthoquinone methides in aqueous solutions has been reported, see: a) S. Arumugam, V. V. Popik, *J. Am. Chem. Soc.* **2009**, *131*, 11892–11899; b) S. Arumugam, V. V. Popik, *J. Am. Chem. Soc.* **2011**, *133*, 5573–5579; for a related example that involves hydroarylation of *o*-QMs generated in situ from 4-hydroxycoumarin, see: A. Kumar, M. Kumar, M. Kumar Gupta, *Green Chem.* **2012**, *14*, 2677–2681; a trifluoroacetic acid mediated generation of *ortho*-quinone methides in water and subsequent trapping with lactams and styrenes has been recently reported, see: R. Sharma, S. Abbat, R. Mudududdla, R. A. Vishwakarma, P. V. Bharatam, S. B. Bharate, *Tetrahedron Lett.* **2015**, *56*, 4057–4059.

[11] For a recent review on biologically active pyrazole derivatives, see: a) A. Ansari, A. Ali, M. Asif, Shamsuzzaman, *New J. Chem.* **2017**, *41*, 16–41; selected examples of thermal reactions of 2-hydroxybenzyl alcohols with azole derivatives under non-aqueous conditions: b) D. V. Osipov, V. A. Osyanin, L. G. Voskressensky, Y. N. Klimochkin, *Synthesis* **2017**, *49*, 2286–2296; c) V. A. Osyanin, N. E. Sidorina, Y. N. Klimochkin, *Synth. Commun.*

2012, *42*, 2639–2647; d) N. E. Sidorina, V. A. Osyanin, *Chem. Heterocycl. Compd.* **2007**, *43*, 1065–1071.

[12] D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shedada, P.J. Dunn, *Green Chem.* **2016**, *18*, 288–296.

[13] M. Ogata, H. Matsumoto, K. Takahashi, S. Shimizu, S. Kida, M. Ueda, S. Kimoto, M. Haruna, *J. Med. Chem.* **1984**, *27*, 1142–1149.

[14] Compound **3aa** was also prepared in 88 % yield from 2-(bromomethyl)phenyl acetate and pyrazole in the presence of NaH (3 equiv.; a pyrophoric chemical), see: Y. L. Choi, H. Lee, B. T. Kim, K. Choi, J.-N. Heo, *Adv. Synth. Catal.* **2010**, *352*, 2041–2049; in a different approach, compound **3aa** was isolated in 57 % yield by reaction of 1-hydroxymethylpyrazole with excess phenol (9 equiv.), see: H. S. Attaryan, V. I. Rstakyan, S. S. Hayotsyan, G. V. Asratyan, *Russ. J. Gen. Chem.* **2012**, *82*, 1319–1321.

[15] For a recent review on the synthesis and pharmaceutical uses of di- and triarylmethane derivatives, see: S. Mondal, G. Panda, *RSC Adv.* **2014**, *4*, 28317–28358; for a review on the synthesis of triarylmethanes by transition-metal catalysts, see: M. Nambo, C. M. Crudden, *ACS Catal.* **2015**, *5*, 4734–4742.

[16] In contrast, the reaction was completely inhibited when a bulky *tert*-butyl group was installed at the benzylic position (R^1 = *tert*-butyl, R^2 = R^3 = H).

[17] For related intramolecular additions of phenolate to unactivated double and triple bonds, see: C. M. Evans, A. J. Kirby, *J. Chem. Soc. Perkin Trans. 2* **1984**, 1269–1275.

[18] The reaction of compound **1q** with pyrazole (**2a**) in D_2O under otherwise identical conditions provided a mixture of **3qa** and the $=CD_2$ product [D_2]-**4**; this result would suggest that the cyclization step is slower than the exchange of the acetylenic proton.

[19] In contrast, under otherwise identical conditions, reactions with indole and pyrrole did not proceed, and the starting materials were recovered unchanged.

[20] For a review on the synthetic applications of *para*-quinone methides, see: A. Parra, M. Tortosa, *ChemCatChem* **2015**, *7*, 1524–1526; for selected recent examples, see: a) P. Goswami, G. Singh, R. V. Anand, *Org. Lett.* **2017**, *19*, 1982–1985; b) C. Jarava-Barrera, A. Parra, A. López, F. Cruz-Acosta, D. Collado-Sanz, D. J. Cárdenas, M. Tortosa, *ACS Catal.* **2016**, *6*, 442–446.

[21] Compound **6aa** was previously obtained in 47 % yield by heating 4-hydroxybenzyl alcohol and pyrazole at 160 °C, see: P. J. Machin, D. N. Hurst, R. M. Bradshaw, L. C. Blaber, D. T. Burden, R. A. Melarange, *J. Med. Chem.* **1984**, *27*, 503–509.

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Chapter 2: Synthesis of metallocene derivatives: trapping of quinone methide intermediates with ferrocene and reaction of ferrocene and ruthenocene with three-membered-ring systems.

II.1. General Introduction

II.1.1. Discovery and structure of ferrocene

In 1951, a new compound containing iron and two cyclopentadienide ligands was reported and has revolutionized the organometallic chemistry. Kealy and Pauson [63] discovered accidently the ferrocene when they were working in the synthesis of fulvalene. Almost at the same time Miller, Tebboth and Tremaine trying to prepare amines using the Harber's method isolated the same compound.[64]

The actual structure of the ferrocene was a controversial issue for many years. Fischer proposed that the iron(II) center should possess a 18 electron configuration with the iron "sandwiched" between two clopentadienide ligands.[65] Based on IR studies, Woodward and Wilkinson found that all CH bonds are chemically equivalent and proposed a structure with the name ferrocene because of the analogies with benzene (Figure 1).[66] According with this structural proposal, there are two possible conformations of the Cp ligands (staggered and eclipsed), which are in equilibrium at room temperature due to the small rotation energy barrier (⊗G = 4 KJ/mol).

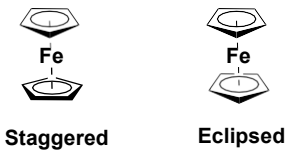
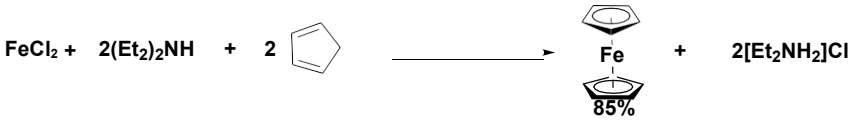


Figure 1. Staggered and eclipsed ferrocene conformations.

Since the serendipitous discovery of ferrocene,[67] numerous cyclopentadienyl derivatives of different metals have been reported with a tremendous impact in theoretical knowledge of chemical bonding as well as in industrial applications. As a result, the Nobel Prize in Chemistry 1973 was awarded to Fischer and Wilkinson "for their pioneering work, performed independently, on the chemistry of the organometallic, so called sandwich compounds".[68]

[63] T. Kealy, P. L. Pauson, *Nature*. **1951**, *168*, 1039-1040.
[64] S. A. Miller, J. A. Tebboth, J. F. Tremaine, *J. Chem. Soc,* **1952**, 632-635.
[65] E. O. Fischer, W. Pfab, *Z. Naturforsch. B,* **1952**, *7*, 377-379.
[66] P. Laszlo, R. Hoffmann, *Angew. Chem*. **2000**, *112*, 127-128.
[67] H. Werner, *Angew. Chem. Int. Ed.* **2012**, *74*, 2125-2126.
[68] Taken from https://www.nobelprize.org/prize/chemistry/1973/press-relase/

More efficient methods for the synthesis of ferrocene are currently available. [69] For example, using sodium cyclopentadiene with iron(II) chloride or using directly iron with cyclopentadiene. However, the most efficient synthesis of ferrocene involves the reaction of cyclopentadiene with iron(II) chloride in the presence of amines.[70] For example, Willkinson reported the synthesis of ferrocene in high yield using anhydrous diethylamine which serves as both solvent and hydrogen halide acceptor (Scheme 1).[71]

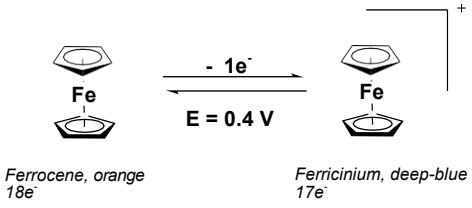


Scheme 1: Synthesis of ferrocene using iron(II) chloride and amines.

II.1.2. Properties of ferrocene

The discovery of ferrocene has revolutionized organometallic chemistry and provided a wide range of applications because of its unique properties: thermal stability, redox activity, chirality, tolerance to moisture, oxygen and many types of reagents. Moreover, in terms of biological effects, the stability in biological media, lipophilicity that makes easy the penetration through cell membranes, low toxicity and several interaction modes with biological substrates are also key features for its applications in medicinal chemistry.

One of the most remarkable properties of ferrocene is its redox potential (reversible oxidation around +0.4 V *versus* saturated calomel electrode). Ferrocene and its derivatives undergo reversible oxidation to the ferrocinium ion (Scheme 2). This redox activity ferrocene/ferricinium is used as standard in electrochemical studies and ferricinium salts are widely used as weak oxidizing agents.[72]



Scheme 2: Reversible oxidation of ferrocene.

[69] a) G. Wilkinson, *Org. Synthesis.* **1956**, *36*; 366-415; b) W. L. Jolly, *The synthesis and Characterization of Inorganic Compounds,* **1970**, New Jersey: Prentice-Hall.
[70] G. Wilkinson, F. A. Cotton, J. M. Birmingham, *J. Inorg. Nucl. Chem.* **1956**, *2*, 95-113.
[71] This procedure for preparing ferrocene has been published in detail in Organic Syntheses: G. Wilkinson, *Org. Synth*. **1956**, *36*, 31.
[72] N. G. Connelly, W. E. Geiger, *Chem. Rev*. **1996**, *96*, 877-910.

This oxidation of ferrocene can be achieved in many ways: electrochemically, photochemically or by oxidizing agents such as HNO_3, $FeCl_3$, I_2, Ag^+ or N-bromosuccinimide. On the other hand, some ferrocene derivatives are chiral.[73] In fact, 1,2- and 1,3-disubstituted ferrocenes with different substituents have planar chirality. In 1962, 1,1'-dimethylferrocene-2-carboxylic acid was reported as the first example of optically active ferrocene derivative (Figure 2).[74]

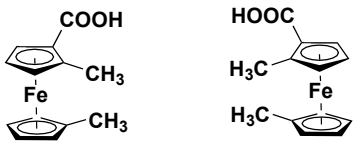


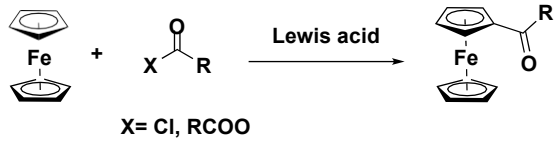
Figure 2: Enantiomers of 1,1'-dimethylferrocene-2-carboxylic acid.

Most of the relevant applications in medicinal chemistry, material science and catalysis displayed by functionalized ferrocene derivatives rely on these exceptional properties. Selected examples will be highlighted in some detail in the next sections.

[73] a) O. Riant, O. Samuel, H. B. Kagan, *J. Am.Chem. Soc.* **1993**, *115,* 5835-5836; b) A. Togni, *Angew. Chem. Int. Ed. Engl.* **1996***, 35,* 1475-1477.
[74] a) L. Westman; K. L. Rinehart, *Acta Chem. Scand.* **1962**, *16*, 1199; b) H. Egger, K. Schlogl, *J.Organomet. Chem*. **1964**, *2*, 398-409.

II.1.3. Reactivity of ferrocene: Synthesis of functionalized ferrocenes

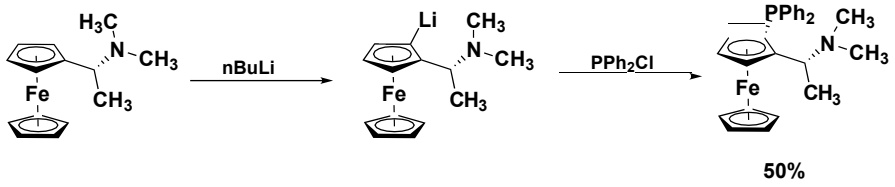
To a large extent, the chemical behaviour of ferrocene mimics that of electron-rich aromatic compounds. Consequently, ferrocene undergoes easily electrophilic aromatic substitutions. In fact, Friedel-Crafts acylation reaction of ferrocene with acid derivatives promoted by Lewis acids is considered the most classic reaction of ferrocene.[75]



Scheme 3: Friedel-Crafts acylation reaction of ferrocene.

In contrast, Friedel-Crafts alkylation of ferrocene has been considered as a useless process because a mixture of polysubstituted products is usually obtained.

Another key reaction is the direct lithiation of ferrocene with butlylithium. [76] Ferrocenyllithium is a highly reactive versatile nucleophile, which can react with several elecrophiles. This methodology has been widely used in the preparation of functionalized ferrocene derivatives, including some of the most widely used as ligands in catalysis. For instance, in 1974 Hayashi and Kumada reported the first example of a planar chiral enantiopure ferrocenyl phospine *N,N*-dimethyl-1-[2-(diphenylphosphino)ferrocenylethylamine) (ppfa), using the diastereoselective lithiation of *N*,*N*-dimethyl-1-ferrocenylethylamine.[77]



Scheme 4: Lithiation of ferrocene and relevant chemistry.

This methodology is particularly useful for the diastereo and enantioselective synthesis of 1,2-disubstituted ferrocenes.[78]

---

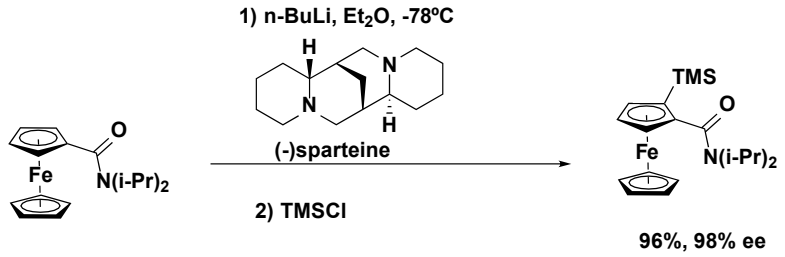
[75] a) R. B. Woodward, M. C. Whiting, *J. Am. Chem. Soc.* **1952**, *74*, 3458; b) M. Rosenblum, R. B. Woodward, *J. Am. Chem. Soc.* **1958**, *80*, 5443-5444.

[76] a) M. D. Rausch, D. J. Ciappene, *J. Organomet. Chem.* **1967**,*10*, 127-133; b) H. Seshadri, C. L. Lovely, *Org. Lett.* **2000**, *2*, 327-330; c) A. H. Stoll, P. Mayer,P. Knohel, *Oganometallics.* **2007,** *26*, 6694-6697.

[77] T. Hayashi, K. Yamamoto, M. Kumada, *Tetrahedrom Lett.* **1974**, 4405-4408.

[78] a) D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389-5393; b) L. F. Battelle, R. Bau, G. W. Gokel, R. Y. Oyakawa, I. K. Ugi, *J. Am. Chem. Soc*. **1973**,*95*, 482-486; c) F. Rebiére, O, Riant, L. Ricard, H. B. Kagan, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 568-570; d) O. Riant, H. Samuel, H. B. Kagan, *J. Am. Chem. Soc.* **1993**, *115*, 5835-5836.

Based on the metalation of ferrocene, in 1996 Snieckus and co-workers reported the first highly entantioselective synthesis of ferrocenyl derivatives. Using (-)sparteine as chiral auxiliary enantiomerically pure ferrocenes are available from achiral precursors (Scheme 5).[79]



Scheme 5: Enantioselective synthesis of ferrocenyl derivatives using sparteine as chiral auxiliary.

In spite of the unquestionable synthetic usefulness of these classical methodologies, their use entails several disadvantages as the use of stoichiometric amounts of organolithium reagents or Lewis acids and low functional group compatibility with the electrophilic partner. To overcome these limitations, catalytic functionalization approaches have recently evolved as highly efficient alternatives.[80]

In these methodologies, the presence of directing groups favours the activation, mostly, of the *ortho* C-H bond through formation of a metallacycle intermediate. For example, several palladium catalysed cross-coupling methodologies involving arylboronic acids,[81] substituted olefins,[82] alkynes[83] and azoles[84] as coupling partners have been recently reported allowing the synthesis of the corresponding functionalized ferrocene.

As important example, the group of You reported the palladium-catalyzed asymmetric coupling with aryl boronic acids using dimethylaminomethyl as directing group. [85] This synthesis uses easily available amino acids as ligands; in particular, when Boc-L-Val-OH was used, the corresponding arylation products were obtained with excellent enantioselectivity (Scheme 6).

[79] M. Tsukazaki, M. Tinkl, A. Roglans, B. J. Chapell, N. J. Taylor, V. Snieckus, *J. Am. Chem. Soc.* **1996**, 118, *3*, 685-686.

[80] For recent revisions on this field, see: a) L. A. López, E. López, *Dalton Trans*. **2015**, *44*, 10128-10135; b) S. Arae, M. Ogasawara, *Tetrahedron Lett.* **2015**, 1751-1761; c) D. -Y. Zhu, P. Chen, J. -B. Xia, *Chem. Cat. Chem.* **2016**, *8*, 68-73; d) D. -W. Gao, Q. Gu, C. Zheng, S. -L. You, *Acc. Chem. Res.* **2017**, *50*, 351-365.

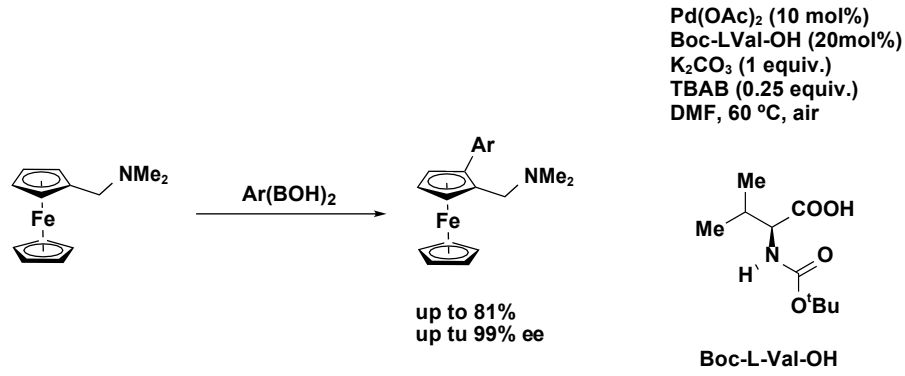
[81] D.-W. Gao, Y. C. Shi, Q. Gu, Z.-L. Zhao, S.-L. You, *J. Am. Chem. Soc*. **2012**, *135*, 86-89.

[82] C. Pi, Y. Li, X. Cui, H. Zhang, Y. Han, Y. Wu, *Chem. Sci*. **2013**, *4*, 2675-2679.

[83] Y.-C. Shi, R. -F. Yang, D.-W. Gao, S.-L.You, *Beilstein J.Org. Chem.* **2013**, *9*, 1891-1896.

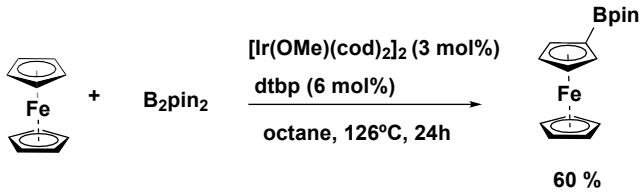
[84] Z .-J. Cai, C.-X. Liu, Q. Gu, C. Zheng, S.-Li You, *Angew. Chem Int. Ed*. **2019**, *131*, 2171-2175.

[85] D. W. Gao, Y. C. Shi, Q. Gu, Z. L. Zhao, S. L. You; *J. Am. Chem. Soc.* **2008**, *47*, 4882-4886.



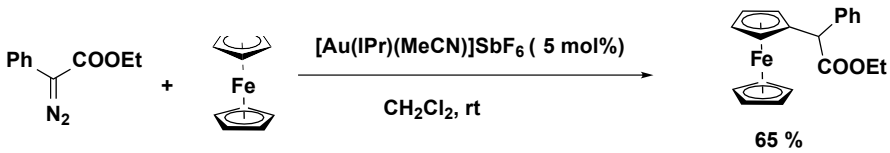
Scheme 6: Synthesis of planar chiral ferrocenes by Pd/amino acid-catalyzed enantioselective arylation.

In contrast, C-H bond functionalizations of ferrocene derivatives lacking directing groups remain highly challenging. In 2004, Plenio and co-workers reported the iridium-catalyzed borylation of ferrocene in moderate yield (Scheme 7).[86]



Scheme 7: Iridium-catalyzed borylation of ferrocene.

In the last few years, our research group has been interested in the synthesis of functionalized ferrocene derivatives based on metal-carbene chemistry.[87] In particular, our group developed the gold-catalyzed intermolecular formal insertion of aryldiazo esters into the Cp-H bond of ferrocene and ruthenocene (Scheme 8). This C-H bond functionalization protocol allows for the synthesis of functionalized metallocene derivatives with difficult-to-access substitution patterns.[25c]



Scheme 8: Gold-catalyzed reaction of aryl diazoacetates with ferrocene.

[86] A. Datta, A. Köllhofer, H. Plenio, *Chem. Commun.* **2004**, 1508-1509.

[87] a) E. López, G. Lonzi, L. A. López, *Organometallics.* **2014**, *33,* 5924-5927; b) E. López, T. Suárez, A. Ballesteros, L. A. López, *Eur. J. Inorg. Chem.* **2017**, *10*, 225-228; c) E. López, J. Borge, L. A. López, *Chem. Eur. J.* **2017**, *23*, 3091-3097.

II.1.4. Applications of ferrocene and its derivatives

As stated before, the fascinating structural, physical and chemical properties exhibited by ferrocene and some of its derivatives are responsible for the applications found in different important areas as asymmetric catalysis, materials and medicine.

For example, there are a large number of polymeric ferrocene derivatives depending on the different monomers used. An example could be the structure of Fc-HTPB, a polybutadiene terminated in hydroxyl groups and with ferrocene. This polymer is obtained by Friedel-Crafts alkylation.[88]

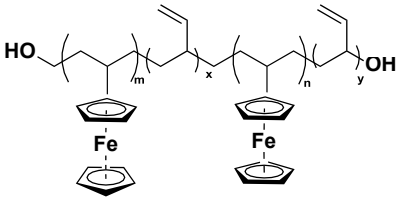


Figure 3: Structure of FcHTPB.

This polymer has been widely used in propellants and explosives and the introduction of ferrocene in the structure improves the performance of the thursters such as compatibility, safety, stability and burning rate.

Among the vast number of chiral ligands used in asymmetric catalysis, chiral ferrocenyl ligands are some of the most important playing a key role in the development of important catalytic systems in industrial processes.[89]

First examples of ferrocene used as chiral ligands were developed in 1970 with a phosphine group. A relevant example with industrial applications is the ligand Josiphos used during the synthesis of biotine (vitamine B soluble in water). Another important example is [1,1'-bis(diphenylphospino)ferrocene] (dppf) being the best known ferrocene ligand and since its discovery ferrocenyl phosphines have been successfully applied in transition-metal-catalyzed processes.

[88] Saravanakumar, D.; Sengottuvelan, N.; Narayanan, V.; Kandaswamy, M., *J. Appl. Polym. Sci.* **2011**, *119*, 2517-2524.

[89] a) I. Cuadrado, M. Morán, C. M. Casado, B. Alonso, J. Losada, *Coord. Chem. Rev.* **1999**, *193-195,* 395-445 ; b) K. Takada, D. J. Díaz, H. D. Abruña, I. Cuadrado, C. Casado, N. Alonso, M. Morán, J. Losada, *J. Am. Chem. Soc.* **1997**, *119,* 10763-10773.

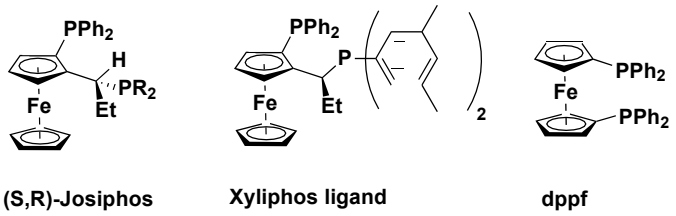
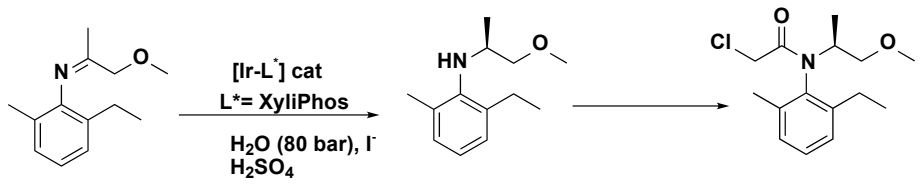


Figure 4: Some ferrocenyl ligands commonly used in catalysis.

A remarkable example of the utility of chiral ferrocene-based ligands in asymmetric catalysis is the synthesis of a precursor of the herbicide (*S*)-metolachlor. The key step in the synthesis of this herbicide, with an industrial production of 10^4 T/year, involves iridium-catalyzed asymmetric hydrogenation of an imine derivative using Xyliphos as ligand. (Scheme 9).[90]



Scheme 9: Synthesis of (*S*)-metolachlor.

On the other hand, ferrocene derivatives have become more and more important in medicinal organometallic chemistry.[91] Indeed, a number of ferrocene derivatives have been reported to display relevant activity. In 1970, Ferrocerone, the sodium salt of *o*-carboxybenzoylferrocene, was used to treat iron deficiency pathologies and was the first example of a ferrocene derivative approved for medical use.[92]

It was found that, in some cases, the *introduction* of the *ferrocenyl group* remarkably increases the activity of a given drug.

For example, ferroquine, a ferrocene-based analogue of chloroquine, has entered phase II clinical trials for the treatment of malaria, displaying promising activity against resistant parasitic strains.[93]

[90] Only de (S)-enantiomer was active. For an interesting discussion on the development of an efficient asymmetric synthesis see: H. U. Blaser, *Adv. Synth. Catal.* **2002**, *344,* 17-31.

[91] R. D. van Staveren, N. Metzler-Nolte, *Chem. Rev.* **2014**, *104*, 5931-5985.

[92] a) USSR Pat. 263870; *Chem. Abstr.* **1978**, 45180; b) USSR Pat. 3957841; *Chem. Abstr.* **1976**, 543305.

[93] For a recent review on ferroquine and its derivatives as antimalarial agents, see: W. A. Wani, E. Jameel, U. Baig, S. Mumtazuddin, L. T. Hun, *Eur. J. Med. Chem.* **2015**, *101*, 534.C. Biot, G. Glorian, L. A. Maciejewski, J. Brocard, *J. Med. Chem.* **1997**, *40,* 3715-3718.

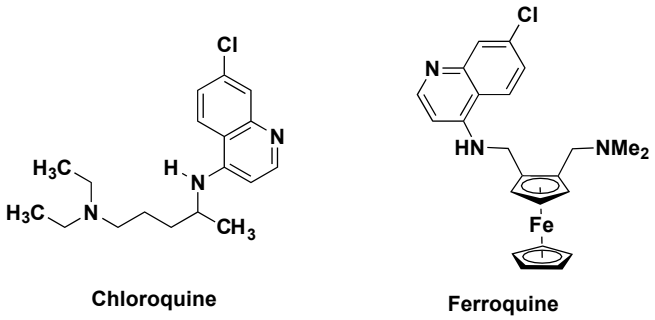


Figure 5: Structure of Chloroquine and ferroquine.

Some ferrocene derivatives have also demonstrated great potential in cancer therapeutics.[94] In particular, ferrocifens (metallocene analogues of the antitumor drug tamoxifen) developed by Jouen and co-workers, have been extensively studied, showing promising results for breast cancer.[95] Hydroxiferrocifene has shown to have higher affinity to estrogen receptors and better cytotoxic effect than hydroxitamoxifen (IC_{50} values are 3.4 and 4.9 μM for (Z) and (E) hydroxiferrocifene respectively versus 6.4 μM for hydorxitamoxifene.[96]

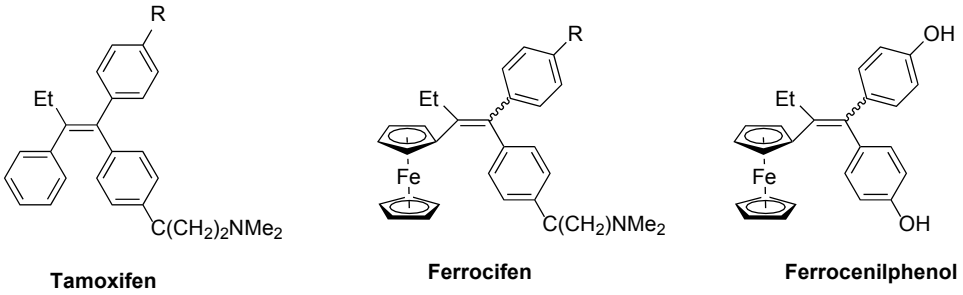


Figure 6: Structure of Tamoxifen and Ferrocifen.

Moreover, several ferrocenyl phenols are also reported to be highly active against several cancer cell lines.[97]

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[94] Selected revisions: a) S. S. Braga, A. M. S. Silva, *Organometallics*, **2013**, *32*, 5626; b) G. Gasser, I. Ott. N. Meltzer-Nolte, *J. Med. Chem.* **2011**, *54*, 3; c) C. Ornelas, *New. J. Chem.* **2011**, *35*, 1973.

[95] a) G. Jaouen, A. Vessieres, *Pure Appl. Chem.,* **1985**, *57*, 1865-1874; b) G. Jaouen, W. Beckm M. J. Mc Glinchey, *Bioorgano-metallics Wiley-VCH, Weinheim*, **2006**, ch. 1,pp. 1–37; c) C. G. Hartinger, P. J. Dyson, *Chem. Soc. Rev.* **2009**, *38*, 391–401; d) N. P. E. Barry, P. J. Sadler, *Chem. Commun*. **2013**, *49*,5106-5131.

[96] a) G. Jaouen, J. Vaissermann, S. Top *J. Orgmet. Chem.* **1997**, *541,* 355-361; B. b) G. Jaouen, A. Vessieres, S. Top, *Chem. Soc. Rev.* **2015**, *44*, 8802-8817**.**

[97] Seminal contributions on the synthesis and biological evaluation of ferrocifen compounds: a) S. Top, J. Tang, A. Vessières, D. Carrez, C. Provot, G. Jaouen, *Chem. Commun.* **1996**, 955; b) S. Top, B. Dauer, J. Vaissermann, G. Jaouen, *J. Organomet. Chem.* **1997**, *541*, 355. Selected reviews on ferrocifen type anti-cancer drugs: c) G. Jaouen, A. Vessières, S. Top, *Chem. Soc. Rev.* **2015**, *44*, 8802; d) A. Vessières, *J. Organomet. Chem.* **2013**, *734*, 3; e) A. Nguyen, A. Vessières, E. A. Hillard, S. Top, P. Pigeon, G. Jaouen, *Chimia*, **2007**, *61*, 716.

In these compounds the presence of a ferrocene group, a conjugated linker, para-aromatic substitution by a protic function and the alkyl group on the same carbon as the ferrocene group have been found as structural requirements for the cytotoxicity activity.[98] Their mode of actions seems to start with the reversible oxidation that can catalyze the intramolecular formation of quinone methides when the ferrocenyl group and phenol group are linked by a conjugated system.

[98]M. Görmen, P. Pigeon, S. Top, E. A. Hillard, M. Huché, C. G. Hartinger, R. Montighy, M. A. Plamont, A. Vessiares, G. Jaouen, *Chem. Med. Chem.* **2010**, *5*, 2039-2050.

II.2. General Objectives

Inspired by these outstanding contributions and continuing with the interest of our group in the chemistry of ferrocene, our goal in this chapter has been the development of new and efficient approaches for the C-H bond functionalization of ferrocene. To this end, first we have studied the feasibility of trapping quinone methide intermediates with ferrocene as a means for the synthesis of new ferrocene-phenol conjugates of interest in medicinal organometallic chemistry.

In the second part, we reported the results obtained in the reaction of ferrocene and ruthenocene with three-membered-ring systems such as donor-acceptor cyclopropanes and aziridines.

Part A Generation of Quinone methide intermediates via $InCl_3$-catalyzed to synthesize ferrocene-decorated phenol derivatives

As we explained in the previous section (see Chapter 1, Part B), Quinone methides are highly reactive intermediates with applications in several fields of chemistry. Moreover, ferrocenyl phenols derivatives have been reported to be highly active against cancer cell lines. In this context, the main objective of this part has been the generation of ferrocene-decorated phenol derivatives.

A.1 Results and discussion

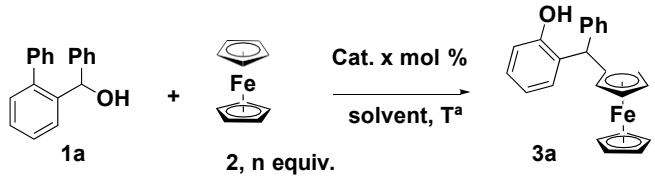
A.1.1 Screening of reactions conditions and scope

A.1.1.a $InCl_3$-catalyzed reaction of *o*-hydroxybenzyl alcohols with ferrocene

For our initial studies, *o*-hydroxybenzyl alcohol (**1a)** was selected as model substrate. Its reaction with ferrocene (**2)** was investigated in the presence of several promoters for the generation of the *ortho* quinone methide intermediate (Table 1). In the case of TfOH as catalyst using 1,2-dicloroethane as solvent at room temperature, the reaction was completely ineffective; however, the desired product was observed in a 20% isolated yield when the reaction was heated at 60 ^{o}C (entry 1). Changes in the catalyst loading (50% and 100%) did not improve the yield of **3a**, while the use of other Brønsted acids such as TFA and *p*-TsOH did no promote the transformation at all. Next, we examined different Lewis acids and we found that using 10 mol% of $InCl_3$ in 1,2-dicloroethane at 60 ^{o}C afforded functionalized ferrocene **3a** in 64% isolated yield (entry 2). The reaction at room temperature was completely ineffective (entry 3). Changing the solvent to toluene, methanol or THF at room temperature or heating the reaction at 60 ^{o}C did not improve the yield (entry 4). Conducting the reaction at different catalyst loadings resulted in lower yields of the desired product (entr7 5). Finally, we found that the use of 3 equivalents slightly improved the formation of **3a** (entries 7-8).

On the other hand, other catalysts such as InI_3, $ZnCl_2$, $Sc(OTf)_3$,$[Cu(CH_3CN)_4][BF_4]$ were tested under similar conditions, delivering the product in low yield or were completely ineffective. Worth to note, in the absence of $InCl_3$, no reaction occurred at all (entry 9).

Table 1: Optimization of reaction conditions.



Entry	n equiv.	Cat	x mol %	solvent	Tª	Yield(%)[a]
1	2	Tf(OH)	50	DCE	60	20
2	**3**	**$InCl_3$**	**10**	**DCE**	**60**	**64**
3	3	$InCl_3$	10	DCE	rt	-
4	3	$InCl_3$	10	Toluene/MeO/HTHF	rt/60	-
5	2	$InCl_3$	5-20	DCE	60	5-38
6	1.5	$InCl_3$	10	DCE	60	5
7	6	$InCl_3$	10	DCE	60	58
8	2	-	-	DCE	60	-

[a] Isolated yield after column chromatography.

The structure of ferrocene **3a** was ascertained by NMR experiments. According to the ^{1}H-NMR experiment, the benzylic hydrogen appears as a singlet at 5.54 ppm. For the substituted Cp group there are 4 signals (3.95, 4.19, 4.22 and 4.25 ppm) while for the unsubstituted Cp there is a singlet at 4.08 ppm for the five equivalent hydrogens.

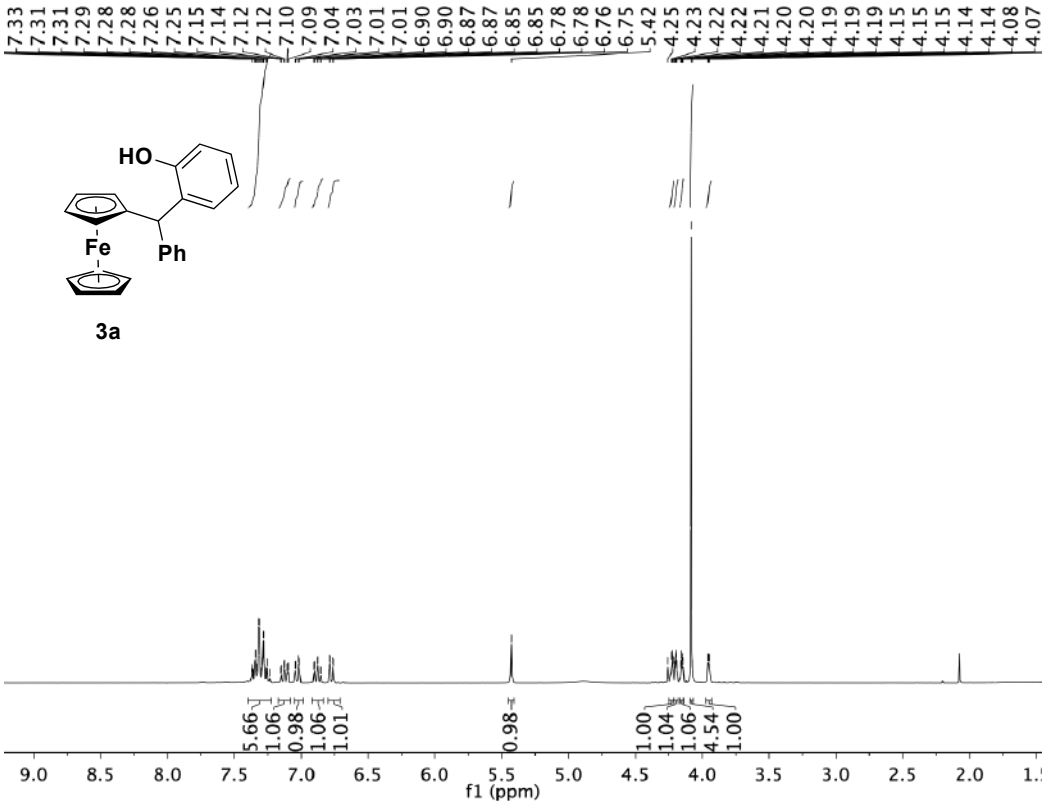


Figure 1: ^{1}H-NMR ($CDCl_3$, 300 MHz) of ferrocene derivative **3a**.

In the ^{13}C-NMR, the signal at 46.0 ppm corresponds to the benzylic carbon. There is one intense signal at 68.8 ppm for the five equivalent carbon atoms of the Cp ligand. The substituted Cp gives rise to four different C-H signals at 67.7, 68.1, 68.6 and 69.1 ppm. The C_{ipso} of the ferrocene appears at 90.7 ppm.

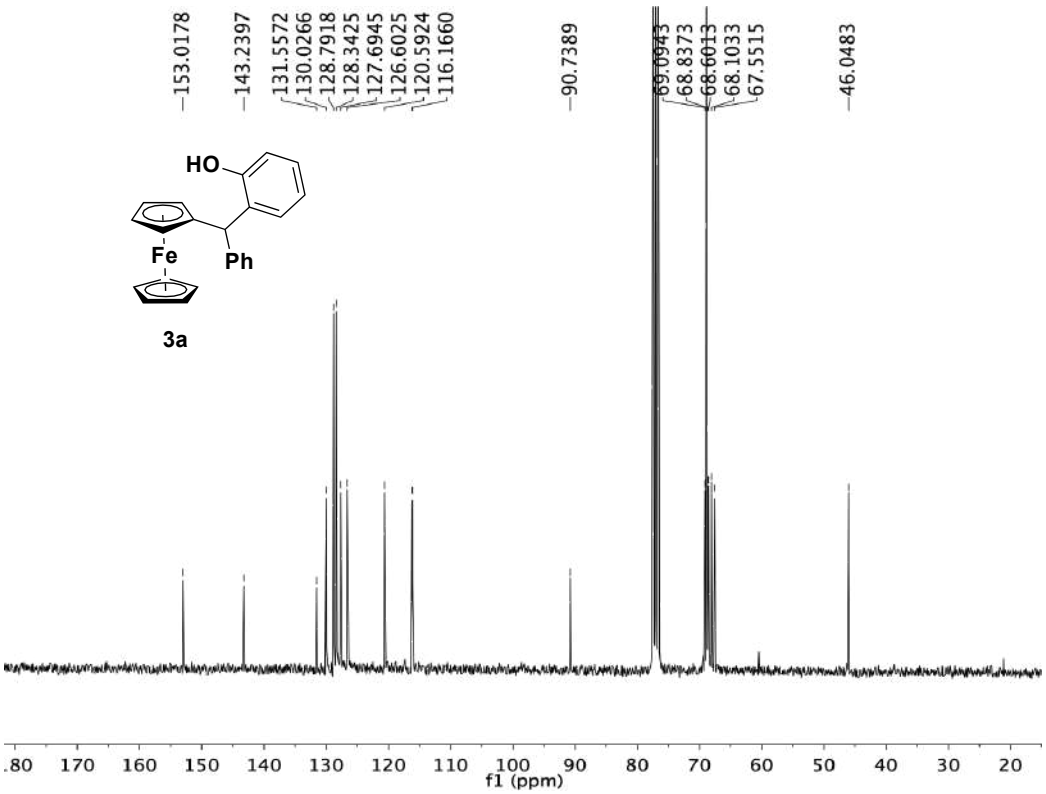


Figure 2: ^{13}C-NMR ($CDCl_3$, 75 MHz) of ferrocene derivative **3a**.

Single crystals of ferrocene derivative **3a** suitable for X-ray crystallographic structure analysis were obtained confirming the initially proposed structure (Figure 3).

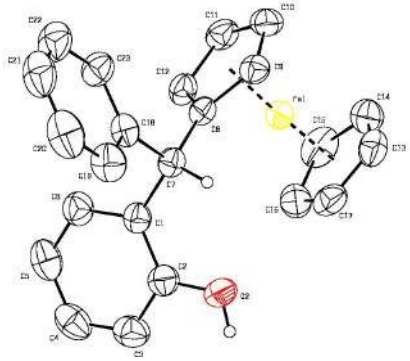


Figure 3: X-ray structure of ferrocene derivative **3a**. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms are excluded, except those bonded to C7 (H7) to O2 (H2O).

The crystallographic study not only confirmed the initially proposed structure but also

revealed some interesting structural features.[99]

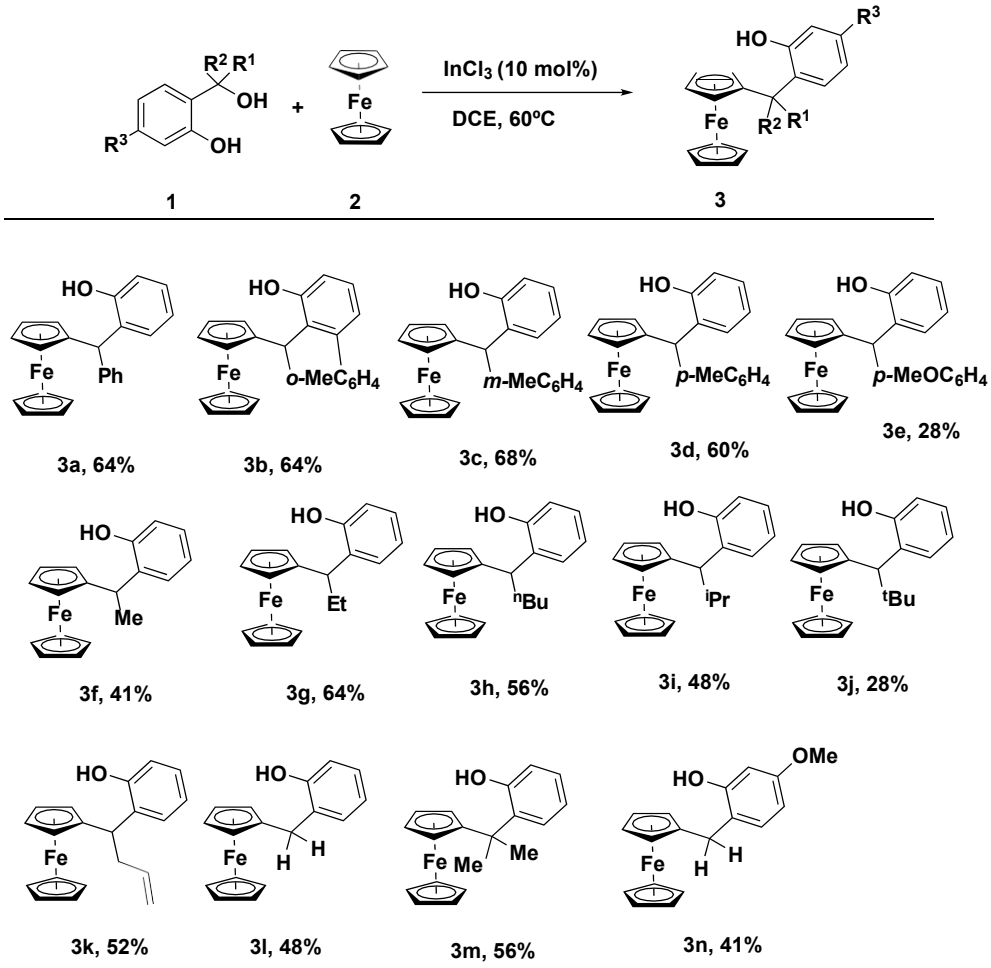
Having demonstrated the validity of our hypothesis, we next turned our attention to assess the scope of this coupling (Table 2). First, we found that *o*-hydroxybenzyl alcohols **1b**-**d** (R^1 = tolyl, R^2 = R^3 = H) with electron-neutral aryl groups installed in the benzylic position are suitable substrates for this transformation. All three isomeric substrates performed comparably, furnishing the desired ferrocene-containing unsymmetrical triarylmethane derivatives **3b**-**d** in moderate isolated yields (60-68%). In contrast, the reaction was less efficient with a strongly electron-donating substituent on the aromatic ring (**1e**; R^1 = *p*-$MeOC_6H_4$, R^2 = R^3 = H) providing the corresponding ferrocenyl phenol derivative **3e** in a significantly lower yield.

Alkyl groups in the benzylic position were also investigated and primary and secondary alkyl groups were well-tolerated as demonstrated by the synthesis of ferrocene derivatives **3f**-**i** in moderate isolated yields (41-64%). However, a substrate bearing a tertiary group (**1j**; R^1 = ^{t}Bu, R^2 = R^3 = H) reacted more sluggishly, affording ferrocene derivative **3j** in a modest yield of 28%. A substrate featuring an unsaturated group (**1k**; R^1 = allyl, R^2 = R^3 = H) posed no problems affording the expected coupling product in acceptable yield.

On the other hand, substitution in the benzylic position is not mandatory as judged by the formation of ferrocene derivative **3l** in 48% isolated yield when the parent substrate (**1l**; R^1 = R^2 = R^3 = H) was subjected to the standard conditions. Additionally, a disubstituted substrate (**1m**; R^1 = R^2 = Me, R^3 = H) was found to undergo the coupling to give rise to ferrocene derivative **3m** in synthetically useful yield. Finally, the reaction could be extended to substrates with additional substitution at the aryl backbone (substrate **1m**; R^1 = R^2 = H, R^3 = MeO), thereby generating the expected functionalized ferrocene **3n** in 41% yield.

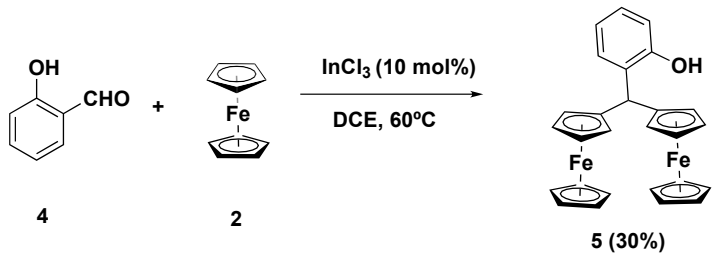
[99] CCDC number 1812859 (**3a**) contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The crystallographic study reveals a non-classical intermolecular interaction of the phenolic OH group with the π cloud of the phenyl group. For selected examples of aromatic rings as weak hydrogen bond acceptors in crystals, see: *An Introduction to Hydrogen Bonding,* G. A. Jeffrey, Oxford University Press, New York, **1997**.

Table 2: $InCl_3$-catalyzed synthesis of ferrocene derivatives **3**.



Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $InCl_3$ (10 mol%), DCE, 60 ^oC. Yields of the isolated products after column chromatography (silica gel, hexanes/ethyl acetate mixtures).

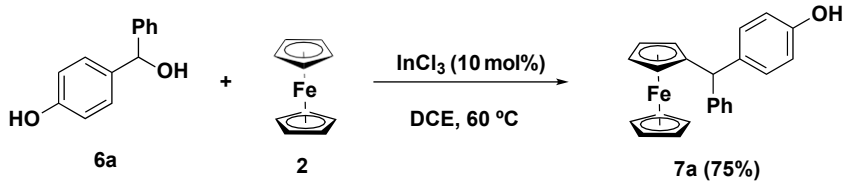
To further expand the scope of this Lewis acid-catalyzed C-H bond functionalization, we envisioned the synthesis of diferrocenylmethyl derivative **4** (Scheme 1). Under standard conditions (10 mol% of $InCl_3$, DCE, 60 ^oC) and by using salicylaldehyde (**4**) as starting material with an excess of ferrocene **2** (4 equiv), we were able to obtain the 2-(diferrocenylmethyl)phenol derivative **5** in 30% yield.



Scheme 1: Synthesis of diferrocenylmethyl derivative **5**.

A.1.1.b $InCl_3$-catalyzed reaction of *p*-hydroxybenzyl alcohols with ferrocene

To further expand this Lewis acid-catalyzed C-H bond functionalization of ferrocene, we also investigated the reaction of *p*-hydroxybenzylalcohol **6a** and we found that under previous conditions we obtained the corresponding coupling product **7a** in a remarkable 75% yield.



Scheme 2: Synthesis of ferrocene derivative **7a**.

The structure of ferrocene derivative **7a** was established by using NMR experiments. In ^{1}H-NMR experiment, the benzylic hydrogen resonates at 5.12 ppm and the hydrogen for the hydroxy group appears at 4.77 ppm. There is one singlet for seven hydrogens at 4.04 ppm that corresponds to the five hydrogens for the unsubstituted Cp and two for the substituted one. The other two hydrogens for the Cp substituted appear at 4.01 and 4.19 ppm.

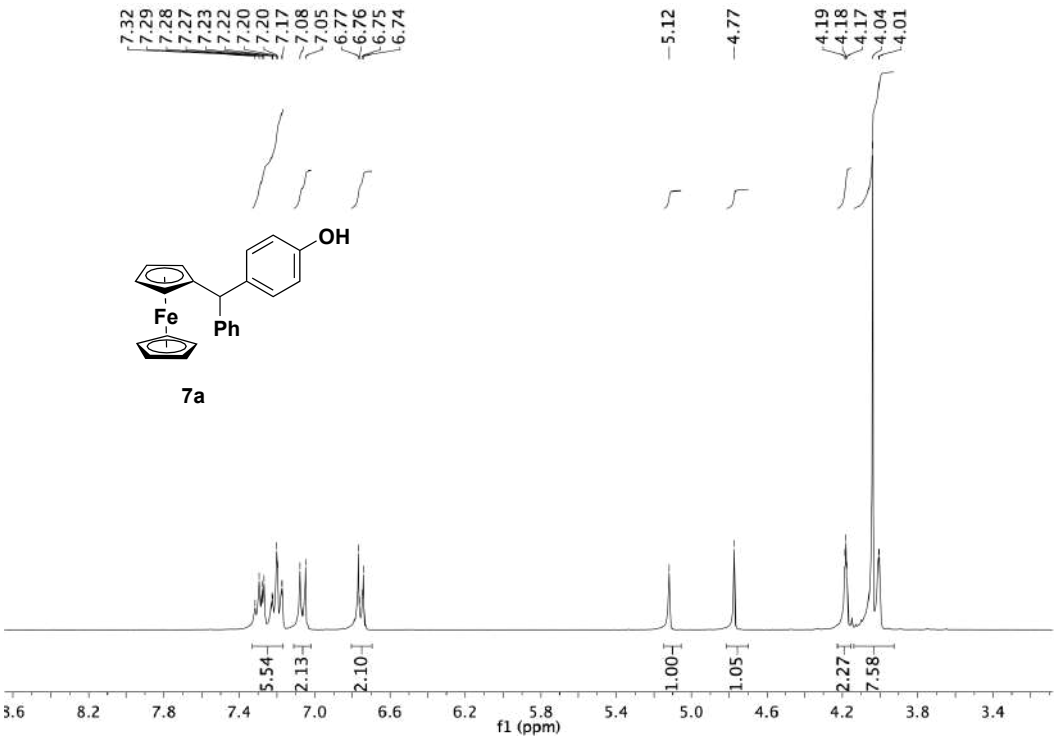


Figure 5: ^{1}H-NMR ($CDCl_3$, 300 MHz) of ferrocene derivative **7a**.

Attending to ^{13}C-NMR, the signal at 51.0 ppm corresponds to the benzylic carbon. There is one intense signal at 68.7 ppm for the five equivalent carbon atoms of the Cp. The substituted Cp gives rise to two different signals at 67.6 and 67.7 ppm and two more that overlap with the signal at 68.7 ppm.

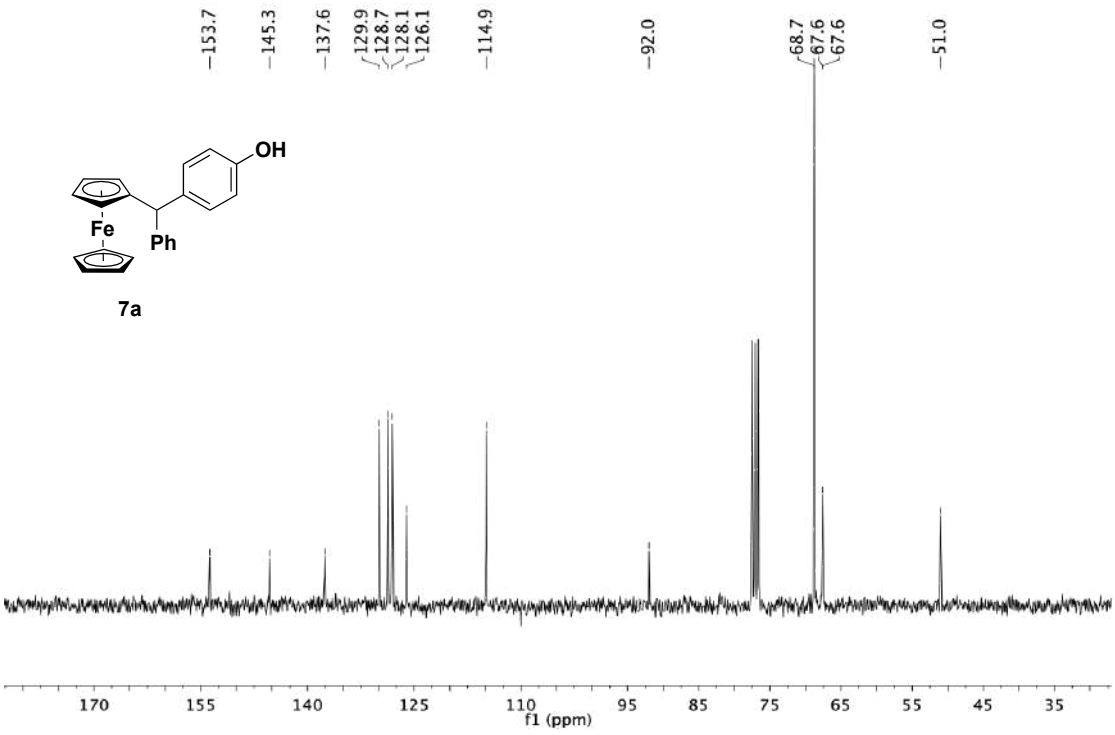


Figure 6: ^{13}C-NMR ($CDCl_3$, 75 MHz) of ferrocene derivative **7a**.

An X-ray crystallographic study confirmed the proposed structure of **7a** (Figure 7).

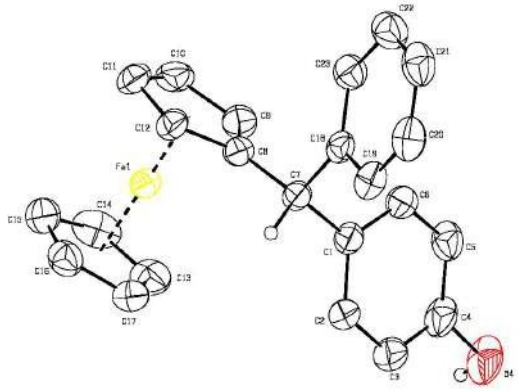
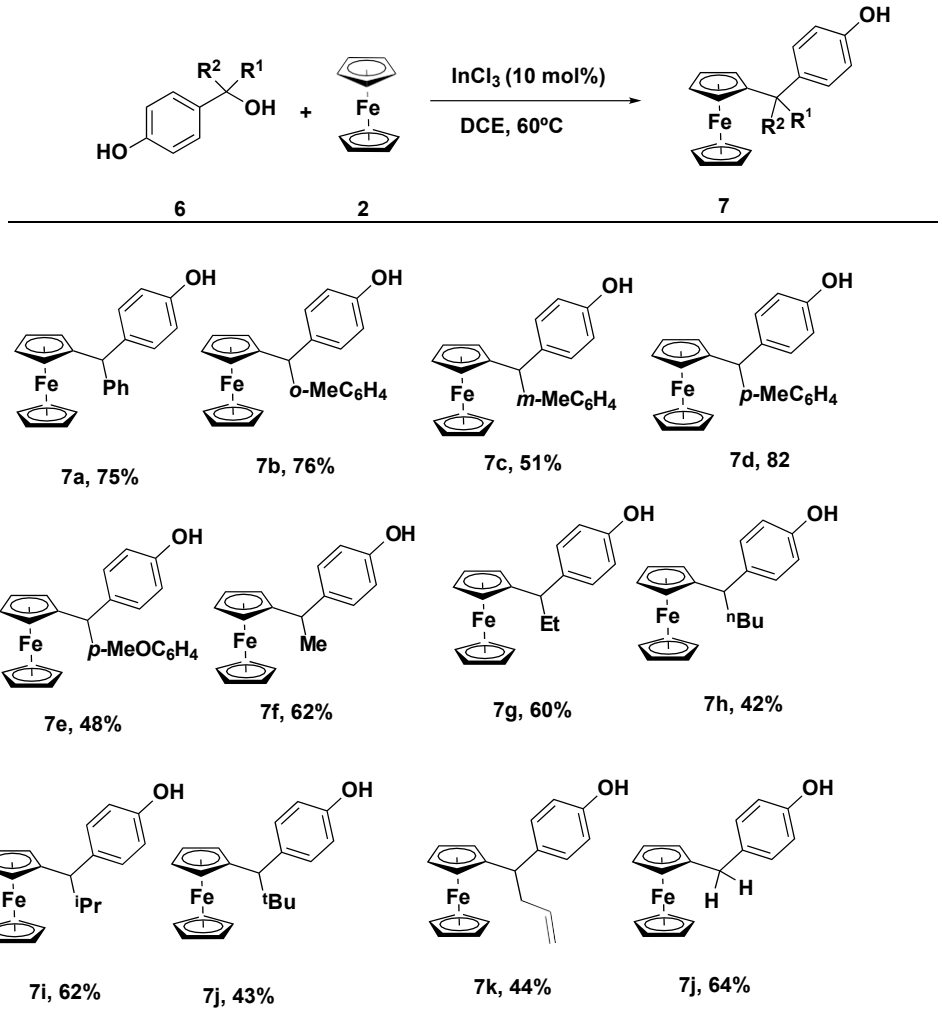


Figure 7: X-ray structure of ferrocene derivative **7a**. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms are excluded, except those bonded to C7 (H7) and O4 (H4O).

Again, the crystallographic study revealed unusual intermolecular non-classical hydrogen bonding between the phenolic O-H group and an aromatic moiety.

We also evaluated a variety of *p*-hydroxybenzylalcohols **6**. An array of substrates **6a**-**k** bearing aryl-, alkyl-, and alkenyl groups at the benzylic position, as well as the unsubstituted one **6l**, served as suitable reaction partners for this process furnishing the desired functionalized ferrocene derivatives **7a**-**l** in moderate to good isolated yields (42-82%). With a few exceptions, the reactions of substrates **6** exhibited consistently higher yields than those involving *ortho*-substituted substrates **2**.

Table 3: $InCl_3$-catalyzed synthesis of ferrocene derivatives **7**.

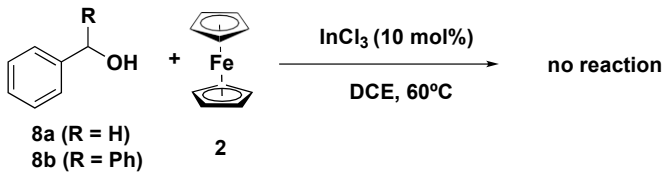


Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $InCl_3$ (10 mol%), DCE, 60 ^oC. Yields of the isolated products after column chromatography (silica gel, hexanes/ethyl acetate mixtures).

A.1.2. Mechanistic control experiments

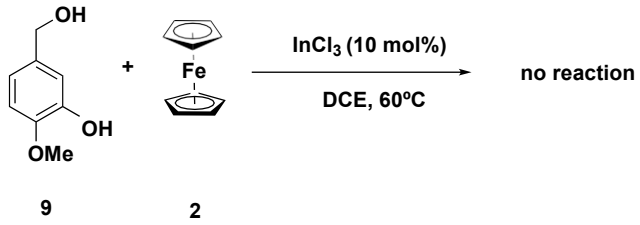
Some control experiments supported the participation of quinone methides as intermediates, which would be subsequently intercepted by ferrocene.

First, we found that under standard conditions, benzylic alcohol (**8a**, R = H) failed to undergo the current reaction (Scheme 3). A similar outcome was obtained with the benzhydryl alcohol (**8b**, R = Ph).



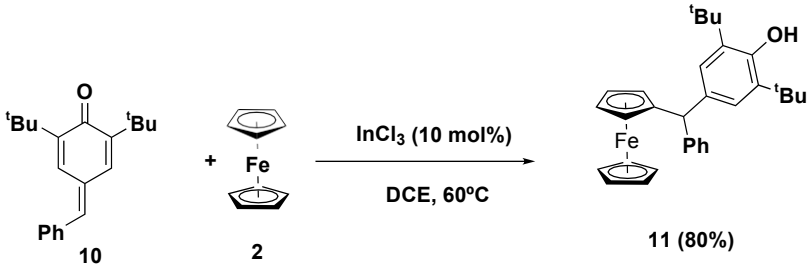
Scheme 3: Reaction of benzylic alcohols and ferrocene under standard condition.

Next, we evaluated the reactivity toward ferrocene of substrate **9** featuring the phenolic OH group in *meta*-position (Scheme 4). Under standard conditions (10 mol% of $InCl_3$, DCE, 60 ^oC), no reaction occurred, thus demonstrating that a phenolic OH group in the *ortho*- or *para*-position is critical for a successful outcome.



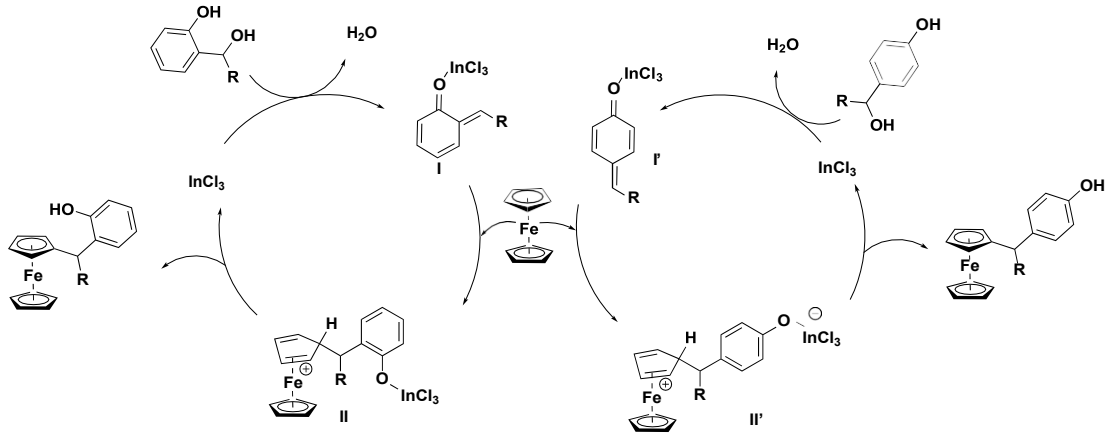
Scheme 4: Reaction of *meta*-hydroxybenzyl alcohol with ferrocene under standard condition.

Finally, we performed an experiment with a stable *p*-quinone methide. Thus, a very low conversion after 24 h was observed in the reaction of *p*-quinone methide **10** and ferrocene (**2**) under standard reaction conditions. Gratifyingly, performing the reaction in toluene at 100 ^oC enabled the preparation of the functionalized ferrocene derivative **11** in 80% isolated yield (Scheme 5).



Scheme 5: $InCl_3$-catalyzed reaction of ferrocene and stable *p*-quinone methide **10**.

According to these control experiments a mechanistic proposal is depicted in Scheme 6. The process would start with the generation of the quinone methide intermediate through dehydratation of the corresponding hydroxybenzyl alcohol. Next, the activation of the quinone methide by Lewis acid complexation would lead to the generation of intermediates **I** and **I'.** These intermediates in presence of ferrocene, would be involved in a Friedel-Crafts reaction forming intermediates **II** and **II**'. Finally, the final product is obtained and $InCl_3$ is recovered as catalyst.



Scheme 6: Mechanistic proposal for the $InCl_3$-catalyzed reaction of phenol derivatives and ferrocene.

A.1.3. Citotoxic screening

As stated in the introduction of this chapter, a number of ferrocenyl phenols have been reported to display significant anticancer properties. For this reason, we performed a preliminary evaluation of the cytotoxic activity of ferrocene derivatives against different cancer cells.[100]

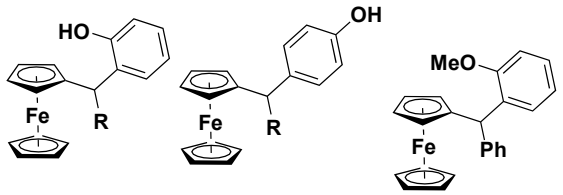
As shown in Table 4, we found cytotoxic activity of some compounds in ovarian cancer cell (A2780) and lung cancer cell (A549).

In ovarian cancer cell line, all derivatives tested **3a** (R_1=H, R_2=Ph, R_3= H), **3f** (R_1=H, R_2=Me, R_3= H), **3g** (R_1=H, R_2=Et, R_3= H) and **7a** (R_1=H, R_2=Ph, R_3= H) showed significant cytoxicity (IC_{50} of 2.68, 1.66, 1.86 and 3.5 μM)[101]

On the other hand, in lung cancer cell line, derivatives **3a** and **3f** from *ortho*-phenol displayed better results in terms of activity (IC_{50} of 2,77 and 1,36 mM, respectively). Ferrocenes **3g** and **7g** showed lower cytotoxicity (IC_{50} of 5.96 and 4,89 mM).

Interestingly, the OH group seems to play a crucial role on the cytotoxicity since the methoxy derivative **3a-Me**[102] showed no toxicity against both cancer cell lines (IC_{50} of > 10 mM).

Table 4: IC_{50} values for selected ferrocenyl compounds on different cell lines



3a, R = Ph
3f, R= Me

7a, R = Ph
7g, R= Et

3a-Me

	3a	3f	3g	7a	7g	3a-Me
A2780	2.68	1.66	1.86	1.07	2.23	> 10
A549	2.77	1.36	5.96	3.55	4.89	> 10

[100] Lung cancer cell line A-549, colon cancer cell line HT-29, gastric cancer cell line AGS and ovarian cancer cell line A-2780 were tested. For the sake comparison, NIH 3T3 were used as normal cell.

[101] IC_{50} is a quantitative measure that indicates how much of an inhibitory substance is needed to inhibit, *in vitro*, a given biological process or biological component by 50.

[102] Ferrocene **3a-Me** was prepared in 62% isolated yield by methylation of **3a** with methyl iodide in the presence of sodium hydride.

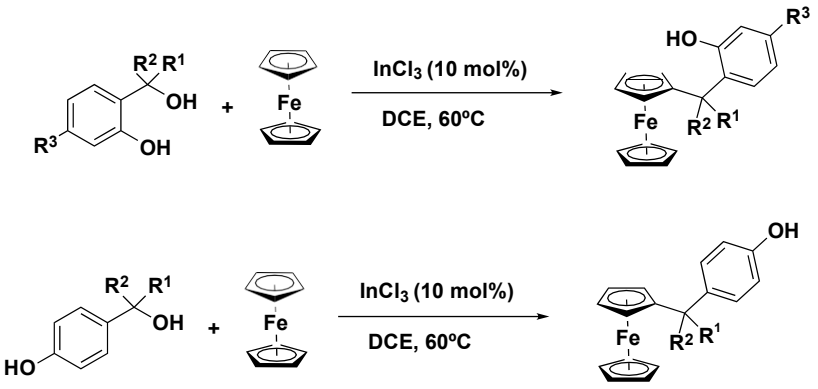
A.2 Conclusions

- In this chapter, we have developed a simple and efficient $InCl_3$-catalyzed synthesis of new phenol-ferrocene conjugates.

- This C-H bond functionalization of ferrocene is believed to proceed through initial generation of quinone methide intermediates, which would be subsequently intercepted by ferrocene.

- Preliminary biological evaluation revealed that some of the ferrocene derivatives available by our methodology exhibit significant cytotoxicity against selected cancer cell lines.

Graphical summary



Ferrocene functionalization | *Very Important Paper* |

Ferrocene-Decorated Phenol Derivatives by Trapping *ortho*-Quinone Methide Intermediates with Ferrocene

Silvia González-Pelayo,[a] Enol López,[a] Javier Borge,[b] Noemí de-los-Santos-Álvarez,[b] and Luis A. López*[a]

Abstract: The $InCl_3$-catalyzed reaction of ferrocene with *ortho*-hydroxybenzyl alcohols is reported and represents a convenient route for the synthesis of ferrocenyl phenols. This carbon–carbon bond forming process is believed to proceed through an *ortho*-quinone methide intermediate that can be intercepted by ferrocene through a Friedel–Crafts-type process. Preliminary cytotoxic screening carried out on several cancer cell lines revealed that some of the compounds exhibit moderate cytotoxicity.

Introduction

Since its discovery in 1951,[1] no other organometallic compound has drawn as much attention from the chemical community as ferrocene.[2] In particular, recent decades have witnessed impressive achievements in the field of ferrocene functionalization. In this regard, although transition metal-catalyzed C–H bond functionalization has very recently evolved into a powerful strategy,[3] classical methodologies such as Friedel–Crafts-type electrophilic substitution reactions[4] or a sequence of initial metalation followed by reaction with an electrophilic reagent[5] have proved extremely useful. Very likely, a major driving force for most of these developments has been the countless applications displayed by functionalized ferrocenes in diverse fields. Indeed, functionalized ferrocenes are key components in ligands widely used in catalysis,[6] polymers and materials,[7] molecular-based devices,[8] etc. Ferrocene derivatives are also of steadily increasing importance in medicinal organometallic chemistry.[9] Indeed, a number of ferrocene derivatives have been reported to display relevant activity (Figure 1). For example, ferroquine, a ferrocene-based analogue of chloroquine, was found to display promising antimalarial properties.[10] Several contributions have also demonstrated the potential of some ferrocene derivatives in cancer therapeutics.[11] In fact, several ferrocenyl phenols are reported to be highly active against several cancer cell lines. In particular, ferrocifens developed by Jouen and co-workers, have been extensively studied, showing promising results for breast cancer.[12] On the basis of electrochemical and chemical oxidation studies, a new mode of action involving ferrocenyl quinone methides has been proposed for these ferrocenyl phenols.[13] Although less studied, unconjugated ferrocenyl diphenols have also found to display significant antitumoral properties.[14,15]

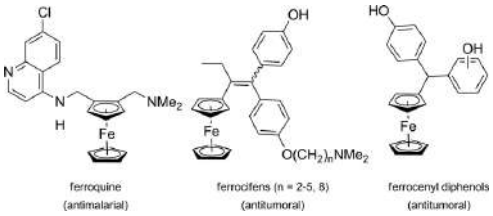


Figure 1. Ferrocene-based organometallic drugs.

On the other hand, *ortho*-quinone methides (*o*-QMs) are highly reactive intermediates that have found a wealth of synthetic applications.[16] Generated in situ from different precursors, they exhibit a rich chemistry that resembles that of unsaturated carbonyl compounds. In fact, they are reactive 4π partners in [4+*n*] cycloaddition reactions[17] and excellent Michael acceptors towards carbo- and heteronucleophiles.[18] In some cases, these transformations have been conducted in an asymmetric manner.[19]

Given our ongoing interest in functionalization of ferrocene derivatives based on the generation and subsequent trapping of highly electrophilic species,[20] we posited that *o*-QMs could be intercepted by ferrocene through a Friedel–Crafts-type reaction, thus delivering ferrocene derivatives featuring a phenolic moiety. Since, as stated before, phenol groups endow several ferrocene derivatives with therapeutic properties, our proposal was not only synthetically appealing, but also potentially relevant in the field of medicinal organometallic chemistry. Consequently, herein we report the Lewis acid-catalyzed reaction of

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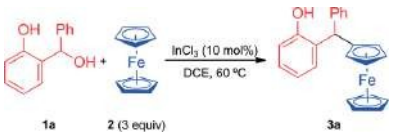
o-hydroxybenzyl alcohols with ferrocene as a convenient route to ferrocene-decorated phenol derivatives. Control experiments support the participation of *o*-QMs, which may be subsequently involved in a Friedel–Crafts-type reaction. A preliminary study demonstrates that some of the prepared ferrocene derivatives are cytotoxic against various cancer cell lines.

Results and Discussion

Using *o*-hydroxybenzyl alcohol **1a** as a model substrate, we first examined its reaction with ferrocene (**2**) in the presence of different promoters for the generation of the required *ortho*-quinone methide intermediate (Table 1). To our delight, we found that heating a solution of **1a** (1 equiv.) and **2** (3 equiv.) in the presence of 10 mol-% of $InCl_3$ in 1,2-dichloroethane (DCE) at 60 °C afforded the targeted functionalized ferrocene derivative **3a** in 64 % isolated yield (Table 1, entry 1).

Table 1. Optimization of reaction conditions.[a]



1a 2 (3 equiv) 3a

Entry	Conditions	Yield [%][b]
1	standard conditions	64
2	no $InCl_3$	–
3	InI_3 instead of $InCl_3$	–
4	$In(OTf)_3$ instead of $InCl_3$	33
5	$AgSbF_6$ instead of $InCl_3$	–
6	$ZnCl_2$ instead of $InCl_3$	–
7	$Sc(OTf)_3$ instead of $InCl_3$	–
8	$[Cu(CH_3CN)_4][BF_4]$ instead of $InCl_3$	–
9	50 mol-% of TFA at rt	–
10	10 mol-% of TfOH at rt	–
11	50 mol-% of TfOH at rt	20
12	100 mol-% of TfOH at rt	–
13	5 mol-% instead of 10 mol-%	5
14	20 mol-% instead of 10 mol-%	38
15	rt instead of 60 °C	–
16	Tol, MeOH or THF instead of DCE	–
17	1.5 equiv. instead of 3 equiv.	36

[a] These exploratory experiments were performed on a 0.1 mmol scale. [b] Isolated yield after chromatographic purification (silica gel; hexanes/ethyl acetate 5:1).

A control experiment demonstrated that no reaction occurred in the absence of catalyst (entry 2). On the other hand, under otherwise similar conditions, InI_3 and $In(OTf)_3$ displayed a lower activity (entries 3 and 4). Other Lewis or Brønsted acids proved ineffective in promoting the formation of the desired functionalized ferrocene derivative (entries 4–12). Various reaction conditions were tested using $InCl_3$ as promoter (entries 13–17). Thus, conducting the reaction with a catalyst loading of 5 mol-% resulted in a decreased yield of the desired product **3a**, as did the use of 20 mol-% (entries 13 and 14). On the other hand, $InCl_3$ (10 mol-%) was completely ineffective at room temperature and the starting materials were recovered unchanged (entry 15). Various solvents were also tested (entry 16). Toluene, methanol or THF were completely ineffective in the present reaction. Finally, it was found that the use of 3 equiv. of ferrocene was required in order to obtain a moderate yield of the coupling product. In fact, the use of only 1.5 equiv. of ferrocene led to a significant decrease in yield (compare entries 1 and 17, 64 vs. 36 %). The structure of ferrocene **3a** was ascertained by NMR spectroscopy and X-ray analysis (Figure 2).[21] The crystallographic study not only confirmed the initially proposed structure but also revealed some interesting structural features.[22]

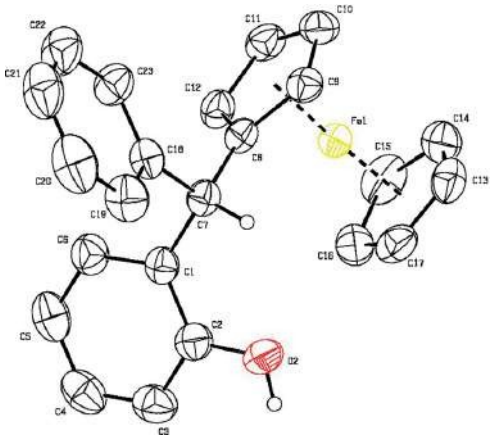


Figure 2. X-ray structure of ferrocene derivative **3a**. Thermal ellipsoids are drawn at the 30 % probability level. Hydrogen atoms are excluded, except those bonded to C7 (H7) and O2 (H_2O).

Having demonstrated the validity of our hypothesis and with suitable conditions in hand for the reaction of **1a** and ferrocene, our attention turned to assess the scope of this coupling process (Table 2). First, we found that *o*-hydroxybenzyl alcohols **1b–d** (R^1 = tolyl, R^2 = R^3 = H) with electron-neutral aryl groups installed in the benzylic position are suitable substrates for this transformation. Interestingly, all three isomeric substrates performed comparably, furnishing the desired ferrocene-containing unsymmetrical triarylmethane derivatives **3b–d** in moderate isolated yields (60–68 %). In contrast, the reaction was less efficient with a strongly electron-donating substituent on the aromatic ring (**1e**; R^1 = *p*-$MeOC_6H_4$, R^2 = R^3 = H) providing the corresponding ferrocenyl phenol derivative **3e** in a significantly lower yield. Substrates having alkyl groups in the benzylic position were also investigated. Both primary and secondary alkyl groups were well tolerated as demonstrated by the synthesis of ferrocene derivatives **3f–i** in moderate isolated yields (41–64 %). However, a substrate bearing a tertiary group (**1j**; R^1 = *t*Bu, R^2 = R^3 = H) reacted more sluggishly, affording ferrocene derivative **3j** in a modest yield of 28 %. A substrate featuring an unsaturated group (**1k**; R^1 = allyl, R^2 = R^3 = H) posed no problems affording the expected coupling product in acceptable yield. On the other hand, substitution in the benzylic position is not mandatory as judged by the formation of ferrocene derivative

3l in 48 % isolated yield when the parent substrate (**1l**; R^1 = R^2 = R^3 = H) was subjected to the standard conditions. Additionally, a disubstituted substrate (**1m**; R^1 = R^2 = Me, R^3 = H) was found to undergo the coupling to give ferrocene derivative **3m** in synthetically useful yield. Finally, the reaction could be extended to substrates with additional substitution at the aryl backbone (substrate **1m**; R^1 = R^2 = H, R^3 = MeO). Thereby, the expected functionalized ferrocene **3n** was obtained in 41 % yield.

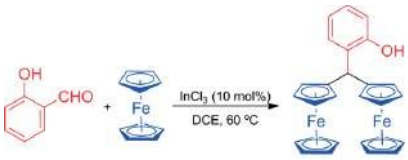
Table 2. $InCl_3$-catalyzed synthesis of ferrocene derivatives **3**.[a]

1 **2** **3**

Entry	R^1	R^2	R^3	**3**	Yield [%][b]
1	Ph	H	H	**3a**	64
2	*o*-MeC_6H_4	H	H	**3b**	64
3	*m*-MeC_6H_4	H	H	**3c**	68
4	*p*-MeC_6H_4	H	H	**3d**	60
5	*p*-$MeOC_6H_4$	H	H	**3e**	28
6	Me	H	H	**3f**	41
7	Et	H	H	**3g**	64
8	*n*Bu	H	H	**3h**	56
9	*i*Pr	H	H	**3i**	48
10	*t*Bu	H	H	**3j**	28
11	allyl	H	H	**3k**	52
12	H	H	H	**3l**	48
13	Me	Me	H	**3m**	56
14	H	H	OMe	**3n**	41

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $InCl_3$ (10 mol-%), DCE, 60 °C. [b] Isolated yields.

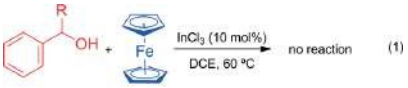
The results obtained with *o*-hydroxybenzyl alcohols prompted us to test whether this coupling protocol might also be suitable for the synthesis of derivatives featuring a diferro- cenylmethyl moiety as well. This goal was achieved by using salicylaldehyde (**4**) and an excess (4 equiv.) of ferrocene (**2**), which, under the typical reaction conditions (10 mol-% of $InCl_3$, DCE, 60 °C), gave 2-(diferrocenylmethyl)phenol derivative **5**, al- beit in low yield (Scheme 1).



4 **2** **5** (30%)

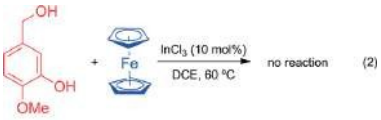
Scheme 1. Synthesis of diferrocenylmethylphenol derivative **5**.

A series of experiments were conducted to gain insight into this coupling reaction. First, under standard reaction conditions, benzylic alcohol (**6a**, R^1 = R^2 = H) was found to be an unproductive reaction partner [Equation (1)]. A similar outcome was obtained with benzydryl alcohol (**6b**, R^1 = Ph; R^2 = H). These results would rule out a direct Lewis acid-promoted displacement of the hydroxyl group.[23]



6a (R = H) **6b** (R = Ph) **2**

Next, we evaluated the reactivity toward ferrocene of substrate **7** featuring the phenolic OH group in *meta*-position [Equation (2)]. Under standard conditions (10 mol-% of $InCl_3$, DCE, 60 °C), no reaction occurred, thus demonstrating that a phenolic OH group in the *ortho*-position is critical for a successful outcome.



7 **2**

Taken together, these control experiments would lend support to the participation of *ortho*-quinone methides as key intermediates. Subsequent Lewis acid activation of the quinone methide would provide a highly electrophilic species that would react with ferrocene through a Friedel–Crafts type event. As stated before, a number of ferrocenyl phenols have been reported to display significant antitumoral properties. For this reason, a preliminary evaluation on the cytotoxic activity of some of the ferrocene derivatives **3** was performed. As shown in Table 3, some compounds display cytotoxic activity on a number of cancer cell lines.[24] First, the activity on A2780 ovarian cancer cell line was evaluated. Compounds **3a**, **3f** and **3g** showed significant toxicity (IC_{50} of 2.68, 1.66 and 1.86 μM, respectively). We also measured the IC_{50} values on A549 lung cancer cells. Once again, compounds **3a** and **3f** showed moderate toxicity (IC_{50} of 2.77 and 1.36 μM, respectively). In contrast, ferrocene derivative **3g** showed lower toxicity (IC_{50} of 5.96 μM). Interestingly, the OH group seems to play a crucial role on the cytotoxicity since the methoxy derivative **3a-Me**[25] showed no significant toxicity on both cancer cell lines (IC_{50} of > 10 μM).

Table 3. IC_{50} [μ_M] values for selected ferrocenyl compounds on different cell lines.[a]

	3a	**3f**	**3g**	**3a-Me**
A2780	2.68	1.66	1.86	> 10
A549	2.77	1.36	5.96	> 10

[a] Measured after 72 h of culture.

Conclusions

We have developed an easy and direct synthesis of ferrocene-containing phenol derivatives that makes use of simple and readily available starting materials. In most cases, this C–H bond functionalization takes place in synthetically useful yields and

under mild reactions conditions. Control experiments support the participation of *o*-QM intermediates, which could be subsequently intercepted by ferrocene. Although further evaluation is required, a preliminary study demonstrated that some of the ferrocene derivatives prepared display significant cytotoxicity. In our opinion, the easy access to these phenol-containing ferrocene derivatives could pave the way for the development of more active derivatives of this promising class of organometallic compounds.

Experimental Section

Representative Procedure (3a): $InCl_3$ (4.4 mg, 0.02 mmol, 10 mol-%) was added to a solution of *o*-hydroxybenzyl alcohol **1a** (40 mg, 0.2 mmol) and ferrocene **2** (111.6 mg, 0.6 mmol) in 1,2-dichloroethane (2 mL). The mixture was stirred at 60 °C for 2 h (disappearance of **1a** checked by TLC). Removal of solvent and chromatographic purification (silica gel, hexanes/ethyl acetate 5:1) afforded compound **3a** (47.1 mg, 64 %) as a yellow solid (m.p. 109–110 °C). Crystals of compound **3a** suitable for X-ray analysis were obtained from diffusion of pentane into dichloromethane at –20 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95–396 (m, 1 H), 4.08 (s, 5 H), 4.14–4.16 (m, 1 H), 4.19–4.21 (m, 1 H), 4.22–4.23 (m, 1 H), 5.43 (s, 1 H), 6.77 (dd, J = 1.1, 8.0 Hz, 1 H), 6.88 (td, J = 1.1, 7.5 Hz, 1 H), 7.03 (dd, J = 1.7, 7.7 Hz, 1 H), 7.12 (td, J = 1.7, 8.0 Hz, 1 H), 7.24–7.37 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.0 (CH), 67.6 (CH), 68.1 (CH), 68.6 (CH), 68.8 (CH), 69.1 (CH), 90.7 (C), 126.6 (CH), 127.7 (CH), 128.3 (CH), 130.0 (CH), 131.6 (C), 143.2 (C), 153.0 (C) ppm. HRMS (EI) calculated for $[C_{23}H_{20}FeO]^+$ (M^+): 368.0864, found 368.0856.

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Keywords: Ferrocene · *ortho*-Quinone methides · Phenols · Friedel–Crafts reaction · Cytotoxicity

[1] a) T. J. Kealy, P. L. Pauson, *Nature* **1951**, *168*, 1039; b) S. A. Miller, J. A. Tebboth, J. F. Tremaine, *J. Chem. Soc.* **1952**, 632.

[2] Selected revisions on properties and applications of ferrocene derivatives: a) D. Astruc, *Eur. J. Inorg. Chem.* **2017**, 6; b) E. S. Phillips, *Ferrocenes: Compounds, Properties and Applications*, Nova Science Publishers, Hauppauge, **2011**; c) *Ferrocenes: Ligands, Materials and Biomolecules* (Ed.: P. Štěpnička), Wiley: Chichester, U. K. **2008**; d) *Ferrocenes* (Eds.: A. Togni, T. Hayashi), VCH, Weinheim, **1995**; e) D. R. Van Staveren, N. Metzler-Nolte, *Chem. Rev.* **2004**, *104*, 5931; f) *Chiral Ferrocenes in Asymmetric Catalysis* (Eds.: L.-X. Dai, X.-L. Hou), Wiley-VCH, Weinheim, **2009**.

[3] For recent reviews on transition-metal-catalyzed C–H bond functionalization of ferrocene derivatives, see: a) D.-W. Gao, Q. Gu, C. Zheng, S.-L. You, *Acc. Chem. Res.* **2017**, *50*, 351; b) D.-Y. Zhu, P. Chen, J.-B. Xia, *ChemCatChem* **2016**, *8*, 68; c) L. A. López, E. López, *Dalton Trans.* **2015**, *44*, 10128.

[4] Seminal contribution: R. B. Woodward, M. Rosenblum, M. C. Whiting, *J. Am. Chem. Soc.* **1952**, *74*, 3458.

[5] Pioneering work on this topic: D. Marquarding, H. Klusacek, G. Gokel, O. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389. Seminal work on enantioselective synthesis of ferrocenes with planar chirality by (–)-sparteine-mediated lithiation M. Tsukazaki, M. Tinkl, A. Roglans, B. J. Chapell, N. J. Taylor, V. Snieckus, *J. Am. Chem. Soc.* **1996**, *118*, 685.

[6] Selected reviews: a) P. Štěpnička, *Coord. Chem. Rev.* **2017**, *353*, 223; b) Š. Toma, J. Csizmadiová, M. Mečiarová, R. Šebesta, *Dalton Trans.* **2014**, *43*, 16557; c) I. R. Butler, *Eur. J. Inorg. Chem.* **2012**, 4387; d) R. Gómez Arrayás, J. Adrio, J. C. Carretero, *Angew. Chem. Int. Ed.* **2006**, *45*, 7674; *Angew. Chem.* **2006**, *118*, 7836; e) T. J. Colacot, *Chem. Rev.* **2003**, *103*, 3101.

[7] D. J. Young, S. W. Chien, T. S. A. Hor, *Dalton Trans.* **2012**, *41*, 12655.

[8] a) D. Thompson, C. A. Nijhuis, *Acc. Chem. Res.* **2016**, *49*, 2061; b) H. Plenio, C. Aberle, *Chem. Eur. J.* **2001**, *7*, 4438.

[9] *Medicinal Organometallic Chemistry* (Eds.: G. Jaouen, N. Metzler-Nolte), Springer-Verlag, Berling Heidelberg, **2010**.

[10] Seminal work on the antimalarial activity of ferroquine: C. Biot, G. Glorian, L. A. Maciejewski, J. S. Brocard, O. Domarle, G. Blampain, P. Millet, A. J. Georges, H. Abessolo, D. Dive, J. Lebibi, *J. Med. Chem.* **1997**, *40*, 3715. For a recent review on ferroquine and its derivatives as antimalarial agents, see:W. A. Wani, E. Jameel, U. Baig, S. Mumtazuddin, L. T. Hun, *Eur. J. Med. Chem.* **2015**, *101*, 534.

[11] Selected revisions: a) S. S. Braga, A. M. S. Silva, *Organometallics* **2013**, *32*, 5626; b) G. Gasser, I. Ott, N. Meltzer-Nolte, *J. Med. Chem.* **2011**, *54*, 3; c) C. Ornelas, *New J. Chem.* **2011**, *35*, 1973.

[12] Seminal contributions on the synthesis and biological evaluation of ferrocifen compounds: a) S. Top, J. Tang, A. Vessières, D. Carrez, C. Provot, G. Jaouen, *Chem. Commun.* **1996**, 955; b) S. Top, B. Dauer, J. Vaissermann, G. Jaouen, *J. Organomet. Chem.* **1997**, *541*, 355. Selected reviews on ferrocifen-type anti-cancer drugs: c) G. Jaouen, A. Vessières, S. Top, *Chem. Soc. Rev.* **2015**, *44*, 8802; d) A. Vessières, *J. Organomet. Chem.* **2013**, *734*, 3; e) A. Nguyen, A. Vessières, E. A. Hillard, S. Top, P. Pigeon, G. Jaouen, *Chimia* **2007**, *61*, 716.

[13] a) E. Hillard, A. Vessières, L. Thouin, G. Jaouen, C. Amatore, *Angew. Chem. Int. Ed.* **2006**, *45*, 285; *Angew. Chem.* **2006**, *118*, 291; b) D. Hamels, P. M. Dansette, E. A. Hillard, S. Top, A. Vessières, P. Herson, G. Jaouen, D. Mansuy, *Angew. Chem. Int. Ed.* **2009**, *48*, 9124; *Angew. Chem.* **2009**, *121*, 9288; c) P. Messina, E. Labbé, O. Buriez, E. A. Hillard, A. Vessières, D. Hamels, S. Top, G. Jaouen, Y. M. Frapart, D. Mansuy, C. Amatore, *Chem. Eur. J.* **2012**, *18*, 6581; d) Y. Wang, P. Pigeon, S. Top, M. J. McGlinchey, G. Jaouen, *Angew. Chem. Int. Ed.* **2015**, *54*, 10230; *Angew. Chem.* **2015**, *127*, 10368.

[14] E. Hillard, A. Vessières, F. Le Bideau, D. Plazuk, D. Spera, M. Huché, G. Jaouen, *ChemMedChem* **2006**, *1*, 551.

[15] The synthesis of some ferrocenyl phenols in moderate overall yields (17–32 %) through a two-step sequence (trifluoroacetic acid promoted reaction of ferrocene with methoxy-substituted benzyl- and benzhydryl alcohols followed by demethylation of the resulting ferrocene derivatives) has been reported. D. Plazuk, A. Vessières, F. Le Bideau, G. Jaouen, J. Zakrewski, *Tetrahedron Lett.* **2004**, *45*, 5425.

[16] Selected recent reviews on the chemistry of *o*-QM intermediates: a) D. V. Osipov, V. A. Osyanin, Y. N. Klimochkin, *Russ. Chem. Rev.* **2017**, *86*, 625; b) A. A. Jaworski, K. A. Scheidt, *J. Org. Chem.* **2016**, *81*, 10145; c) M. S. Singh, A. Nagaraju, N. Anand, S. Chowdhury, *RSC Adv.* **2014**, *4*, 55924; d) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu, T. R. R. Pettus, *Acc. Chem. Res.* **2014**, *47*, 3655; e) N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160; f) T. P. Pathak, M. S. Sigman, *J. Org. Chem.* **2011**, *76*, 9210.

[17] For selected applications of [4+2] cycloadditions of *ortho*-quinone methide intermediates, see: a) J.-P. Lumb, K. C. Choong, D. Trauner, *J. Am. Chem. Soc.* **2008**, *130*, 9230; b) L. Xu, F. Liu, L.-W. Xu, Z. Gao, Y.-M. Zhao, *Org. Lett.* **2016**, *18*, 369. For [4+1] cycloaddition reactions of *ortho*-quinone methide intermediates, see: c) N. Meisinger, L. Roiser, U. Monkowius, M. Himmelsbach, R. Robiette, M. Wasser, *Chem. Eur. J.* **2017**, *23*, 5137 and references cited therein. For a recent [4+3] cycloaddition reaction, see: d) G.-J. Mei, Z.-Q. Zhu, J.-J. Zhao, C.-Y. Bian, J. Chen, R.-W. Chen, F. Shi, *Chem. Commun.* **2017**, *53*, 2768. For a formal [4+4] cycloaddition reaction, see: e) T. B. Samarakoon, M. Y. Hur, R. D. Kurtz, P. R. Hanson, *Org. Lett.* **2010**, *12*, 2182.

[18] Selected examples: a) D. V. Osipov, V. A. Osyanin, L. G. Voskressensky, Y. N. Klimochkin, *Synthesis* **2017**, *49*, 2286; b) H. Huang, J. Y. Kang, *Org.*

Lett. **2017**, *19*, 5988; c) Y. Wang, M. Chu, C. Zhang, J. Shao, S. Qi, B. Wang, X. Du, D. Xu, *Adv. Synth. Catal.* **2017**, *359*, 4170; d) S. González-Pelayo, L. A. López, *Eur. J. Org. Chem.* **2017**, 6003; e) Z. Lai, J. Sun, *Synlett* **2016**, *27*, 558; f) Z. Lai, Z. Wang, J. Sun, *Org. Lett.* **2015**, *17*, 6058; g) W. F. Veldhuyzen, A. J. Shallop, R. A. Jones, S. E. Rokita, *J. Am. Chem. Soc.* **2001**, *123*, 11126.

[19] For selected reviews on asymmetric reactions of *ortho*-quinone methides, see: a) Z. Wang, J. Sun, *Synthesis* **2015**, *47*, 3626; b) L. Caruana, M. Fochi, L. Bernardi, *Molecules* **2015**, *20*, 11733. For representative examples: c) M.-M. Xu, H.-Q. Wang, Y. Wan, J. Yan, S. Zhang, S.-L. Wang, F. Shi, *Org. Chem. Front.* **2017**, *4*, 358; d) Y. Xie, B. List, *Angew. Chem. Int. Ed.* **2017**, *56*, 4936; *Angew. Chem.* **2017**, *129*, 5018; e) J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu, F. Shi, *Angew. Chem. Int. Ed.* **2015**, *54*, 5460; *Angew. Chem.* **2015**, *127*, 5550; f) W. Zhao, Z. Wang, B. Chu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 1910; *Angew. Chem.* **2015**, *127*, 1930; g) S. Saha, S. K. Alamsetti, C. Schneider, *Chem. Commun.* **2015**, *51*, 1461; h) S. Saha, C. Schneider, *Chem. Eur. J.* **2015**, *21*, 2348; i) C.-C. Hsiao, S. Raja, H.-H. Liao, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, *54*, 5762; *Angew. Chem.* **2015**, *127*, 5854; j) O. El-Sepelgy, S. Haseloff, S. K. Alamsetti, C. Schneider, *Angew. Chem. Int. Ed.* **2014**, *53*, 7923; *Angew. Chem.* **2014**, *126*, 8057; k) C.-C. Hsiao, H.-H. Liao, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 13258; *Angew. Chem.* **2014**, *126*, 13474.

[20] For recent work from our group on the synthesis of functionalized ferrocene derivatives based on gold-carbene chemistry, see: a) E. López, J. Borge, L. A. López, *Chem. Eur. J.* **2017**, *23*, 3091; b) E. López, T. Suárez, A. Ballesteros, L. A. López, *Eur. J. Inorg. Chem.* **2017**, 225; c) E. López, G. Lonzi, L. A. López, *Organometallics* **2014**, *33*, 5924.

[21] CCDC 1812859 (for **3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[22] The crystallographic study reveals a non-classical intermolecular interaction of the phenolic OH group with the π cloud of the phenyl group. For selected examples of aromatic rings as weak hydrogen-bond acceptors in crystals, see: *An Introduction to Hydrogen Bonding*, G. A. Jeffrey, Oxford University Press, New York, **1997**.

[23] For the alkylation of ferrocene with some benzyl alcohols, see: R. Abdullah, K. Chung, Y.-W. Kim, I. S. Hong, *Bull. Korean Chem. Soc.* **2015**, *36*, 32. This process was reported to occur at 176 °C in molten ferrocene as a solvent. For a related transformation, see: E. W. Neuse, D. S. Trifan, *J. Am. Chem. Soc.* **1962**, *84*, 1850. See also reference [15].

[24] For the sake of comparison, NIH 3 T3 cells were used as normal control cell line.

[25] Ferrocene **3a-Me** was prepared in 62 % isolated yield by methylation of **3a** with methyl iodide in the presence of sodium hydride.

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Trapping *para*-Quinone Methide Intermediates with Ferrocene: Synthesis and Preliminary Biological Evaluation of New Phenol-Ferrocene Conjugates

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Abstract: The reaction of *para*-hydroxybenzyl alcohols with ferrocene in the presence of a catalytic amount of $InCl_3$ provided ferrocenyl phenol derivatives, an interesting class of organometallic compounds with potential applications in medicinal chemistry. This transformation exhibited a reasonable substrate scope delivering the desired products in synthetically useful yields. Evidence of involvement of a *para*-quinone methide intermediate in this coupling process was also provided. Preliminary biological evaluation demonstrated that some of the ferrocene derivatives available by this methodology exhibit significant cytotoxicity against several cancer cell lines with IC_{50} values within the range of 1.07–4.89 μM.

Keywords: ferrocene; phenol; *para*-quinone methides; cytotoxic activity

1. Introduction

Since the discovery of ferrocene in the 1950s [1,2], the interest in this organometallic compound has not declined. In fact, its chemistry remains one of the most active areas of research. Very likely, this enduring interest resides in the fact that many functionalized ferrocene derivatives display a wide number of applications in a diverse range of fields [3–9]. For example, recent investigations have demonstrated the potential of some ferrocene derivatives in medicinal chemistry [10,11]. Particularly, some ferrocene-containing phenols have proved to be of great interest in cancer therapeutics because of their antitumoral activity [12–16]. Among them, a family of ferrocene analogues of hydroxytamoxifen, the so-called ferrocifens (Figure 1a), have been the subject of in-depth investigations showing exceptional cytotoxic activities against some types of breast cancer [17–19]. The mode of action of these organometallic drug candidates has been elucidated by electrochemical and chemical oxidation methods. According to these studies, ferrocenyl quinone methides have been suggested to play a key role in the antiproliferative activity [20–24]. The antitumoral activity of some unconjugated bisphenol derivatives of ferrocene (Figure 1b) has also been evaluated [25,26].

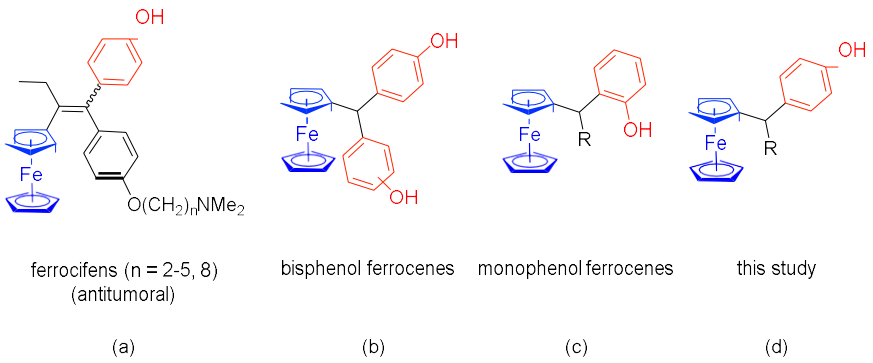


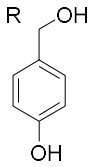
Figure 1. Phenol-ferrocene conjugates: (**a**) Ferrocifen family; (**b**) ferrocene bisphenol derivatives; (**c**) *ortho*-substituted ferrocenyl phenols previously developed in our group; (**d**) *para*-substituted ferrocenyl phenols reported in this study.

In connection with our studies on C–H bond functionalization of ferrocene based on the trapping of highly electrophilic species [27–29], we have recently described the trapping of *ortho*-quinone methide intermediates with ferrocene [30]. Interestingly, some of the ferrocene-containing monophenol derivatives available by this methodology (Figure 1c) display remarkable cytotoxic activity against various cancer cell lines.

In order to elucidate the structural requirements for cytotoxicity and, eventually, to identify more bioactive derivatives, we decided to develop a synthetic methodology for the synthesis of the isomeric *para*-substituted ferrocenylphenol analogues (Figure 1d). Herein, we report the results of this study; specifically, we describe the generation of *para*-quinone methide intermediates and their trapping with ferrocene. Preliminary biological evaluation of some of the functionalized ferrocene derivatives prepared in this study is also disclosed.

2. Results and Discussion

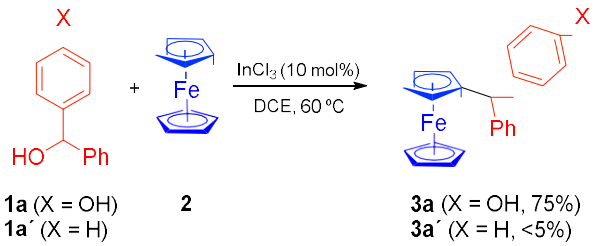
The present study was carried out using easily available *p*-hydroxybenzyl alcohols **1a–l** outlined in Figure 2.



1a (R = Ph)
1b (R = *o*-Tol)
1c (R = *m*-Tol)
1d (R = *p*-Tol)
1e (R = *p*-MeOC$_6$H$_4$)
1f (R = Me)
1g (R = Et)
1h (R = Bu)
1i (R = *i*-Pr)
1j (R = *t*-Bu)
1k (R = allyl)
1l (R = H)

Figure 2. Starting *p*-hydroxybenzyl alcohols **1** used in this work.

For our initial study, *p*-hydroxybenzyl alcohol **1a** was chosen as the model substrate (Scheme 1). On the basis of our previous investigations in the *ortho* series, $InCl_3$ in dichloroethane (DCE) was selected as the catalytic system. Pleasingly, we found that heating a mixture of **1a** (1 equiv.), ferrocene (**2**, 3 equiv.), and $InCl_3$ (10 mol%) in DCE at 60 °C led to complete disappearance of the starting *p*-hydroxybenzyl alcohol after 2 h (checked by thin layer chromatography, TLC). Chromatographic purification (SiO_2, 5:1 hexane ethyl acetate) provided the desired functionalized ferrocene derivative **3a** in a remarkable 75% yield. Interestingly, under otherwise similar conditions, benzydryl alcohol **1a′** was found to be a fruitless reaction partner, thus demonstrating the key role of the phenolic OH group in the reaction course [31,32].



Scheme 1. Trapping of *p*-quinone methides with ferrocene: proof of concept. DCE: dichloroethane.

Ferrocenyl phenol **3a** was characterized by Nuclear Magnetic Resonance (NMR) spectroscopy Moreover, crystals of compound **3a** were obtained from diffusion of pentane into a dichloromethane solution at —20 °C and its molecular structure in the solid state has been determined by single-crysta X-ray diffraction (Figure 3 and Appendix A) [33,34]. The electrochemical behavior of compound **3a** was investigated by cyclic voltammetry (Appendix B).

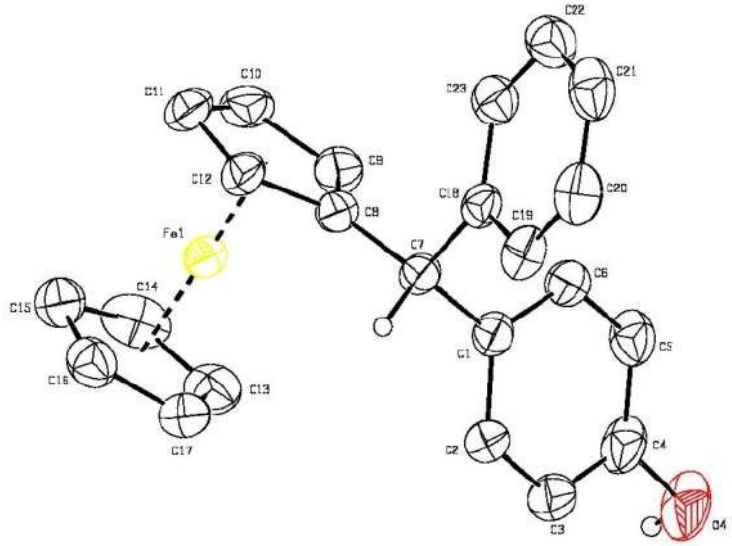
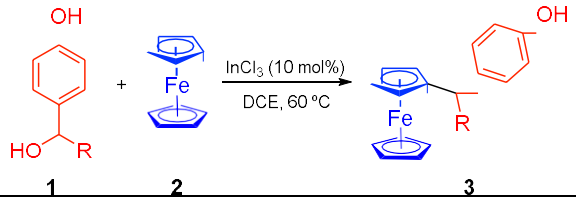


Figure 3. X-ray structure of ferrocene derivative **3a**. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms are excluded, except those bonded to C7 (H7) and O4 (H4O).

With suitable reaction conditions in hand (10 mol% of $InCl_3$, DCE as solvent, 60 °C), a variety of *p*-hydroxybenzyl alcohols were then evaluated for their suitability for this C–H bond functionalization process (Table 1). First, some *p*-hydroxybenzyl alcohols substituted with various ary groups were investigated (entries 2–5). As shown, all three isomeric 4-[hydroxy(tolyl)methyl]pheno derivatives **1b–d** (R = tolyl) served as suitable reaction partners for this process furnishing the desired functionalized ferrocene derivatives **3b–d** in acceptable isolated yields (51–82%, entries 2–4). Similarly *para*-methoxy substituted substrate **1e** (R = *p*-$MeOC_6H_4$) delivered the corresponding product **3e** in moderate isolated yield (48%, entry 5).

Table 1. $InCl_3$-catalyzed reaction of *p*-hydroxybenzyl alcohols **1** and ferrocene (**2**).



1 **2** **3**

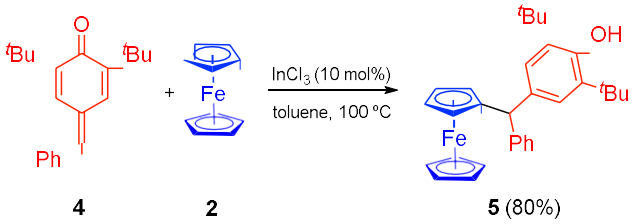
Entry	Substrate	R	3	Yield (%) [a]
1	**1a**	C_6H_5	**3a**	75
2	**1b**	*o*-MeC_6H_4	**3b**	76
3	**1c**	*m*-MeC_6H_4	**3c**	51
4	**1d**	*p*-MeC_6H_4	**3d**	82
5	**1e**	*p*-$MeOC_6H_4$	**3e**	48
6	**1f**	Me	**3f**	62
7	**1g**	Et	**3g**	60
8	**1h**	*n*-Bu	**3h**	42
9	**1i**	*i*-Pr	**3i**	62
10	**1j**	*t*-Bu	**3j**	43
11	**1k**	Allyl	**3k**	44
12	**1l**	H	**3l**	64

[a] Isolated yield after chromatographic purification.

Next, substrates **1f–j** with alkyl groups in the benzylic position were tested (entries 6–10). As shown, primary, secondary and tertiary alkyl groups were well tolerated delivering functionalized ferrocene derivatives **3f–j** in moderate yields (42–62%).

This transformation was compatible with unsaturated functional groups in the benzylic position as demonstrated by the synthesis of ferrocene derivative **3k** in moderate yield when substrate **1k** (R = allyl) was subjected to the standard reaction conditions. Finally, we found that the parent *p*-hydroxybenzyl alcohol **1l** (R = H) is also a viable substrate affording the desired product **3l** in 64% yield (entry 12).

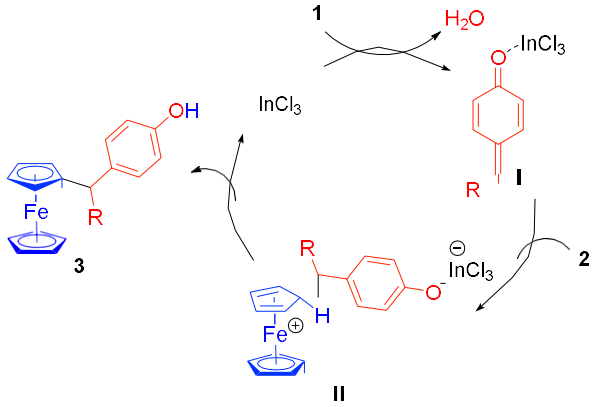
Next, to provide further evidence for the involvement of *p*-quinone methide intermediates in the present coupling, we performed an experiment with a stable *p*-quinone methide. Thus, 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dienone (**4**) and ferrocene (**2**) were subjected to the standard reaction conditions (10 mol% of $InCl_3$, DCE, 60 °C). However, a very low conversion was observed after 24 h very likely due to steric hindrance by the *tert*-butyl groups. Gratifyingly, performing the reaction in toluene at 100 °C enabled the preparation of ferrocene derivative **5** in 80% yield (Scheme 2). Notably, in the absence of $InCl_3$, no reaction occurred at all.



4 **2** **5** (80%)

Scheme 2. $InCl_3$-catalyzed reaction of ferrocene and stable *p*-quinone methide **4**.

Based on these control experiments and on previous related literature precedents, a mechanistic proposal for the reaction of hydroxybenzyl alcohols **1** and ferrocene (**2**) is outlined in Scheme 3. In the present process, the Lewis acid is proposed to play a dual role. Firstly, it would promote the generation of the key quinone methide intermediate through dehydration of hydroxybenzyl alcohol **1**. Subsequent activation of the quinone methide by Lewis acid complexation would provide intermediate **I**. This intermediate, with a high electrophilic character at the exocyclic C=C bond, may be involved in a Friedel-Crafts type electrophilic aromatic substitution [35]. Indeed, 1,6-addition of ferrocene would provide the *s*-complex intermediate **II**, which would evolve to the final product with regeneration of the catalyst [36].



Scheme 3. Mechanism for the $InCl_3$-catalyzed reaction of phenol derivatives **1** and ferrocene (**2**).

Some of the functionalized ferrocene derivatives prepared were evaluated for their cytotoxicity against several cancer cell lines (Table 2). In this preliminary study, ferrocene derivatives **3a** and **3g** were identified as the most active ones [37]. For example, **3a** displayed significant toxicity against A2780 ovarian cancer cell line (IC_{50} of 1.07 μM). Compared with the value previously reported for the *ortho*-isomer (IC_{50} of 2.68 μM), ferrocene derivative **3a** has superior characteristics. Ferrocene **3g** also displayed toxicity against this cell line (IC_{50} of 2.23 μM), although somewhat lower than that found for the *ortho*-analogue (IC_{50} of 1.86 μM). We have also studied the cytotoxicity profile of ferrocene derivatives **3a** and **3g** against A549 lung cancer cells. Both derivatives exhibited moderate cytotoxicity with IC_{50} values of 3.55 and 4.89 μM, respectively. These values are comparable to that previously measured for the *ortho*-isomers (IC_{50} of 2.77 and 5.96 μM, respectively).

Table 2. IC_{50} [μM] values for selected ferrocenyl compounds on different cell lines [a].

	3a	**3g**
A2780	1.07	2.23
A549	3.55	4.89

[a] Measured after 72 h of culture.

3. Materials and Methods

3.1. General

NMR spectra were recorded at room temperature in $CDCl_3$ on a Bruker DPX-300 or Bruker AVANCE-300 MHz instruments (Bruker, Billerica, MA, USA). Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). High-resolution mass spectra were determined on a VG Autospec M mass spectrometer (Waters Corporation, Milford, MA, USA). Cyclic voltammetric studies were performed using a μ-AutoLab type II equipped with GPES 4.9 software (EcoChemie, Utrecht, The Netherlands). All measurements were carried out using a conventional three electrode system in phosphate saline buffer (pH 7.4). A modified carbon paste acted as the working electrode and a Pt wire as a counter electrode. All potentials were referred to a Ag | AgCl | $KCl_{(sat)}$ reference electrode. Experiments were carried out under nitrogen using standard Schlenck techniques. 1,2-Dichloroethane was distilled from CaH_2. Toluene was distilled from sodium-benzophenone ketyl prior to use. TLC was performed on aluminum-backed plates coated with silica gel 60 with F_{254} indicator. Flash column chromatography was carried out on silica gel (230–240 mesh). The solvents used in column chromatography, hexane and ethyl acetate, were obtained from commercial suppliers and used without further purification.

p-Hydroxybenzyl alcohols **1a–k** were prepared by reaction of 4-hydroxybenzaldehyde with the corresponding Grignard reagents following a literature procedure [38]. *p*-Hydroxybenzyl alcohol **1l** was obtained by the reaction of 4-hydroxybenzaldehyde with $NaBH_4$ [39]. 4-Benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dienone (**4**) was prepared from 2,6-di-*tert*-butylphenol and benzaldehyde according to a literature procedure [40]. Ferrocene (**2**) was commercially available and used without further purification.

3.2. *General Procedure for the Synthesis of Ferrocene Derivatives* **3a–l**

$InCl_3$ (4.4 mg, 0.02 mmol, 10 mol%) was added to a solution of *p*-hydroxybenzyl alcohols **1** (0.2 mmol) and ferrocene **2** (111.6 mg, 0.6 mmol) in 1,2-dichloroethane (2 mL). The mixture was stirred at 60 °C for 2–14 h (disappearance of **1** checked by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, mixtures of hexanes/ethyl acetate). Two fractions were collected. The first fraction was unreacted ferrocene and the second one was the corresponding functionalized ferrocene derivative **3**. Crystals of compound **3a** suitable for X-ray analysis were obtained from diffusion of pentane into dichloromethane at −20 °C. Copies of ^{1}H- and ^{13}C-NMR spectra are provided in the Supplementary Materials.

4-[(Ferrocenyl)(phenyl)methyl]phenol (**3a**): yellow solid; melting point (m.p.) 63–64 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): 4.02 (s, 2H, Cp), 4.05 (s, 5H, Cp), 4.19 (s, 2H, Cp), 4.83 (s, 1H, OH), 5.13 (s, 1H, CH), 6.76 (d, *J* = 8.1 Hz, 2H, Ar), 7.07 (d, *J* = 8.1 Hz, 2H, Ar), 7.19–7.33 (m, 5H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 51.0 (CH), 67.59 (CH), 67.63 (CH), 68.7 (CH), 92.0 (C), 114.9 (CH), 126.1 (CH), 128.1 (CH), 128.7 (CH), 129.9 (CH), 137.6 (C), 145.3 (C), 153.7 (C); HRMS (EI) calculated for $[C_{23}H_{20}FeO]^+$ (M^+): 368.0858, found 368.0856.

4-[(Ferrocenyl)(2-methylphenyl)methyl]phenol (**3b**): yellow solid; m.p. 66–67 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): 2.25 (s, 3H, CH_3), 3.81 (s, 1H, Cp), 4.07 (s, 5H, Cp), 4.16–4.12 (m, 1H, Cp), 4.20–4.16 (m, 1H, Cp), 4.76 (s, 1H, Cp), 5.25 (s, 1H, CH), 6.78 (d, *J* = 8.6 Hz, 2H, Ar), 6.96 (s, 1H, OH), 7.09–7.14 (m, 6H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 20.3 (CH_3), 47.9 (CH), 67.4 (CH), 68.5 (CH), 68.8 (CH), 69.1 (CH), 69.9 (CH), 93.4 (C), 115.1 (CH), 125.9 (CH), 126.5 (CH), 128.6 (CH), 130.5 (CH), 130.9 (CH), 135.5 (C), 136.0 (C), 144.7 (C), 154.1 (C); HRMS (EI) calculated for $[C_{24}H_{22}FeO]^+$ (M^+): 382.1015, found 382.1009.

4-[(Ferrocenyl)(3-methylphenyl)methyl]phenol (**3c**): yellow solid; m.p. 72–73 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): 2.32 (s, 3H, CH_3), 4.02–4.05 (m, 7H, Cp), 4.18 (m, 2H, Cp), 4.62 (s, 1H, OH), 5.06 (s, 1H, CH), 6.75 (d, *J* = 8.4 Hz, 2H, Ar), 7.00–7.17 (m, 6H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 21.5 (CH_3), 50.9 (CH),

67.7 (CH), 68.9 (CH), 92.3 (C), 114.7 (CH), 120.5 (CH), 125.6 (CH), 126.8 (CH), 127.9 (CH), 129.4 (CH), 129.9 (CH), 137.5 (C), 145.2 (C), 153.7 (C); HRMS (EI) calculated for $[C_{24}H_{22}FeO]^+$ (M^+): 382.1015, found 382.1011.

4-[(Ferrocenyl)(4-methylphenyl)methyl]phenol (**3d**): yellow solid; m.p. 64–65 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): 2.33 (s, 3H, CH_3), 3.99 (m, 2H, Cp), 4.03 (s, 5H, Cp), 4.17 (m, 2H, Cp), 4.73 (s, 1H, OH), 5.08 (s, 1H, CH), 6.74 (d, *J* = 8.5 Hz, 2H, Ar), 7.04–7.11 (m, 6H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 21.4 (CH_3), 51.0 (CH), 67.9 (CH), 69.1 (CH), 92.6 (C), 115.2 (CH), 128.9 (CH), 129.1 (CH), 130.2 (CH), 135.9 (C), 138.2 (C), 142.7 (C), 154.1 (C); HRMS (EI) calculated for $[C_{24}H_{22}FeO]^+$ (M^+): 382.1015, found 382.1009.

4-[(Ferrocenyl)(4-methoxyphenyl)methyl]phenol (**3e**): yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.80 (s, 3H, OMe), 3.98 (s, 2H, Cp), 4.04 (s, 5H, Cp), 4.17 (s, 2H, Cp), 4.72 (s, 1H, CH), 5.06 (s, 1H, OH), 6.79–6.73 (m, 2H, Ar), 6.80–6.84 (m, 2H, Ar), 7.03–7.10 (m, 4H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 50.5 (CH), 55.7 (CH_3), 68.0 (CH), 69.2 (CH), 92.9 (C), 113.8 (CH), 115.2 (CH), 130.0 (CH), 130.2 (CH), 138.1 (C), 138.3 (C), 154.1 (C), 158.2 (C); HRMS (EI) calculated for $[C_{24}H_{22}FeO_2]^+$ (M^+): 398.0964, found 398.0972.

4-(1-Ferrocenylethyl)phenol (**3f**): yellow solid; m.p. = 95–96 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): 1.57 (d, *J* = 7.2 Hz, 3H, CH_3), 3.90 (q, *J* = 7.2 Hz, 1H, CH), 4.09 (s, 1H, Cp), 4.10–4.18 (m, 8H, Cp), 4.63 (s, 1H, OH), 6.74 (d, *J* = 8.6 Hz, 2H, Ar), 7.05 (d, *J* = 8.6 Hz, 2H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 23.1 (CH_3), 39.3 (CH), 66.7 (CH), 67.3 (CH), 67.9 (CH), 68.2 (CH), 69.0 (CH), 95.1 (C), 115.4 (CH), 128.6 (CH), 140.4 (C), 153.9 (C); HRMS (EI) calculated for $[C_{18}H_{18}FeO]^+$ (M^+): 306.0702, found 306.0701. Ferrocene **3f** is a known compound; our characterization data match those previously reported in the literature [25].

4-(1-Ferrocenylpropyl)phenol (**3g**): yellow solid; m.p. = 87–88 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): 0.85 (t, *J* = 7.4 Hz, 3H, CH_3), 1.67–1.83 (m, 1H, CH_2), 2.07–2.14 (m, 1H, CH_2), 3.41–3.46 (dd, *J* = 10.7 and 4.3 Hz, 1H, CH), 4.06 (s, 1H, Cp), 4.05–4.10 (m, 7H, Cp), 4.17 (s, 1H, Cp), 4.73 (s, 1H, OH), 6.78 (d, *J* = 8.5 Hz, 2H, Ar), 7.06 (d, *J* = 8.5 Hz, 2H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 12.7 (CH_3), 30.0 (CH_2), 47.0 (CH), 66.8 (CH), 66.9 (CH), 67.3 (CH), 67.4 (CH), 68.6 (CH), 94.8 (C), 114.9 (CH), 129.0 (CH), 137.8 (C), 153.6 (C); HRMS (EI) calculated for $[C_{19}H_{20}FeO]^+$ (M^+): 320.0858, found 320.0853.

4-(1-Ferrocenylpentyl)phenol (**3h**): yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89 (t, *J* = 7.0 Hz, 3H, CH_3), 1.16–1.40 (m, 4H, CH_2), 1.70–1.82 (m, 1H, CH_2), 2.01–2.08 (m, 1H, CH_2), 3.53 (dd, *J* = 10.8 and 4.3 Hz, 1H, CH), 3.95 (s, 1H, Cp), 4.05–4.11 (m, 7H, Cp), 4.18 (s, 1H, Cp), 4.80 (s, 1H, OH), 6.76 (d, *J* = 8.3 Hz, 2H, Ar), 7.06 (d, *J* = 8.3 Hz, 2H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 22.7 (CH_2), 30.2 (CH_2), 36.8 (CH_2), 45.1 (CH), 66.8 (CH), 66.9 (CH), 67.3 (CH), 67.4 (CH), 68.6 (CH), 95.1 (C), 114.9 (CH), 128.9 (CH), 138.1 (C), 153.6 (C); HRMS (EI) calculated for $[C_{21}H_{24}FeO]^+$ (M^+): 348.1171, found 348.1184.

4-[1-(Ferrocenyl)(2-methyl)propyl]phenol (**3i**): yellow solid; m.p. = 95–96 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): 0.74 (d, *J* = 6.6 Hz, 3H, CH_3), 0.92 (d, *J* = 6.6 Hz, 3H, CH_3), 1.97–2.03 (m, 1H, CH), 3.08 (d, *J* = 8.7 Hz, 1H, CH), 3.94 (s, 5H, Cp), 4.13–4.27 (m, 4H, Cp), 4.74 (s, 1H, OH), 6.75 (d, *J* = 8.3 Hz, 2H, Ar), 7.05 (d, *J* = 8.3 Hz, 2H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 21.7 (CH_3), 22.2 (CH_3), 53.1 (CH), 66.7 (CH), 67.2 (CH), 68.4 (CH), 69.3 (CH), 70.4 (CH), 94.7 (C), 114.9 (CH), 129.6 (CH), 137.8 (C), 153.5 (C); HRMS (EI) calculated for $[C_{20}H_{22}FeO]^+$ (M^+): 334.1015, found 334.1012.

4-[1-(Ferrocenyl)(2,2-dimethyl)propyl]phenol (**3j**): yellow solid; m.p. = 105–106 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84 (s, 9H, CH_3), 3.23 (s, 1H, CH), 3.73 (s, 5H, Cp), 4.07 (s, 1H, Cp), 4.14 (d, *J* = 6.2 Hz, 2H, Cp), 4.24 (s, 1H, Cp), 4.93 (s, 1H, OH), 6.84 (d, *J* = 8.4 Hz, 2H, Ar), 7.27–7.29 (m, 2H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 28.7 (CH_3), 35.2 (C), 57.3 (CH), 65.7 (CH), 68.0 (CH), 68.1 (CH), 68.5 (CH), 69.2 (CH), 72.1 (CH), 90.4 (C), 114.2 (CH), 132.0 (CH), 136.9 (C), 153.6 (C); HRMS (EI) calculated for $[C_{21}H_{24}FeO]^+$ (M^+): 348.1171, found 348.1182.

4-[1-(Ferrocenyl)but-3-enyl]phenol (**3k**): yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 2.53–2.62 (m, 1H, CH_2), 2.80–2.89 (m, 1H, CH_2), 3.65 (dd, *J* = 10.5 and 4.7 Hz, 1H, CH), 4.08 (s, 1H, Cp), 4.13–4.10 (m, 7H, Cp), 4.19 (s, 1H, Cp), 4.67 (s, 1H, OH), 4.93–5.04 (m, 2H, =CH_2), 5.76–5.77 (m, 1H, =CH), 6.76 (d, *J* = 8.6 Hz, 2H, Ar), 7.06 (d, *J* = 8.6 Hz, 2H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 12.7 (CH_3), 30.0 (CH_2), 47.0 (CH), 66.8 (CH), 66.9 (CH), 67.3 (CH), 67.4 (CH), 68.6 (CH), 94.8 (C), 114.9 (CH), 129.0 (CH), 137.8 (C), 153.6 (C); HRMS (EI) calculated for $[C_{20}H_{20}FeO]^+$ (M^+): 332.0858, found 332.0855.

4-(Ferrocenylmethyl)phenol (**3l**): yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.64 (s, 2H, CH_2), 4.11 (s, 4H, Cp), 4.15 (s, 5H, Cp), 4.84 (s, 1H, OH), 6.75 (d, *J* = 8.2 Hz, 2H, Ar), 7.02 (d, *J* = 8.2 Hz, 2H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 45.2 (CH_2), 77.6 (CH), 78.7 (CH), 78.8 (CH), 98.7 (C), 125.1 (CH), 139.6 (CH), 144.0 (C), 163.7 (C); HRMS (EI) calculated for $[C_{17}H_{16}FeO]^+$ (M^+): 292.0545, found 292.0524. Ferrocene **3l** is a known compound [25].

3.3. Synthesis of Ferrocene Derivative **5**

$InCl_3$ (4.4 mg, 0.02 mmol, 10 mol%) was added to a solution of 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dienone **4** (58.9 mg, 0.2 mmol) and ferrocene **2** (111.6 mg, 0.6 mmol) in toluene (2 mL). The mixture was stirred at 100 °C for 6 h (disappearance of **4** checked by TLC). Then, the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate 5:1) to yield ferrocene derivative **5** (76.9 mg, 80%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 1.44 (s, 18H, CH_3), 3.98–3.99 (m, 1H, Cp), 4.01 (s, 5H, Cp), 4.03–4.04 (m, 1H, Cp), 4.16–4.17 (m, 1H, Cp), 4.91 (s, 1H, Cp), 5.06 (s, 1H, CH), 5.09 (s, 1H, OH), 7.04 (s, 2H, Ar), 7.18–7.21 (m, 3H, Ar), 7.26–7.29 (m, 2H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$): 30.0 (CH_3), 34.4 (CH), 51.8 (CH), 67.3 (CH), 67.6 (CH), 68.6 (CH), 68.7 (CH), 68.8 (CH), 92.8 (C), 125.4 (CH), 125.8 (C), 127.9 (CH), 128.6 (CH), 135.1 (C), 135.4 (C), 143.8 (C), 151.9 (C); HRMS (EI) calculated for $[C_{31}H_{36}FeO]^+$ (M^+): 480.2110, found 480.2124.

3.4. Cytotoxic Assays

Cell Counting Kit-8 (CCK-8) from Sigma-Aldrich (Madrid, Spain) was used according to the protocol provided by the company. The A2780 and A549 cell lines were used in this preliminary study. First, cell lines were cultured for 7 days in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% (*v*/*v*) fetal bovine serum (FBS). Then, cells were seeded into a 96-well flat-bottom culture plate at a cell density of 500–2000 cells/well and incubated for 24 h in the same medium (DMEM/10% FBS). After that, 10 μL of a solution of the corresponding ferrocene derivative at different concentrations were added and the cells were incubated for 72 h. Then, 10 μL of the CCK-8 solution were added to each well of the plate. After 2 h of incubation the absorbance at 450 nm was recorded using a BioTek ELx800 Absorbance Microplate Reader (BioTek, Bad Friedrichshall, Germany). Measurements were performed in triplicate, and each experiment was repeated three times. The IC_{50} values (μm) were estimated by treatment of the data obtained with the statistical program GraphPad Prism5 (version 5.04).

4. Conclusions

Guided by earlier work from our group, we have developed a convenient synthesis of *para*-substituted phenol derivatives containing a ferrocenyl moiety. Salient features of our protocol include (i) easy availability of the required starting materials, (ii) synthetically useful yields, and (iii) mild reaction conditions. This C–H bond functionalization of ferrocene relies on the generation of a *para*-quinone methide intermediate that, activated by Lewis acid complexation, would serve as electrophilic partner in an aromatic electrophilic substitution. Preliminary biological evaluation revealed that some of the ferrocene derivatives available by this protocol display significant cytotoxicity against ovarian and lung cancer cell lines. Further studies aimed at the preparation of new ferrocene derivatives with enhanced antiproliferative properties are being pursued in our laboratory.

Supplementary Materials: Supplementary Materials available online: Copies of ^{1}H- and ^{13}C-NMR spectra, X-Ray crystallography (printcif and checkcif).

Author Contributions: L.A.L. conceived the experiments; S.G.-P. and E.L. designed and performed the experiments; J.B. performed the X-ray crystallographic study; N.d.-l.-S.-A. performed the voltammetry study; L.A.L., J.B. and N.d.-l.-S.-A. wrote the paper.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. Crystal Data for Ferrocene Derivative 3a

Crystal Data for $C_{23}H_{20}FeO$ (M_r = 368.24 g/mol): monoclinic, space group $P2_1/n$ (No. 14), a = 15.662(1) Å, b = 6.0219(3) Å, c = 18.786(1) Å, β = 96.990(6)°, V = 1758.6(2) Å^3, Z = 4, T = 299 K, μ(Cu$K\alpha$)= 6.91 mm^{-1}, D_x = 1.391 g/cm^3, 8336 measured reflections (3.5° < θ < 69.6°), 3254 independent reflections, 2641 observed reflections ($I > 2\sigma(I)$), R_{int} = 0.045. Final $R[F^2 > 2\sigma(F^2)]$ was 0.079 and $wR(F^2)$ = 0.255.

Appendix B. Electrochemical Study for Ferrocene Derivative 3a

Compound **3a** was studied by cyclic voltammetry (CV). All potentials were referred to a Ag|AgCl|KCl$_{(sat)}$ reference electrode. The ferrocene/ferrocenium couple (I_a/I_c) is clearly observed at a formal potential, $E^{\circ\prime}$ = 0.352 V (Figure A1a). The anodic peak current is higher than the cathodic one indicating that some ferrocenium ions diffuse from the carbon paste electrode to the bulk solution due to the positive charge of the cation. Nucleation at potentials ~0.450 V points out to a dissimilar electrochemical behavior with other structurally related compounds. When the potential is swept up to +0.6 V, a second redox process (II_a/II_c) appears causing the decrease of I_a (Figure A1b). The reduction of ferrocenium species (I_c) remains visible but progressively shifted towards less positive potentials in subsequent scans. Process II_a at about +0.570 V is clear and well-shaped but process II_c at 0.426 V is partially overlapped with I_c. Of note, a notably increase in the non-faradaic current is observed. When the potential is extended to +1.3 V, additional oxidation reactions take place (see the rising anodic current) probably associated to phenolic compounds. Only one reduction process is observed as a result of I_c and II_c overlapping (Figure A1c). The potential of both oxidation and reduction peaks shift to more extreme potentials which indicates that the process is irreversible. The origin of the irreversibility might be the formation of non-conducting products on the electrode surface that hinder the electron transfer. The appearance of resistance affecting the CV shape strongly supports this explanation.

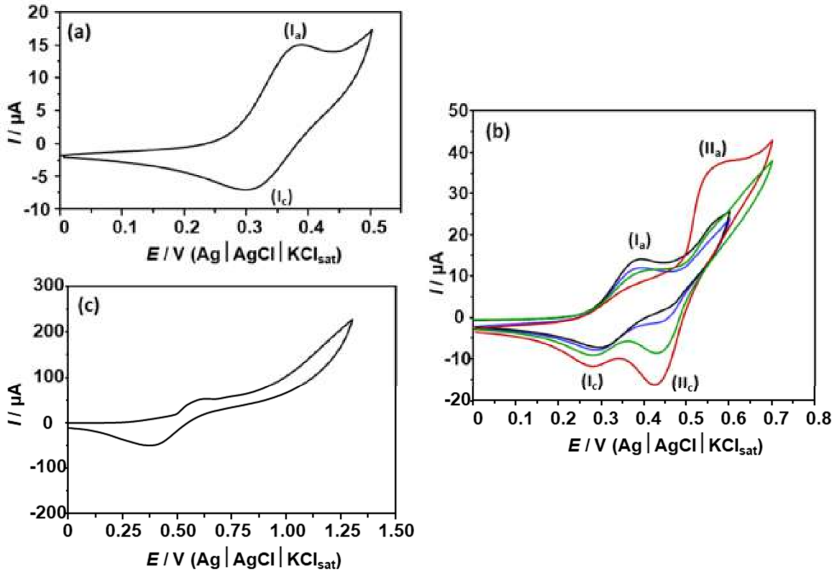


Figure A1. Cyclic voltammetry of compound **3a** incorporated to the carbon paste electrode in phosphate saline buffer (pH 7.4). Scan rate = 50 mV/s. Potential scan from 0 V to +0.5 V; (**a**) +0.6 (first scan, black; second scan, blue) and +0.7 (first scan, green; second scan, red) (**b**) and +1.3 V (**c**).

References and Notes

1. Kealy, T.J.; Pauson, P.L. A New Type of Organo-Iron Compound. *Nature* **1951**, *168*, 1039–1040. [CrossRef]
2. Miller, S.A.; Tebboth, J.A.; Tremaine, J.F. Dicyclopentadienyliron. *J. Chem. Soc.* **1952**, 632–635. [CrossRef]
3. Štěpnička, P. *Ferrocenes: Ligands, Materials and Biomolecules*; Wiley: Chichester, UK, 2008.
4. Phillips, E.S. *Ferrocenes: Compounds, Properties and Applications*; Nova Science Publishers: New York, NY, USA, 2011.
5. *Ferrocenes. Homogeneous Catalysis. Organic Synthesis. Materials Science*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, Germany, 1995.
6. *Chiral Ferrocenes in Asymmetric Catalysis*; Dai, L.-X., Hou, X.-L., Eds.; Wiley-VCH: Weinheim, Germany, 2009.
7. Astruc, D. Why is Ferrocene so Exceptional? *Eur. J. Inorg. Chem.* **2017**, *1*, 6–29. [CrossRef]
8. Arrayás, R.G.; Adrio, J.; Carretero, J.C. Recent Applications of Chiral Ferrocene Ligands in Asymmetric Catalysis. *Angew. Chem. Int. Ed.* **2006**, *45*, 7674–7715. [CrossRef] [PubMed]
9. Van Staveren, D.R.; Metzler-Nolte, N. Bioorganometallic Chemistry of Ferrocene. *Chem. Rev.* **2004**, *104*, 5931–5986. [CrossRef] [PubMed]
10. Patra, M.; Gasser, G. The medicinal chemistry of ferrocene and its derivatives. *Nat. Rev. Chem.* **2017**, *1*, 066. [CrossRef]
11. Dive, D.; Biot, C. Ferroquine as an Oxidative Shock Antimalarial. *Curr. Top. Med. Chem.* **2014**, *14*, 1684–1692. [CrossRef] [PubMed]
12. Braga, S.S.; Silva, A.M.S. A New Age for Iron: Antitumoral Ferrocenes. *Organometallics* **2013**, *32*, 5626–5639. [CrossRef]
13. Melendez, E. Metallocenes as target specific drugs for cancer treatment. *Inorg. Chim. Acta* **2012**, *393*, 36–52. [CrossRef] [PubMed]
14. Ornelas, C. Application of ferrocene and its derivatives in cancer research. *New J. Chem.* **2011**, *35*, 1973–1985. [CrossRef]

15. Schatzschneider, U.; Metzler-Nolte, N. New Principles in Medicinal Organometallic Chemistry. *Angew. Chem. Int. Ed.* **2006**, *45*, 1504–1507. [CrossRef] [PubMed]
16. Gasser, G.; Ott, I.; Metzler-Nolte, N. Organometallic Anticancer Compounds. *J. Med. Chem.* **2011**, *54*, 3–25. [CrossRef] [PubMed]
17. Jaouen, G.; Vessières, A.; Top, S. Ferrocifen type anti cancer drugs. *Chem. Soc. Rev.* **2015**, *44*, 8802–8817. [CrossRef] [PubMed]
18. Nguyen, A.; Vessières, A.; Hillard, E.A.; Top, S.; Pigeon, P.; Jaouen, G. Ferrocifens and ferrocifenols as new potential weapons against breast cancer. *Chimia* **2007**, *61*, 716–724. [CrossRef]
19. Vessières, A. Metal carbonyl tracers and the ferrocifen family: Two facets of bioorganometallic chemistry. *J. Organomet. Chem.* **2013**, *734*, 3–16. [CrossRef]
20. Hillard, E.A.; Vessières, A.; Jaouen, G. Ferrocene functionalized endocrine modulators as anticancer agents. *Top. Organomet. Chem.* **2010**, *32*, 81–117.
21. Hillard, E.; Vessières, A.; Thouin, L.; Jaouen, G.; Amatore, C. Ferrocene-mediated proton-coupled electron transfer in a series of ferrocifen-type breast-cancer drug candidates. *Angew. Chem. Int. Ed.* **2006**, *45*, 285–290. [CrossRef] [PubMed]
22. Hamels, D.; Dansette, P.M.; Hillard, E.A.; Top, S.; Vessières, A.; Herson, P.; Jaouen, G.; Mansuy, D. Ferrocenyl quinone methides as strong antiproliferative agents: Formation by metabolic and chemical oxidation of ferrocenyl phenols. *Angew. Chem. Int. Ed.* **2009**, *48*, 9124–9126. [CrossRef] [PubMed]
23. Messina, P.; Labbé, E.; Buriez, O.; Hillard, E.A.; Vessières, A.; Hamels, D.; Top, S.; Jaouen, G.; Frapart, Y.M.; Mansuy, D.; et al. Deciphering the activation sequence of ferrociphenol anticancer drug candidates. *Chem. Eur. J.* **2012**, *18*, 6581–6587. [CrossRef] [PubMed]
24. Wang, Y.; Pigeon, P.; Top, S.; McGlinchey, M.J.; Jaouen, G. Organometallic antitumor compounds: ferrocifens as precursors to quinone methides. *Angew. Chem. Int. Ed.* **2015**, *54*, 10230–10233. [CrossRef] [PubMed]
25. Hillard, E.; Vessières, A.; Le Bideau, F.; Plazuk, D.; Spera, D.; Huché, M.; Jaouen, G. A Series of Unconjugated Ferrocenyl Phenols: Prospects as Anticancer Agents. *Chem. Med. Chem.* **2006**, *1*, 551–559. [CrossRef] [PubMed]
26. Plazuk, D.; Vessières, A.; Le Bideau, F.; Jaouen, G.; Zakrzewski, J. Synthesis of Benzyl- and Benzhydrylferrocenes via Friedel-Crafts Alkylation of Ferrocene. Access to Ferrocenyl Bisphenols with High Affinities for Estrogen Receptors. *Tetrahedron Lett.* **2004**, *45*, 5425–5427. [CrossRef]
27. López, E.; Lonzi, G.; López, L.A. Gold-Catalyzed C-H Bond Functionalization of Metallocenes: Synthesis of Densely Functionalized Ferrocene Derivatives. *Organometallics* **2014**, *33*, 5924–5927. [CrossRef]
28. López, E.; Borge, J.; López, L.A. Gold-Catalyzed Intermolecular Formal Insertion of Aryldiazo Esters into Cp-H Bonds of Iron and Ruthenium Metallocenes. *Chem. Eur. J.* **2017**, *23*, 3091–3097. [CrossRef] [PubMed]
29. López, E.; Suárez, T.; Ballesteros, A.; López, L.A. Gold(I)-Catalyzed Reaction of Ferrocene and Propargylic Esters: Synthesis of Functionalized Ferrocene Derivatives. *Eur. J. Inorg. Chem.* **2017**, 225–228. [CrossRef]
30. González-Pelayo, S.; López, E.; Borge, J.; de-los-Santos-Álvarez, N.; López, L.A. Ferrocene-Decorated Phenol Derivatives by Trapping of *ortho*-Quinone Methide Intermediates with Ferrocene. *Eur. J. Org. Chem.* **2018**. [CrossRef]
31. The Lewis acid-catalyzed monoalkylation of ferrocene with some benzyl alcohols has been reported. This process takes place in molten ferrocene as solvent at high temperature (176 °C): Abdullah, R.; Chung, K.; Kim, Y.-W.; Hong, I.S. An Efficient Synthesis of Mono-Substituted Benzyl Ferrocene Derivatives. *Bull. Korean Chem. Soc.* **2015**, *36*, 32–35. [CrossRef]
32. For a similar methodology for the alkylation of ferrocene, see: Neuse, E.W.; Trifan, D.S. Alkylation of Ferrocene with ⇂-Aryl Alcohols. *J. Am. Chem. Soc.* **1962**, *84*, 1850–1856.
33. COD 3000199 Contains the Supplementary Crystallographic Data for This Paper. These Data Can Be Obtained Free of Charge via. See also Supplementary Materials. Available online: http://www.crystallography.net/search.html (accessed on 30 May 2018).
34. A detailed analysis revealed a non-classical intermolecular interaction of the phenolic OH group with the ↑ cloud of the aromatic ring. For selected examples of aromatic rings as weak hydrogen bond acceptors in crystals, see: Jeffrey, G.A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, NY, USA, 1997.
35. Seminal contribution on Friedel-Crafts acylation of ferrocene: Woodward, R.B.; Rosenblum, M.; Whiting, M.C. A new aromatic system. *J. Am. Chem. Soc.* **1952**, *74*, 3458–3459. [CrossRef]

36. For a recent related arylation process involving electron-rich arenes, see: Gao, S.; Xu, X.; Yuan, Z.; Zhou, H.; Yao, H.; Lin, A. 1,6-Addition arylation of *para*-quinone methides: An approach to unsymmetrical triarylmethanes. *Eur. J. Org. Chem.* **2016**, *2016*, 3006–3012. [CrossRef]
37. In this study, NIH 3T3 cells were used as normal control cell line.
38. Wong, Y.F.; Wang, Z.; Sun, J. Chiral phosphoric acid catalyzed asymmetric addition of naphthols to *para*-quinone methides. *Org. Biomol. Chem.* **2016**, *14*, 5751–5754. [CrossRef] [PubMed]
39. McNulty, J.; McLeod, D. A scalable process for the synthesis of (*E*)-Pterostilbene involving aqueous Wittig olefination chemistry. *Tetrahedron Lett.* **2013**, *54*, 6303–6306. [CrossRef]
40. Chu, W.-D.; Zhang, L.-F.; Bao, X.; Zhao, X.-H.; Zeng, C.; Du, J.-Y.; Zhang, G.-B.; Wang, F.-X.; Ma, X.-Y.; Fan, C.-A. Asymmetric catalytic 1,6-conjugate addition/aromatization of *para*-quinone methides: Enantioselective introduction of functionalized diarylmethine sterogenic centers. *Angew. Chem. Int. Ed.* **2013**, *52*, 9229–9233. [CrossRef] [PubMed]

Sample Availability: Samples of the compounds are available from the authors.

Part B The reaction of ferrocene and ruthenocene with three-membered-ring systems

B.1. Reaction of D-A cyclopropanes and ferrocene:

B.1.1. Introduction and Objective

In organic chemistry, ring strain release has been one of the most widely used strategies to enable synthetically useful transformations.[103] In this field, cyclopropane derivatives have arguably played a key role. In fact, impressive progress in developing synthetic methodologies using cyclopropane derivatives as building blocks has been made in recent decades.[104]

Donor-acceptor (D-A) cyclopropanes are a class of particularly useful cyclopropane reagents.[105] The cooperative effect of the vicinal donor and acceptor groups present in their structure provides unique reactivity profiles that have been recently exploited in a wealth of synthetic applications. Specifically, D-A cyclopropanes have been widely used as masked 1,3-zwitterionic species because their marked tendency to undergo heterolytic cleavage of the highly polarized carbon-carbon bond between the carbon atoms bearing the donor and acceptor groups.

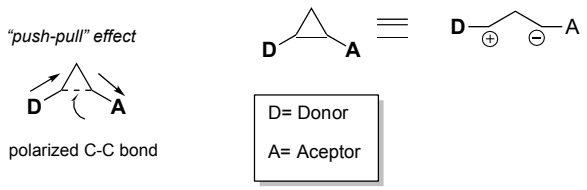


Figure 1: Zwitterionic relationship in D-A cyclopropanes.

[103] For a review on the concept of ring strain and the implications in Organic Chemistry, see: K. B. Wiberg, *Angew.Chem. Int. Ed. Engl.* **1986**, *25*, 312-322.

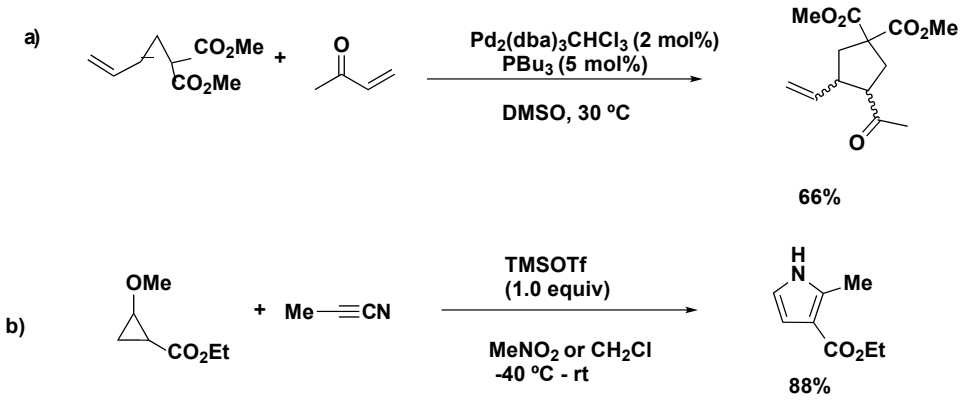
[104] a) A. de Meijire, Small Ring Compounds in Organic Synthesis VI Ed.;Topics in Current Chemistry, Vol.207; Springer: Berlin, **2000**; b) A. Meijere, Bonding Properties of Cyclopropane and TheirChemical Consequences. *Angew. Chem., Int. Ed*. *Engl*. **1979**,*18,* 809-886; c) P. Tang, Y. Qin, *Synthesis,* **2012**, *44*, 2969-2984.

[105] For representative reviews on the chemistry of donor-acceptor cyclopropanes, see: a) B. L. Pagenkopf, N. Vemula, *Eur. J. Org. Chem.* **2017**, 2561-2567; b) M. A. Kerr, *Isr. J. Chem.* **2016**, *56*, 476-487; c) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**,***13***, 655-671; d) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem.* **2014**, *126*, 5608-5628; *Angew. Chem. Int. Ed.* **2014**, *53*, 5504-5523; e) M. A. Cavitt, L. H. Phun, S. France**,** *Chem. Soc. Rev.* **2014**, *43*, 804-818; f) F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano, J. Waser, *Chem. Commun.* **2014**, *50*, 10912-10928; g) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151-1196.

On the basis of this 1,3-zwitterionic relationship, D-A cyclopropanes can undergo regioselective formal (3+n) cycloadditions with compounds containing polarized multiple bonds.

In particular, (3+2) cycloadditions have been widely explored with different alkenes, alkynes, carbonyls, heterocumulenes and others as a methodology for the synthesis of five membered carbo- and heterocyclic compounds.[106]

For example, Tsuji and co-workers reported the Pd-catalyzed cycloaddition of vinylciclopropanes with methyl vinyl ketone to give the corresponding cyclopentane.[107] Moreover, there are examples using nitriles, which allow the synthesis of pyrrol derivatives through cycloaddition reactions.[108]



Scheme 1: (3+2) Cycloaddition reactions of D-A cyclopropanes.

Some examples of (3+3) and (3+4) cycloadditions are also known.[109] For example, Trushkow and Ivanova recently reported the first example of (3+3) annulation of two different three-

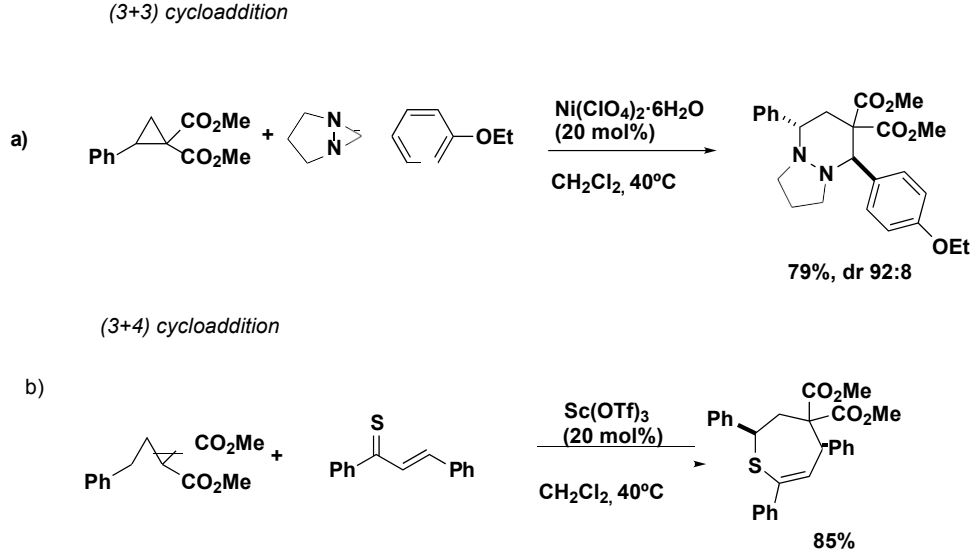
[106] Selected formal (3+2) cycloadditions: a) D. Perrotta, M.-M. Wan, J. Waser, *Angew. Chem.* **2018**, *130*, 5214-5217; *Angew. Chem. Int. Ed*. **2018**, *57*, 5120-5123; b) A. Augustin, M. Busse, P. G. Jones, D. B. Werz, *Org. Lett.* **2018**, *20*, 820-823; d) L. K. B. Garve, A. Kreft, P. G. Jones, D. B. Werz, *J. Org. Chem.* **2017**, *82*, 9235-9242; e) A. Augustin, M. Sensse, P. G. Jones, D. B. Werz, *Angew. Chem.* **2017**, *129*, 14481-14485; *Angew. Chem. Int. Ed.* **2017**, *56*, 14293-14296; f) S. Chakrabarty, I. Chatterjee, B. Wibbeling, C. G. Daniliuc, A. Studer, *Angew. Chem.* **2014**, *126*, 6074-6078; *Angew. Chem. Int. Ed.* **2014**, *53*, 5964-5968; g) B. Cui, J. Ren, Z. Wang, *J. Org. Chem.* **2014**, *79*, 790-796; h) A. F. G. Goldberg, N. R. O'Connor, R. A. Craigll, B. M. Stoltz, *Org. Lett.* **2012**, *14*, 5314–5317; i) X. Qi, J. M. Ready, *Angew. Chem.* **2008**, *120*, 7176-7178; *Angew. Chem. Int. Ed.* **2008**, *47*, 7068-7070; j) C. A. Carson, M. A. Kerr, *J. Org. Chem*. **2005**, *70*, 8242-8244; k) M. Yu, B. L. Pagenkopf, *J. Am. Chem. Soc.* **2003**, *125*, 8122-8123; l) M. Yu, B. L. Pagenkopf, *Org. Lett.* **2003**, *5*, 5099-5101.

[107] I. Shimizu, Y. Ohashi, J. Tsuji, *Tetrahedron Lett.* **1928**, *23*, 3825-3828.

[108] M. Yu, B. L. Pagenopf, *Org. Lett.* **2003**, *5*, 5099-5101.

[109] Seminal work on (3+3) cycloadditions of D-A cyclopropanes: a) I. S. Young, M. A. Kerr, *Angew. Chem.* **2003**, *115*, 3131-3134; *Angew. Chem. Int. Ed.* **2003**, *42*, 3023-3026. For representative (4+3) cycloaddition of D-A cyclopropanes: a) Z.-H. Wang, H.-H. Zhang, D.-M. Wang, P.-F. Xu, Y.-C. Luo, *Chem. Commun.* **2017**, *53*, 8521-8524; b) H. Xu, J.-L. Hu, L. Wang, S. Liao, Y. Tang, *J. Am. Chem. Soc.* **2015**, *137*, 8006-8009; c) O. A. Ivanova, E. M. Budynina, Y. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Angew. Chem.* **2008**, *120*, 1123-1126; *Angew. Chem. Int. Ed.* **2008**, *47*, 1107-1110.

membered rings employing D-A cyclopropane and diaziridines to afford perhydropyridazine derivatives (Scheme 2, a).[110] On the other hand, very recently Werz and co-workers reported the (3+4) cycloaddition of D-A cyclopropanes and thiochalcones as general approach for the formation of tetrahydrothiepines (Scheme 2,b).[111]



Scheme 2: (3+3) and (3+4) cycloaddition reactions of D-A cyclopropanes.

Besides cycloaddition reactions, D-A cyclopropanes also undergo nucleophilic ring-opening reactions. These processes take place with predictable regiochemistry with the attack of the nucleophile at the carbon atom next to the donor group. In this regard, heteroatom nucleophiles as water, phenol, amines, thiols or azides have proved particularly useful.[112]

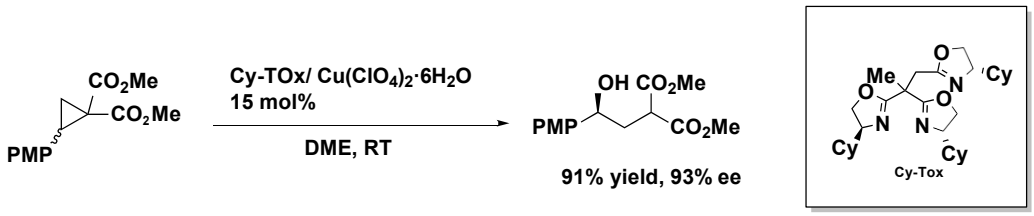
As example of heteroatom nucleophilic ring-opening reaction of D-A cyclopropanes, Tang and co-workers reported the first example of catalytic enantioselective ring-opening reaction of D-A cyclopropanes with water employing Cy-TOX/Cu(II) as catalyst.[113]

[110] A. O. Chagarovskiy, V. S. Vasin, V. V. Kuznetsov, O. A. Ivanova, V. B. Rybakov, A. N. Shumsky, N. N, Makhova, I. V. Trushkov, *Angew. Chem.Int. Ed*. **2018**, *57*, 10338−10342.

[111] A. U. Augustin, J. L. Merz, P. G. Jones, G. Mloston, D. B. Werz, *Org. Lett.* **2019**, *21*, 9405-9409.

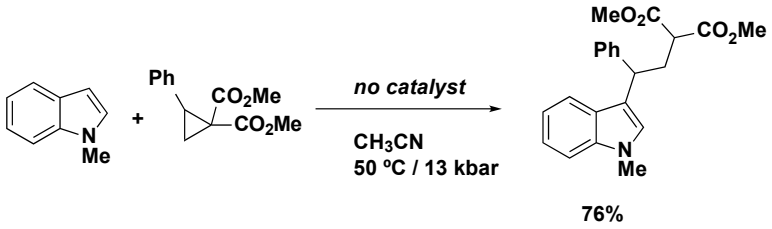
[112] For a recent review on ring-opening reactions of D-A cyclopropanes with *N*-nucleophiles, see: E. M. Budynina, K. L. Ivanov, I. D. Sorokin, M. Y. Melnikov, *Synthesis*, **2017**, *49*, 3035-3068. For selected examples: a) M. R. Emmett, H. K. Grover, M. A. Kerr, *J. Org. Chem.* **2012**, *77*, 6634-6637; b) O. Lifchits, D. Alberico, I. Zakharian, A. B. Charette, *J. Org. Chem.* **2008**, *73*, 6838-6840; c) O. Lifchits, A. B. Charette, *Org. Lett.* **2008**, *10*, 2809-2812.

[113] Q.-K. Kang, L. Wang, Q.-J. Liu, J.-F. Li, Y. Tang, *J. Am. Chem. Soc.* **2015**, *137*, 14594-14597.



Scheme 3: Heteroatom nucleophilic ring-opening reaction of D-A cyclopropanes.

The use of carbon nucleophiles in ring-opening reactions of D-A cyclopropanes has also become of interest but is still rare. Specifically, indoles,[114] 2-naphthols[115] and a few electron-rich (hetero)arenes [116] have been successfully used leading to the corresponding ring-opening products in a high regioselective manner. For instance, in 2011, Kerr and co-workers reported a catalyst-free route to 1,3-functionalized indole derivatives with excellent yields.[117]



Scheme 4: Carbon nucleophilic ring-opening reaction.

Taking into account the reactivity profiles of D-A cyclopropanes and continuing with our interest in the development of new methodologies for the functionalization of ferrocene, we realized that ferrocene could be able to undergo similar ring-opening reactions, thus providing access to new functionalized ferrocene derivatives. In the following sections, we will disclose the results of this study.

[114] a) P. Harrington, M. Kerr, *Tetrahedron Lett.* **1997**, *38*, 5949-5952; b) M. R. Emmet, H. K. Grover, M. A. Kerr, *J. Org. Chem.* **2012**, *77*, 6634-6637.
[115] T. Kaicharla, T. Roy, M. Thangarai, R.G. Gonnade, A. T. Biju, *Angew. Chem. Int. Ed.* **2016**, *55*, 10061-10064.
[116] a) C. C. Dulin, K. L. Murphy, K. A. Nolin*Tetrahedron Lett*., **2014**, *55,* 5280-5282; b) F. D. Nanteuil, J. Loup, J. Waser, *Org. Lett*. **2013**, *15*, 3738-3741; c) V. Piccialli, M. L. Graziano, M. R. Iesce, F. Cermola, *Tetrahedron Lett*. **2002**, *43*, 8067-8070.
[117] M. R. Emmett, M. A. Kerr, *Org. Lett.* **2011**, *13*, 4180-4183.

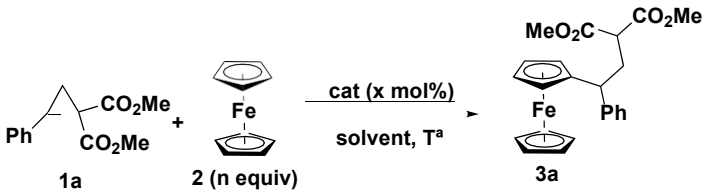
B.1.2. Results and Discussion

B.1.2.a. Screening of reactions conditions and scope

Initially, readily available dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1a**) was selected as model substrate. We first examined its reaction with ferrocene (**2**) in the presence of different Lewis and Brønsted acids. Unfortunately, several Lewis acids commonly used in catalytic ring-opening transformations of D-A cyclopropanes did not afford the desired product. In the case of $Sc(OTf)_3$ as catalyst we only observed traces of the desired product **3a** and the unreacted starting material (entry 1). Changes in the catalyst loading of $Sc(OTf)_3$ (20% and 50%) did not improve the formation of **3a**.

Moreover, the use of Brønsted acids such as *p*-TsOH and TFA as catalyst did not afford the product (entries 2 and 3). However, we found that in the presence of 10 mol% of trifluoromethanesulfonic acid (TfOH) in 1,2-dichloroethane (DCE) at rt the desired ferrocene derivative **3a** was isolated in 42% yield (entry 4). Next, a variety of solvents and different temperature conditions were tested and we found that conducting the reaction at 50 ºC resulted in an increased yield of **3a** (60%, entry 5). We also investigated the use of hexafluoroisopropanol (HFIP) as solvent that was found to be beneficial in some nucleophilic ring opening reactions of D-A cyclopropane derivatives;[118] however, it proved useless in the present transformation (entry 9). On the other hand, performing the reaction with a different catalyst loading produced the desired functionalized ferrocene derivative in very low yield (entry 11). The use of more equivalents of ferrocene (entry 10) did not improve the yield.

Table 1: Reaction of D-A cyclopropane **1a** with ferrocene **2**: Screening of the reaction conditions.



Entry	n equiv.	Cat	x mol %	Solvent	Tª	Yield (%)
1	2	$Sc(OTf)_3$	10	DCE	60	Trazes/SM
2	2	*p*-TsOH	10	DCE	60	-
3	2	TFA	10	DCE	60	-
4	2	TfOH	10	DCE	rt	42
5	**2**	**TfOH**	**10**	**DCE**	**50**	**60**
6	5	TfOH	10	DCE	rt	45
7	2	TfOH	5	DCE	50	5
8	2	TfOH	20	DCE	50	5
9	2	TfOH	10	HFIP	50	-
10	5	TfOH	10	DCE	rt	45
11	2	TfOH	5/20	DCE	50	5

[118] E. Richmond, V. D. Vukovic, J. Moran, *Org. Lett.* **2018**, *20*, 574-577.

The reaction took place with expected regiochemistry in this type of ring-opening reactions. The structure of ferrocene **3a** was deduced by NMR experiments. As shown in the ^{1}H-NMR spectrum (Figure 2), different signals can be assigned to the substituted and unsubsituted Cp rings of the ferrocene. For the unsubstituted Cp there is a singlet at 4.15 ppm for 5H, while the monosubstituted ring gives four different multiplets for each C-H bond (4.26, 4.15, 4.10 and 3.97 ppm). Multiplets at 2.87 and 2.32 ppm correspond to the diastereotopic hydrogens of the methylene group. The doublet of doublets at 2.82 and 2.37 ppm correspond to the benzylic hydrogen and to the hydrogen between the ester groups, respectively.

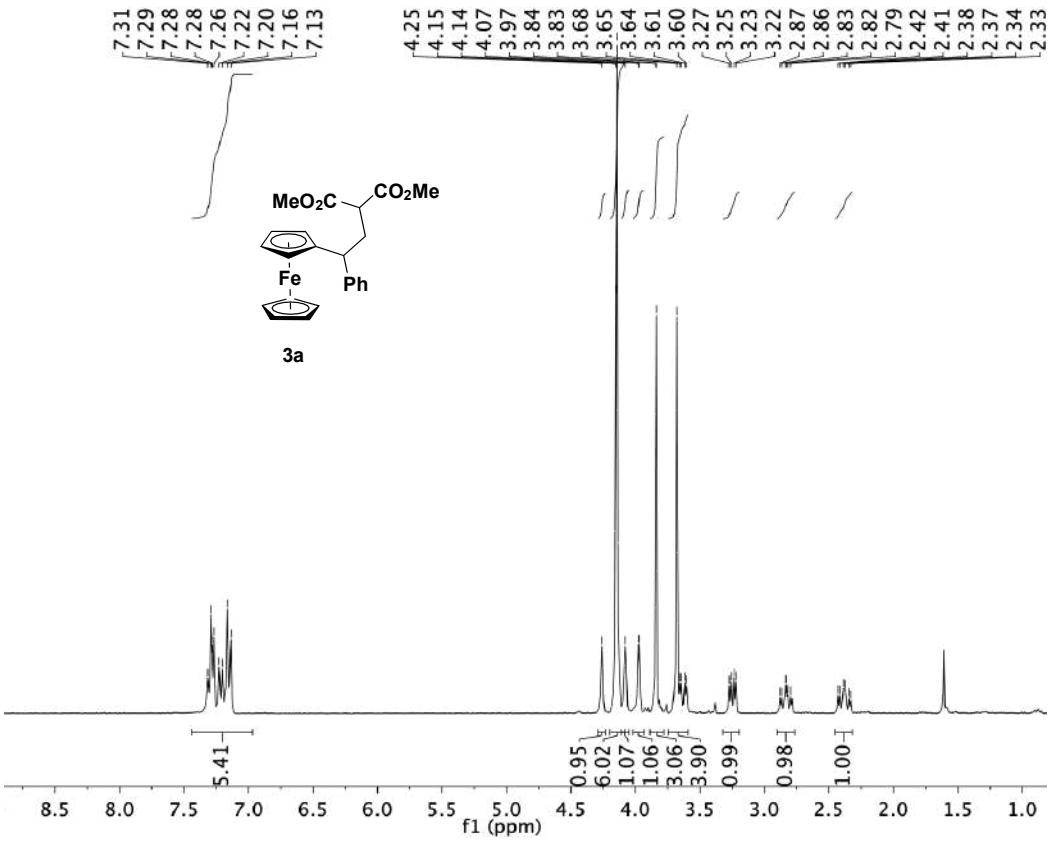


Figure 2: ^{1}H-NMR ($CDCl_3$, 300 MHz) of ferrocene derivative **3a.**

In the ^{13}C-NMR spectrum (Figure 3), attending to the ferrocene moiety, there is an intense signal at 68.7 ppm for the five equivalent carbon atoms of the unsubstituted cyclopentadienyl ligand, while the substituted Cp gives rise to four different CH signals at 67.8, 67.7, 67.0 and 66.4 ppm. The C_{ipso} of the ferrocene appears at 92.8 ppm. The carbons for the phenyl group appear at lower fields (128.5, 127.8 and 126.7 ppm). The signal at 169.8 ppm belongs to the carbon of the ester functions.

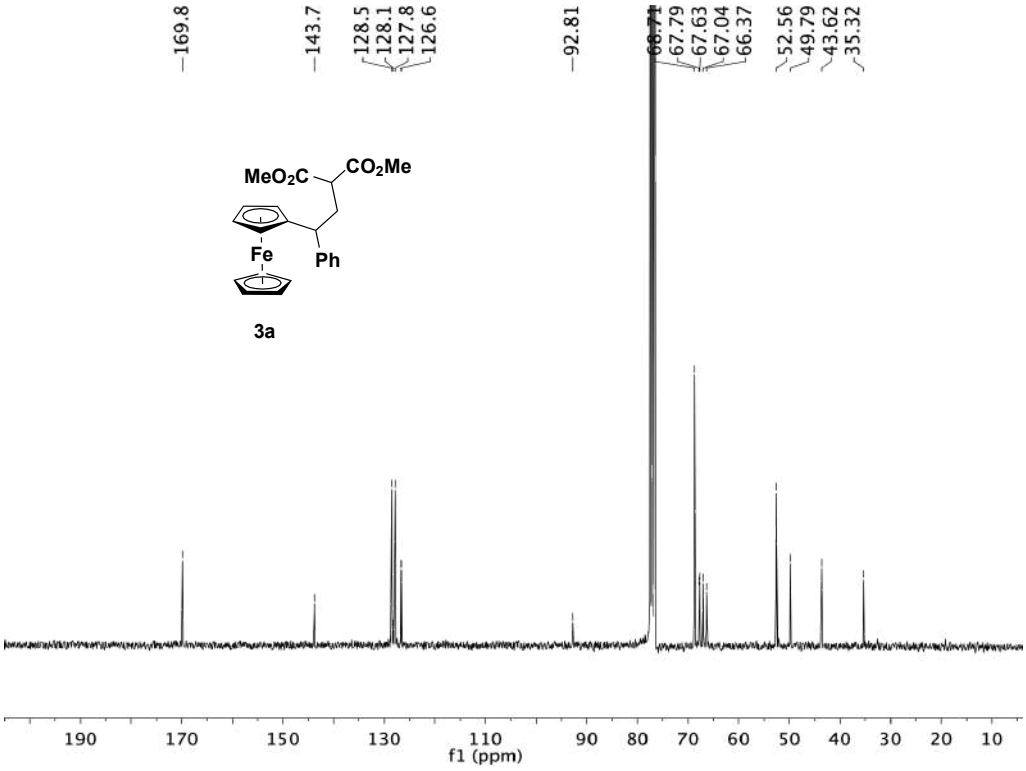


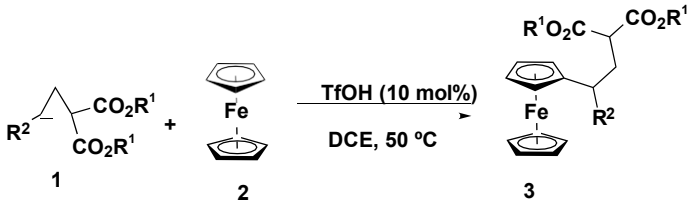
Figure 3: ^{13}C-NMR ($CDCl_3$, 75 MHz) of compound **3a**.

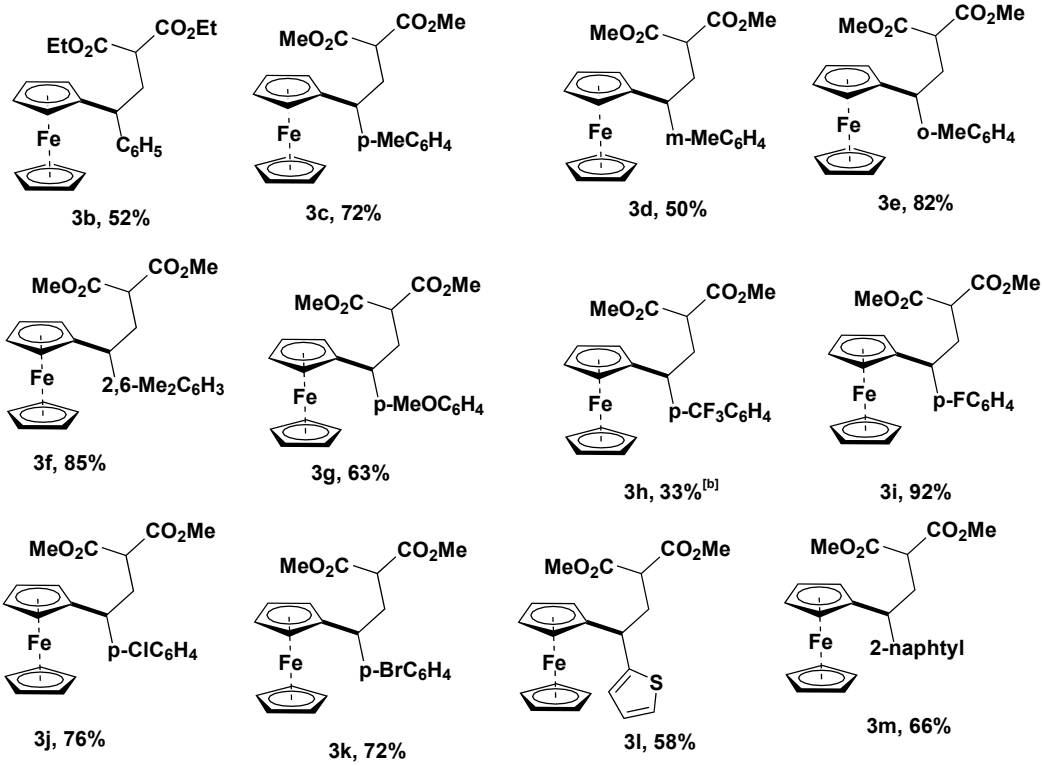
With optimal conditions in hand, the substrate scope was next investigated. As expected, substitution at the ester group has a marginal effect in the reaction outcome. For example, reaction of 2-diethylphenylcyclopropane-1-1-dicarboxylate **1b** and ferrocene provided the expected functionalized ferrocene derivative **3b** in similar yield to that reached for the model reaction. Modification of the aryl group was also accomplished. D-A cyclopropanes bearing *para*-, *meta*- and *ortho*-methyl groups at the phenyl ring performed well, producing ferrocene derivatives **3c-e** in good yields. Surprisingly, the *ortho*-isomer **1e** provides the highest yield (80%) in spite of the high steric hindrance by *ortho*-substituents. Furthermore, we could isolate the derivative **3f** (R^1 = Me; R^2 = 2,6-$Me_2C_6H_3$) in a notable yield (85%), which confirmed that the reaction is not particularly sensitive to steric hindrance exerted by ortho group.

Next, we studied cyclopropanes with a strong electron-donating group **1g** (R^1 = Me; R^2 = *p*-$MeOC_6H_4$) and with electron-withdrawing group **1h** (R^1 = Me; R^2 = *p*-$CF_3C_6H_4$). Cyclopropane **1g** led to the corresponding functionalized ferrocene **3g** in moderate yield (63%). In contrast, the reaction with cyclopropane **1h** required the use of a stoichiometric amount of TfOH to provide the corresponding ferrocene derivative **3h** in lower yield. Notably, D-A cyclopropanes containing halogen groups at the arene moiety were perfectly compatible with the present conditions. Cyclopropanes **1j** (R^2 = *p*-ClC_6H_4) and **1k** (R^2 = *p*-BrC_6H_4) performed similarly (yields of 76 and 72%, respectively) and substituted with fluorine on the aryl group (**1i**, R^2 = *p*-FC_6H_4) delivered the corresponding product in excellent yield (92%).

In addition, D-A cyclopropane derivative containing a thienyl group (**1l** R^1 = Me; R^2 = 2-thienyl) was also studied providing compound **3l** in 58% yield. Finally, we tested the reaction of naphthyl-substituted D-A cyclopropane **1m** observing the desired product **3m** with 66% yield.

Table 2: TfOH-catalyzed reaction of D-A cyclopropanes **1** and ferrocene **2**.[a]





Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), TfOH (10 mol%), DCE (0.1 M), rt. Yields of the isolated products after column chromatography (silica gel, hexanes/ethyl acetate mixtures). [b] 1.0 equivalent of TfOH was used.

There are few examples of transformations of D-A cyclopropane derivatives in which the donor is an alkyl group with the recent exception involving the cyclopropyl group as

donor.[119] Unfortunately, D-A cyclopropane derivatives **1n** (R^1 = Me; R^2 = Bu) and derivative **1o** (R^1 = Me; R^2 = Cyclopropyl) were proved unsuccessful under standard conditions (Figure 4).[120] D-A cyclopropane derivative **1p** (R^1 = Me; R^2 = styryl) also failed to undergo the present ring opening processwere.

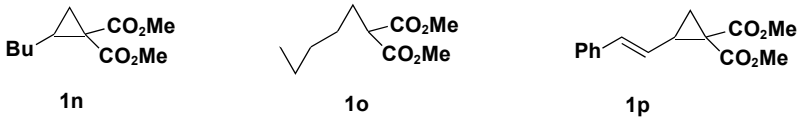


Figure 4: Unsuccessfully substrates

It is worth noting that all of the transformations depicted in table 2 proceeded with complete regioselectivity. A single crystal X-ray analysis of compound **3k** confirmed the proposed structure (Figure 5).

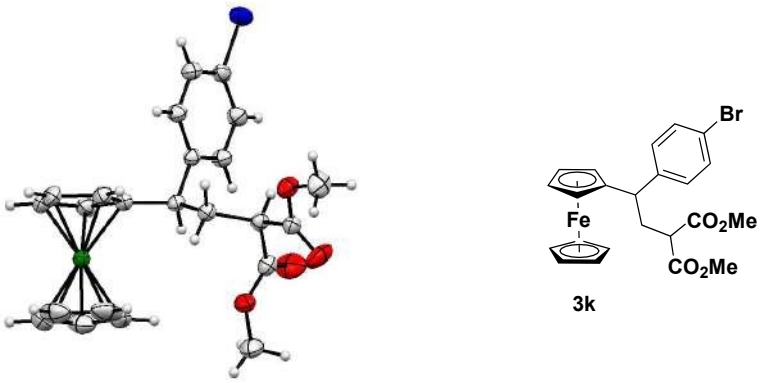


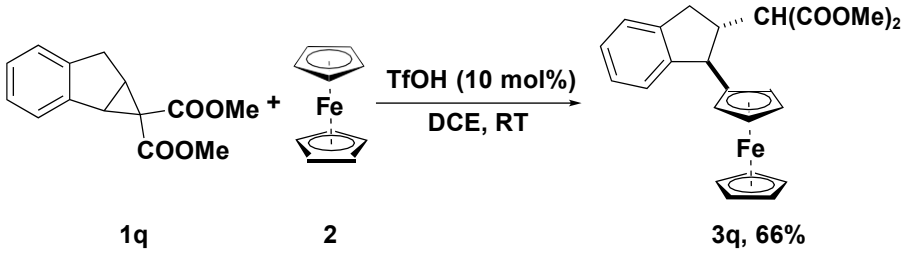
Figure 5: X-ray structure of ferrocene **3k**. Thermal ellipsoids are drawn at the 30% probability level.

To further expand the scope of this TfOH-catalyzed ring-opening transformation, we also investigated the reaction of D-A cyclopropane **1q** arising from indene with ferrocene under the standard conditions.

The reaction proceeded with complete regio- and stereoselectivity furnishing ferrocene derivative **3q** as a single isomer in 66% yield (Scheme 5).

[119] A. Kreft, P. G. Jones, D. B. Werz, *Org. Lett.* **2018**, *20*, 2059-2062

[120] The formation of compounds 3 is supposed to proceed by initial protonation of the ester function followed by ring opening of the cyclopropane with generation of a cationic intermediate. Apparently, an aryl group attached to the cyclopropane would stabilize the proposed intermediate being paramount to reaction success.



Scheme 5: TfOH-catalyzed reaction of D-A cyclopropanes **1q** and ferrocene **2**.

Using the X-ray diffraction analysis of this derivative, we could confirm the regio- and stereochemistry of compound **3q** (Figure 6). As expected, the attack of ferrocene occurred exclusively at the benzylic position of D-A cyclopropane. The diffraction data clearly illustrated the *trans* arrangement of ferrocenyl and malonyl moieties.

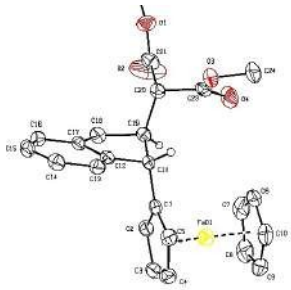
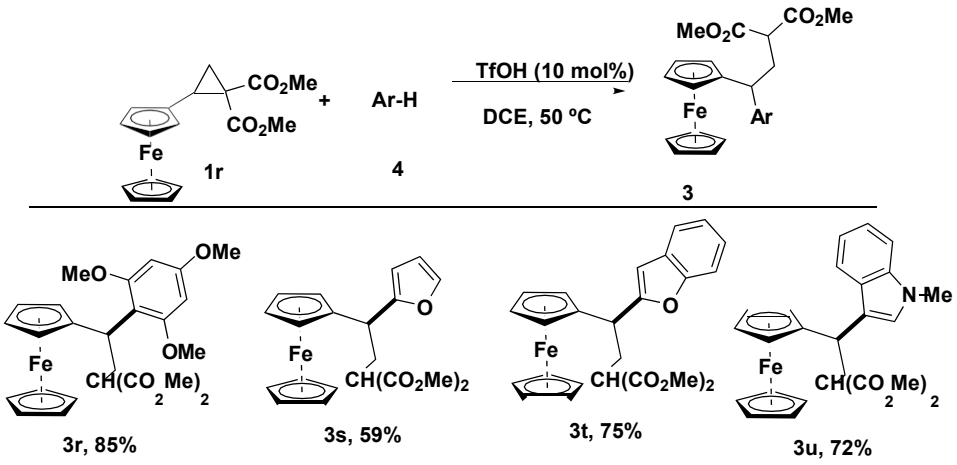


Figure 6: X-ray structure of ferrocene **3q**. Thermal ellipsoids are drawn at the 30% probability level.

B.1.2.b An alternative approach to the synthesis of functionalized ferrocene derivatives using dimethyl 2-ferrocenylcyclopropane-1,1-dicarboxylate

In order to extend our research, we studied the reactivity of dimethyl 2-ferrocenylcyclopropane-1,1-dicarboxylate (**1r**)[121] as D-A cyclopropane. It should be noted that the reactivity of this D-A cyclopropane with a ferrocenyl group as the donor group has been almost unexplored. In fact, to the best of our knowledge, only one isolated example of a (3+2) cycloaddition reaction of D-A cyclopropane **1r** with diphenylcyclopropenone has been reported in the literature.[122] We wondered if dimethyl 2-ferrocenylcyclopropane-1,1-dicarboxylate would mimic the reactivity toward electron-rich (hetero)arenes found in aryl-substituted D-A cyclopropanes, thus providing and alternative and potentially complementary approach to the synthesis of functionalized ferrocene derivatives. To this end, first we reacted D-A cyclopropane **1r** with 1,3,5-trimethoxybenzene **4a** under the standard reaction conditions and ferrocene derivative **3r** was obtained in an excellent 85% yield (Table 3). Several heteroarenes such as furan **4b**, benzofuran **4c**, and *N*-methylindole **4d** could be employed in this transformation affording the corresponding arylation products **3s**-**u** in yields ranging from 59 to 75%. Notably, these ferrocene derivatives are formed as single regioisomers. The observed regioselectivity in these arylation reactions involving heteroarenes parallels that found in aromatic electrophilic substitutions.

Table 3: TfOH-catalyzed reaction of D-A cyclopropane **1r** and electron-rich (hetero)arenes.[a]

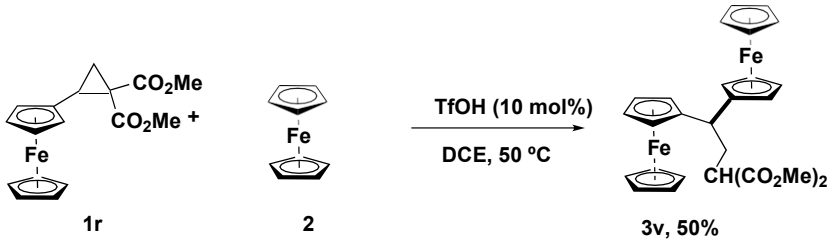


[a] Reaction conditions: **1r** (0.1 mmol), **4** (or **2**) (0.2 mmol), TfOH (10 mol%), DCE (0.1 M), 50 ^{o}C, isolated yields.

[121] D-A cyclopropane **1r** was obtained by rhodium-catalyzed cyclopropanation of vinylferrocene with dimethyl diazomalonate: F. González-Bobes, M. D. B. Fenster, S. Kiau, L. Kolla, S. Kolotuchin, M. Soumeillant, *Adv. Synth. Catal.* **2008**, *350*, 813-816.

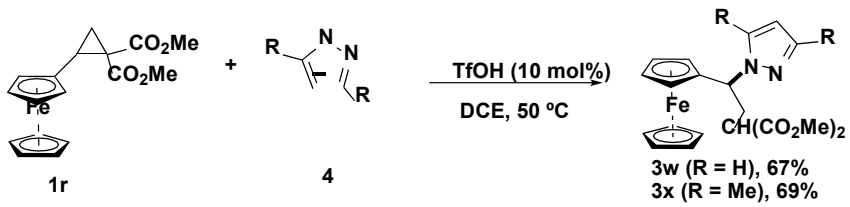
[122] A. R. Rivero, I. Fernández, C. Ramírez de Arellano, M. A. Sierra*, J. Org. Chem.* **2015**, *80*, 1207-1213.

Under otherwise similar conditions, treatment of cyclopropane **1r** with ferrocene delivered the corresponding product **3v** featuring a diferrocenylmethane moiety in synthetically useful yield (Scheme 6).



Scheme 6: TfOH-catalyzed reaction of D-A cyclopropane **1r** and ferrocene.

Finally, we evaluated the suitability of D-A cyclopropane **1r** for the synthesis of new ferrocene pyrazole conjugates given that some *N*-substituted pyrazole derivatives exhibit outstanding biological properties.[123] As shown in Scheme 7, under the standard conditions (TfOH 5 mol%, DCE as solvent, 50 ºC), the reaction of cyclopropan**e 1r** with pyrazole **(4a**, R = H**)** provided the desired product **3w** in satisfactory yield (67%). Similarly, the reaction with 3,5-dimethylpyrazole proceeded uneventfully affording the expected product **3x** in nearly identical yield (69%).



Scheme 7: TfOH-catalyzed reaction of D-A cyclopropane **1r** with pyrazole derivatives.

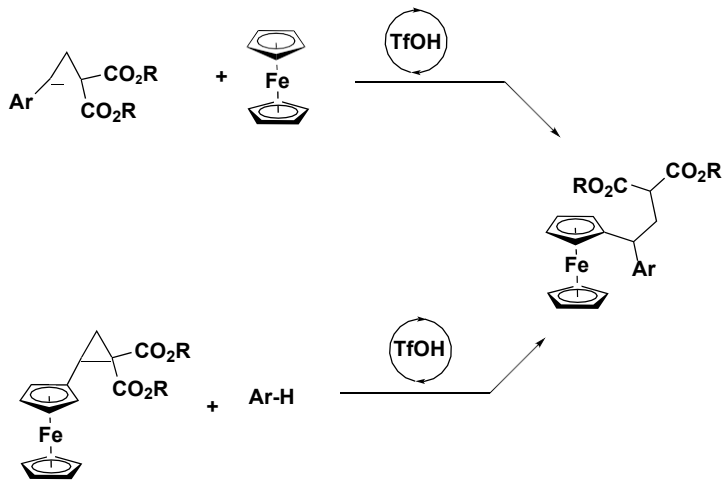
[123] Recent reviews on pyrazoles: a) S.G. Kucukguzel, S. Senkardes, *Eur. J. Med. Chem.* **2015**, *97*, 786-815; b) H. M. T. Albuquerque, C. M. Santos, J. A. S. Cavaleiro, A. M. S. Silva, *Curr. Org. Chem.* **2014**, *18*, 2750-2775; d) S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev.* **2011**, *111*, 6984-7034.

B.1.3. General conclusions

- Based on the facile ring-opening of D-A cyclopropanes, we have developed two efficient and complementary methodologies for the synthesis of functionalized ferrocene derivatives containing a malonate moiety.

- Both protocols exhibit exquisite regioselectivity providing the corresponding ferrocene derivatives in good to excellent yields.

Graphical Summary



Synthesis of Functionalized Ferrocene Derivatives from Donor—Acceptor Cyclopropanes

Silvia González-Pelayo and Luis A. López*[a]

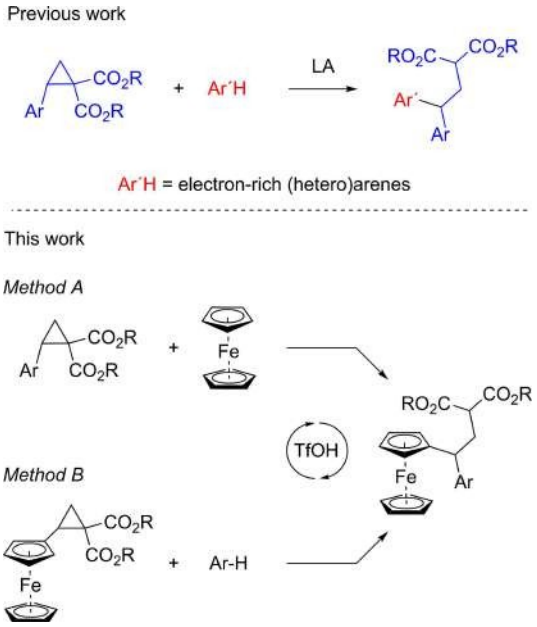
Dedicated to Professor Carmen Nájera on the occasion of her retirement.

The TfOH-catalyzed reaction of aryl-substituted donor–acceptor yields. An alternative approach to these functionalized ferro- cyclopropane derivatives with ferrocene provided new function- cene derivatives involving arylation of a ferrocene-decorated alized ferrocene derivatives. This process exhibited a reasonable donor–acceptor cyclopropane derivative is also disclosed. Both scope with respect to the cyclopropane component affording processes rely on a facile regioselective ring-opening of the the corresponding alkylated ferrocene derivatives in useful donor—acceptor cyclopropane.

Introduction

Breaking carbon-carbon σ-bonds in a predictable and useful way is not a common process in organic synthesis. Donor-acceptor (D-A) cyclopropanes are one such reagent for which this process is feasible and has been extensively documented. The most salient feature of these compounds is the presence of a highly polarized bond between the carbon atoms supporting the donor and acceptor groups with a marked tendency to heterolytic cleavage. A wealth of synthetic applications has been developed on the basis of this chemical behavior.[1] In particular, D-A cyclopropanes can undergo regioselective formal (3 + n) cycloadditions with compounds containing multiple bonds.[2] Moreover, nucleophilic ring-opening reactions of D-A cyclopropanes have been also successfully developed. These processes take place with predictable regiochemistry with attack of the nucleophile at the carbon atom next to the donor group. In this regard, heteroatom nucleophiles such as water, phenol, amines, thiols or azides have proved particularly useful.[3] Although in general less reactive, various carbon nucleophiles are also able to participate in ring-opening reactions of D-A cyclopropanes. Specifically, indoles,[4] 2-naphthols,[5] and some other electron-rich (hetero)arenes[6] demonstrated their suitability for this reactivity affording the corresponding arylation products (Scheme 1).[7]

Given that numerous functionalized ferrocene derivatives display significant applications in a number of important areas[8] and continuing with our current interest in the functionalization of ferrocene,[9] we were intrigued whether ferrocene would be able to undergo similar ring-opening reactions of D-A cyclopropanes. As a result, we report the synthesis of functionalized ferrocene derivatives based on a facile ring opening of three-membered carbocyclic systems. Specifically, herein we report: i) the TfOH-catalyzed reaction of D-A cyclopropane derivatives with ferrocene (Scheme 1, Method A), and ii) a related complementary approach demonstrating the previously overlooked potential of a ferrocenyl group as donor group in D-A cyclopropane chemistry (Scheme 1, Method B).



Scheme 1. Ring-opening reactions of D-A cyclopropane derivatives involving aromatic compounds as carbon nucleophiles. LA= Lewis acid; TfOH = trifluoromethanesulfonic acid.

Results and Discussion

Using dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1 a**) as a model substrate, we first examined its reaction with ferrocene

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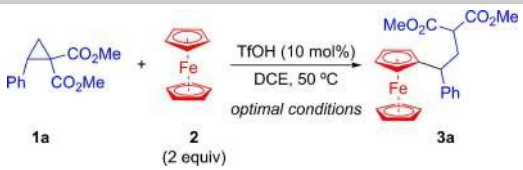
Supporting information for this article is available on the WWW under https://doi.org/10.1002/cplu.201800468

Table 1. Optimization of reaction conditions.[a]



1a 2 (2 equiv) 3a

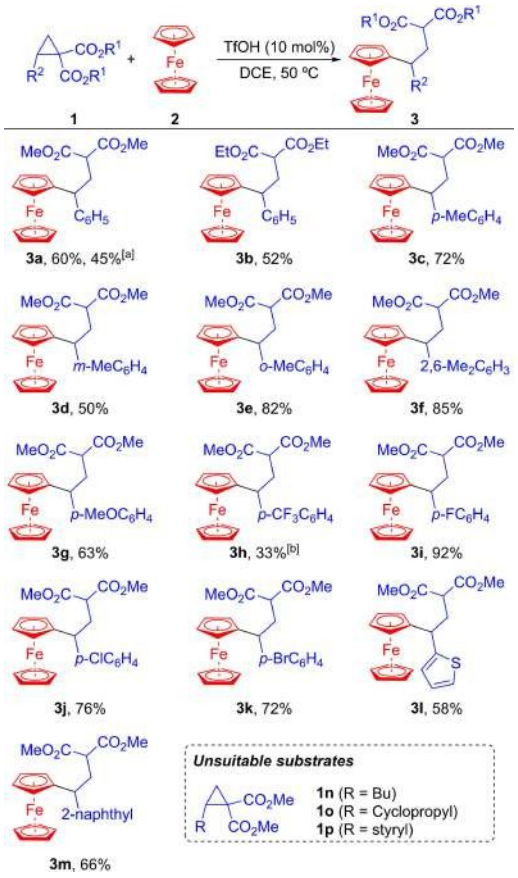
Entry	Variation from optimal conditions	Yield [%][b]
1	–	60
2	*p*-TsOH instead of TfOH	–
3	TFA instead of TfOH	–
4	$SnCl_2$ instead of TfOH	–
5	$Sc(OTf)_3$ instead of TfOH	–
6	$Bi(OTf)_3$ instead of TfOH	–
7	$Cu(OTf)_2$ instead of TfOH	–
8	$AlCl_3$ instead of TfOH	–
9	$ZnCl_2$ instead of TfOH	–
10	$FeCl_3$ instead of TfOH	–
11	RT instead of 50 °C	42
12	HFIP instead of DCE	–
13	5 mol% instead of 10 mol%	5

[a] These exploratory experiments were performed on a 0.1 mmol scale. [b] Yield of isolated product after chromatographic purification (silica gel; hexanes/ethyl acetate 10 : 1). DCE= 1,2-dichloroethane; TfOH= trifluoromethanesulfonic acid; *p*-TsOH= *p*-toluenesulfonic acid; TFA= trifluoroacetic acid; HFIP= hexafluoroisopropanol.

(**2**) in the presence of different Lewis and Brønsted acids (Table 1). To our delight, we found that heating a solution of **1 a** (1 equiv) and **2** (3 equiv) in the presence of 10 mol% of trifluoromethanesulfonic acid (TfOH) in 1,2-dichloroethane (DCE) at 50 °C afforded the desired ferrocene derivative **3 a** in 60 % isolated yield (entry 1). Other Brønsted acids such as *p*-toluenesulfonic acid (*p*-TosOH) or trifluoroacetic acid (TFA) proved ineffective in the present ring-opening transformation (entries 2 and 3). On the other hand, several Lewis acids commonly used in catalytic ring opening transformations of D-A cyclopropanes did not afford the desired product (entries 4–10). Conducting the reaction with TfOH at room temperature resulted in a decreased yield of **3 a** (entry 11). Although the use of hexafluoroisopropanol (HFIP) as solvent proved beneficial in some nucleophilic ring-opening of D-A cyclopropanes,[10] it is not a useful solvent for the present transformation (entry 12). Finally, performing the reaction with a catalyst loading of 5 mol % produced the desired functionalized ferrocene derivative in very low yield (entry 13).

With suitable conditions in hand, the substrate scope was next investigated by using a range of D-A cyclopropane derivatives **1** (Scheme 2).[11]

As expected, the nature of the ester alkyl group has a marginal effect in the reaction outcome. Thus, reaction of diethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1 b**, R^1 = Et; R^2 = Ph) and ferrocene (**2**) provided the expected functionalized ferrocene derivative **3 b** in nearly identical yield. Next, variation of the donor aryl group was accomplished. As shown, D-A cyclopropanes **1 c–e** (R^1 = Me; R^2 = tolyl) bearing *para*-, *meta*- and *ortho*-methyl groups at the phenyl ring performed well, furnishing the desired ferrocene derivatives **3 c–e** in acceptable yields



Scheme 2. TfOH-catalyzed reactions of D-A cyclopropanes **1** and ferrocene (**2**). Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), TfOH (10 mol%), DCE (0.1 M), 50 °C. Yields of the isolated products after column chromatography (silica gel, hexanes/ethyl acetate 10 : 1). [a] Reaction performed on a 1 mmol scale. [b] 1.0 equivalent of TfOH was used.

(50–82 %). Notably, the *ortho*-isomer **1 e** (R^1 = Me; R^2 = *o*-tolyl) provided the highest isolated yield of this series (82 %), revealing that the reaction is not particularly sensitive to steric hindrance by *ortho*-substituents. This assumption could be further confirmed by the isolation of ferrocene derivative **3 f** in a notable 85 % yield when *ortho*, *ortho*-disubstituted aryl D-A cyclopropane **1 f** (R^1 = Me; R^2 = 2,6-$Me_2C_6H_3$) was subjected to the standard reaction conditions. Cyclopropane **1 g** (R^1 = Me; R^2 = *p*-$MeOC_6H_4$) with a strong electron-donating group was also amenable to this reaction furnishing the expected ring-opening product **3 g** in moderate yield (63 %). In contrast, the reaction with a cyclopropane containing an electron-withdrawing substituent attached to the aryl group (**1 h**, R^1 = Me; R^2 = *p*-$CF_3C_6H_4$) was more sluggish requiring the use of a stoichiometric amount of TfOH and providing the corresponding ferrocene derivative **3 h** in lower yield. Conversely, D-A cyclopropanes **1 i–k** (R^1 = Me; R^2 = *p*-XC_6H_4) containing halogen groups at the arene moiety were

perfectly compatible with the present conditions. While cyclopropanes **1 j** (R^2 = *p*-ClC_6H_4) and **1 k** (R^2 = *p*-BrC_6H_4) performed similarly (yields of 76 and 72 %, respectively), that substituted with a fluorine on the aryl group (**1 i**, R^2 = *p*-FC_6H_4) delivered the corresponding product in excellent yield (92 %). The reaction is also amenable to D-A cyclopropane derivatives containing heteroaryl groups. For instance, reaction of 2-thienyl-substituted D-A cyclopropane **1 l** (R^1 = Me; R^2 = 2-thienyl) proceeded satisfactorily providing compound **3 l** in 58 % yield. Finally, polycyclic aromatic groups are well tolerated as illustrated by the formation of naphthyl-substituted ferrocene derivative **3 m** (66 %) from D-A cyclopropane **1 m** (R^1 = Me; R^2 = 2-naphthyl).

It must be noted that alkyl-substituted D-A cyclopropane derivatives **1 n** (R^1 = Me; R^2 = *n*-Bu) and **1 o** (R^1 = Me; R^2 = Cyclopropyl) failed to undergo the present reaction.[12] Reaction with an alkenyl-substituted D-A cyclopropane **1 p** (R^1 = Me; R^2 = styryl) also proved unsuccessful.

The reaction of D-A cyclopropane **1 q** arising from indene with ferrocene under the standard conditions deserves some comments. The reaction proceeded with complete regio- and stereoselectivity furnishing ferrocene derivative **3 q** as a single isomer in 66 % yield (Scheme 3). The regio- and stereochemistry

Scheme 3. TfOH-catalyzed reaction of D-A cyclopropane **1 q** and ferrocene (**2**). Yield of isolated product.

of compound **3 q** have been determined by X-ray crystallography (Figure 1).[13] Consistent with the well-established regiochemical pattern in ring-opening reactions of D-A cyclopropanes, the attack of ferrocene occurred exclusively at the benzylic position of the D-A cyclopropane. In addition, the

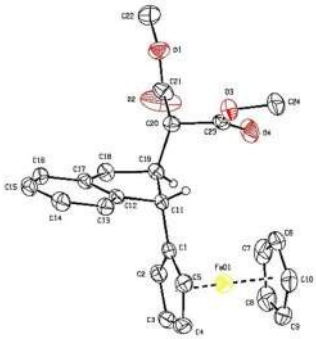
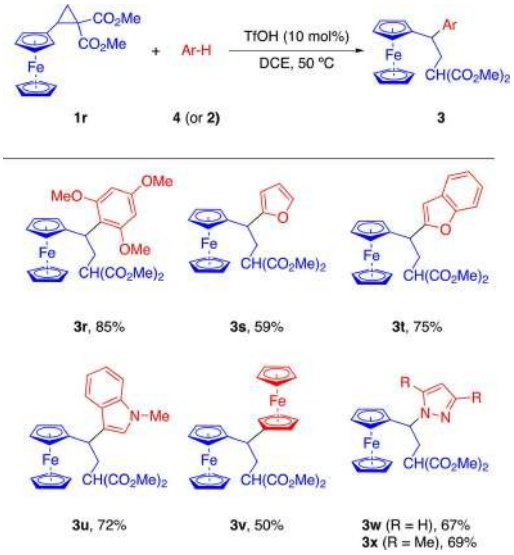


Figure 1. X ray structure of ferrocene **3 q**. Thermal ellipsoids are drawn at the 30 % probability level.

diffraction data clearly illustrated the *trans* arrangement of ferrocenyl and malonyl moieties.

In the course of this study, we envisioned an alternative and potentially complementary approach for the synthesis of functionalized ferrocene derivatives **3** involving dimethyl 2-ferrocenylcyclopropane-1,1-dicarboxylate (**1 r**).[14] Although the reactivity of D-A cyclopropanes has been intensively investigated during the last decades, the use of a ferrocenyl group as donor in D-A cyclopropane chemistry remains almost unexplored. To the best of our knowledge, only one isolated example of a [3 + 2] cycloaddition reaction of D-A cyclopropane **1 r** with diphenylcyclopropenone has been reported in the literature.[15] Specifically, no arylation reactions with electron-rich (hetero)arenes have been reported so far. For this reason, we questioned whether cyclopropane **1 r** would exhibit a similar reactivity to that previously found in common aryl-substituted D-A cyclopropanes. To this end, first we reacted D-A cyclopropane **1 r** with 1,3,5-trimethoxybenzene (**4 a**) under the standard reaction conditions (Scheme 4). Pleasingly, ferrocene



Scheme 4. TfOH-catalyzed reaction of D-A cyclopropane **1 r** and electron-rich (hetero)arenes. Reaction conditions: **1 r** (0.1 mmol), **4** (or **2**) (0.2 mmol), TfOH (10 mol%), DCE (0.1 M), 50 °C, yields of isolated products.

derivative **3 r** was obtain in an excellent 85 % yield, thus demonstrating our initial hypothesis. Gratifyingly, several heteroarenes such as furan (**4 b**), benzofuran (**4 c**), and *N*-methylindole (**4 d**) could be employed in this transformation affording the corresponding arylation products **3 s–u** in yields ranging from 59 to 75 %. Notably, these ferrocene derivatives are formed as single regioisomers. The observed regioselectivity in these arylation reactions involving heteroarenes parallels that found in aromatic electrophilic substitutions.

Next, we wondered whether the present protocol would be suitable for the synthesis of a product containing a diferrocenylmethane moiety. In this regard, we were pleased to find that reaction of dimethyl 2-ferrocenylcyclopropane-1,1-dicarboxylate (**1 r**) with ferrocene (**2**) under the developed reaction conditions produced compound **3 v** in moderate yield.

Finally, given that some *N*-substituted pyrazole derivatives exhibit outstanding biological properties,[16] we evaluated the suitability of D-A cyclopropane **1 r** for the synthesis of new ferrocene pyrazole conjugates.[17,18] Pleasingly, reaction of cyclopropane **1 r** with pyrazole (**4 e**) under the standard conditions proceeded smoothly to provide the desired product **3 w** in satisfactory yield (67 %). Similarly, the reaction with 3,5-dimethylpyrazole (**4 f**) proceeded uneventfully affording the expected product **3 x** in nearly identical yield (69 %).

Conclusion

In summary, we have developed two efficient complementary methodologies for the synthesis of functionalized ferrocene derivatives containing a malonate moiety. Specifically, in this study we have established that: (1) ferrocene is a suitable carbon nucleophile for ring-opening reactions of aryl-substituted D-A cyclopropanes, and (2) the ferrocenyl group is able to act as an excellent donor in D-A cyclopropane chemistry. Complete regioselectivity and synthetically useful yields were observed for most substrates. Further studies focused on potential applications of this new class of functionalized ferrocene derivatives are currently under investigation in our laboratory.

Experimental Section

General procedure for the TfOH-catalyzed reaction of D-A cyclopropane derivatives 1 with ferrocene (2): Synthesis of ferrocene derivatives 3 a–m: TfOH (1.5 mg, 0.01 mmol, 10 mol%) was added to a solution of the corresponding D-A cyclopropane **1** (0.1 mmol) and ferrocene (**2**, 37.2 mg, 0.2 mmol) in DCE (1 mL). The resulting mixture was stirred at 50 °C until the disappearance of the starting cyclopropane (monitored by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 10 : 1) to afford ferrocene derivatives **3 a**–**m**.

General procedure for the TfOH-catalyzed reaction of D-A cyclopropane 1 r with ferrocene (2): Synthesis of ferrocene derivatives 3 r–x: TfOH (1.5 mg, 0.01 mmol, 10 mol%) was added to a solution of D-A cyclopropane **1r** (34.2 mg, 0.1 mmol) and the corresponding (hetero)arene **4** (or **2**) (0.2 mmol) in DCE (1 mL). The resulting mixture was stirred at 50 °C until the disappearance of **1r** (monitored by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 10 : 1) to afford ferrocene derivatives **3r**–**x**.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: cyclopropanes · donor-acceptor systems · ferrocene · ring-opening reactions

[1] For representative reviews on the chemistry of D-A cyclopropanes, see: a) B. L. Pagenkopf, N. Vemula, *Eur. J. Org. Chem.* **2017**, 2561–2567; b) M. A. Kerr, *Isr. J. Chem.* **2016**, *56*, 476–487; c) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**, *13*, 655–671; d) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem.* **2014**, *126*, 5608–5628; *Angew. Chem. Int. Ed.* **2014**, *53*, 5504–5523; e) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804–818; f) F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano, J. Waser, *Chem. Commun.* **2014**, *50*, 10912–10928; g) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196.

[2] Selected formal (3 + 2) cycloadditions: a) D. Perrotta, M.-M. Wan, J. Waser, *Angew. Chem.* **2018**, *130*, 5214–5217; *Angew. Chem. Int. Ed.* **2018**, *57*, 5120–5123; b) A. Augustin, M. Busse, P. G. Jones, D. B. Werz, *Org. Lett.* **2018**, *20*, 820–823; c) Y. Matsumoto, D. Nakatake, R. Yazaki, T. Ohshima, *Chem. Eur. J.* **2018**, *24*, 6062–6066; d) L. K. B. Garve, A. Kreft, P. G. Jones, D. B. Werz, *J. Org. Chem.* **2017**, *82*, 9235–9242; e) A. Augustin, M. Sensse, P. G. Jones, D. B. Werz, *Angew. Chem.* **2017**, *129*, 14481–14485; *Angew. Chem. Int. Ed.* **2017**, *56*, 14293–14296; f) S. Chakrabarty, I. Chatterjee, B. Wibbeling, C. G. Daniliuc, A. Studer, *Angew. Chem.* **2014**, *126*, 6074–6078; *Angew. Chem. Int. Ed.* **2014**, *53*, 5964–5968; g) B. Cui, J. Ren, Z. Wang, *J. Org. Chem.* **2014**, *79*, 790–796; h) A. F. G. Goldberg, N. R. O'Connor, R. A. Craigll, B. M. Stoltz, *Org. Lett.* **2012**, *14*, 5314–5317; i) X. Qi, J. M. Ready, *Angew. Chem.* **2008**, *120*, 7176–7178; *Angew. Chem. Int. Ed.* **2008**, *47*, 7068–7070; j) C. A. Carson, M. A. Kerr, *J. Org. Chem.* **2005**, *70*, 8242–8244; k) M. Yu, B. L. Pagenkopf, *J. Am. Chem. Soc.* **2003**, *125*, 8122–8123; l) M. Yu, B. L. Pagenkopf, *Org. Lett.* **2003**, *5*, 5099–5101; Seminal work on (3 + 3) cycloadditions of D-A cyclopropanes: m) I. S. Young, M. A. Kerr, *Angew. Chem.* **2003**, *115*, 3131–3134; *Angew. Chem. Int. Ed.* **2003**, *42*, 3023–3026. For further examples, see reference [1b]. For representative (4 + 3) cycloaddition of D-A cyclopropanes: n) Z.-H. Wang, H.-H. Zhang, D.-M. Wang, P.-F. Xu, Y.-C. Luo, *Chem. Commun.* **2017**, *53*, 8521–8524; o) H. Xu, J.-L. Hu, L. Wang, S. Liao, Y. Tang, *J. Am. Chem. Soc.* **2015**, *137*, 8006–8009; p) O. A. Ivanova, E. M. Budynina, Y. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Angew. Chem.* **2008**, *120*, 1123–1126; *Angew. Chem. Int. Ed.* **2008**, *47*, 1107–1110; For a recent (3 + 1) cycloaddition: q) A. Ghosh, S. Mandal, P. K. Chattaraj, P. Banerjee, *Org. Lett.* **2016**, *18*, 4940–4943

[3] For a recent review on ring-opening reactions of D-A cyclopropanes with *N*-nucleophiles, see: E. M. Budynina, K. L. Ivanov, I. D. Sorokin, M. Y. Melnikov, *Synthesis*, **2017**, *49*, 3035–3068. For selected examples: a) Q.-K. Kang, L. Wang, Q.-J. Liu, J.-F. Li, Y. Tang, *J. Am. Chem. Soc.* **2015**, *137*, 14594–14597; b) M. C. Martin, D. V. Patil, S. france, *J. Org. Chem.* **2014**, *79*, 3030–3039; c) M. R. Emmett, H. K. Grover, M. A. Kerr, *J. Org. Chem.* **2012**, *77*, 6634–6637; d) Y.-Y. Zhou, L.-J. Wang, J. Li, X.-L. Sun, Y. Tang , *J. Am. Chem. Soc.* **2012**, *134*, 9066–9069; e) O. Lifchits, D. Alberico, I. Zakharian, A. B. Charette, *J. Org. Chem.* **2008**, *73*, 6838–6840; f) O. Lifchits, A. B. Charette, *Org. Lett.* **2008**, *10*, 2809–2812; g) M. Yu, B. L. Pagenkopf, *Tetrahedron*, **2003**, *59*, 2765–2771.

[4] For selected ring-opening reactions of D-A cyclopropanes with indole nucleophiles, see: a) L. C. Irwin, C. R. Renwick, M. A. Kerr, *J. Org. Chem.* **2018**, *83*, 6235–6242; b) S. Das, C. G. Daniliuc, A. Studer, *Angew. Chem.*

2018, *130*, 4117–4121; *Angew. Chem. Int. Ed.* **2018**, *57*, 4053–4057; c) S. M. Wales, M. M. Walker, J. S. Johnson, *Org. Lett.* **2013**, *15*, 2558–2561; d) F. de Nanteuil, J. Loup, J. Waser, *Org. Lett.* **2013**, *15*, 3738–3741; e) M. R. Emmett, M. A. Kerr, *Org. Lett.* **2011**, *13*, 4180–4183; f) B. Bajitos, M. Yu, H. Zhao, B. L. Pagenkopf, *J. Am. Chem. Soc.* **2007**, *129*, 9631–9634; g) P. Harrington, M. A. Kerr, *Tetrahedron Lett.* **1997**, *38*, 5949–5952.

[5] T. Kaicharla, T. Roy, M. Thangaraj, R. G. Gonnade, A. T. Biju, *Angew. Chem.* **2016**, *128*, 10215–10218; *Angew. Chem. Int. Ed.* **2016**, *55*, 10061–10064;

[6] Selected examples: a) T. P. Maloney, K. L. Murphy, T. L. Mainsah, K. A. Nolin, *Tetrahedron Lett.* **2018**, *59*, 18–21; b) R. Talukdar, A. Saha, D. P. Tiwari, M. K. Ghorai, *Tetrahedron* **2016**, *72*, 613–624; c) J.-T. Sim, S.-G. Kim, *J. Korean Chem. Soc.* **2016**, *60*, 374–377.

[7] For an alternative approach in which the nucleophilic component was generated from a naphthoquinone derivative, see: A. Lücht, L. J. Patalag, A. U. Augustin, P. G. Jones, D. B. Werz, *Angew. Chem.* **2017**, *129*, 10723–10727; *Angew. Chem. Int. Ed.* **2017**, *56*, 10587–10591.

[8] Selected reviews on properties and applications of ferrocene derivatives: a) D. Astruc, *Eur. J. Inorg. Chem.* **2017**, 6–29; b) M. Patra, G. Gasser, *Nat. Rev. Chem.* **2017**, *1*, 066; c) E. López, L. A. López, *Dalton Trans.* **2015**, *44*, 10128–10135; d) G. Jaouen, A. Vessières, S. Top, *Chem. Soc. Rev.* **2015**, *44*, 8802–8817; e) S. S. Braga, A. M. S. Silva, *Organometallics* **2013**, *32*, 5626–5639; f) *Chiral Ferrocenes in Asymmetric Catalysis*, (Eds.: L.-X. Dai, X.-L. Hou), Wiley-VCH, Weinheim, **2009**; g) *Ferrocenes: Ligands, Materials and Biomolecules* (Ed.: P. Štěpnička) Wiley: Chichester, U. K., **2008**; h) R. G. Arrayás, J. Adrio, J. C. Carretero, *Angew. Chem.* **2006**, *118*, 7836–7878; *Angew. Chem. Int. Ed.* **2006**, *45*, 7674–7715; i) D. R. Van Staveren, N. Metzler-Nolte, *Chem. Rev.* **2004**, *104*, 5931–5986; j) *Ferrocenes*, (Eds.: A. Togni, T. Hayashi), VCH, Weinheim, **1995**.

[9] Selected recent contributions from our group: a) S. González-Pelayo, E. López, J. Borge, N. de-los-Santos-Álvarez, L. A. López, *Eur. J. Org. Chem.* **2018**, 2858–2862; b) E. López, J. Borge, L. A. López, *Chem. Eur. J.* **2017**, *23*, 3091–3097; c) E. López, T. Suárez, A. Ballesteros, L. A. López, *Eur. J. Inorg. Chem.* **2017**, 225–228; d) E. López, G. Lonzi, L. A. López, *Organometallics* **2014**, *33*, 5924–5927.

[10] E. Richmond, V. D. Vukovic, J. Moran, *Org. Lett.* **2018**, *20*, 574–577. See also ref. [4a].

[11] Regarding the ferrocene component, we conducted some experiments with a few commercially available monosubstituted ferrocene derivatives. For example, we found that the reaction of D-A cyclopropane **1 a** with acetylferrocene did not proceed and the starting materials were recovered unchanged even after prolonged heating. Reaction of **1 a** with (dimethylaminomethyl)ferrocene also proved unsuccessful.

[12] There are very few examples of transformations of D-A cyclopropane derivatives in which the donor is an alkyl group. For a notable recent exception involving the cyclopropyl group as donor, see: A. Kreft, P. G Jones, D. B. Werz, *Org. Lett.* **2018**, *20*, 2059–2062.

[13] CCDC 1853694 (**3 q**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre.

[14] D-A cyclopropane **1 r** was obtained by rhodium-catalyzed cyclopropanation of vinylferrocene with dimethyl diazomalonate: F. González-Bobes, M. D. B. Fenster, S. Kiau, L. Kolla, S. Kolotuchin, M. Soumeillant *Adv. Synth. Catal.* **2008**, *350*, 813–816.

[15] A. R. Rivero, I. Fernández, C. Ramírez de Arellano, M. A. Sierra *, J. Org Chem.* **2015**, *80*, 1207–1213.

[16] Recent reviews on pyrazoles: a) S. G. Kucukguzel, S. Senkardes, *Eur. J Med. Chem.* **2015**, *97*, 786–815; b) H. M. T. Albuquerque, C. M. Santos J. A. S. Cavaleiro, A. M. S. Silva, *Curr. Org. Chem.* **2014**, *18*, 2750–2775; d) S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev* **2011**, *111*, 6984–7034.

[17] Selected examples of ferrocene-containing pyrazole derivatives: a) Z Chen, L. Han, S.-K. Tian, *Org. Lett.* **2017**, *19*, 5852–5855; b) S. Tampier S. M. Bleifuss, M. M. Abd-Elzaher, J. Sutter, F. W. Heinemann, N. Burzlaff *Organometallics* **2013**, *32*, 5935–5945; c) C. López, A. González, R Bosque, P. K. Basu, M. Font-Bardía, M. T. Calvet, *RSC Adv.* **2012**, *2*, 986–2002; d) W. Tan, Z. Yu, W. He, L. Wang, J. Sun, J. Chen, *Organometallics* **2008**, *27*, 4833–4836; e) P. K. Basu, A. González, C. López, M. Font-Bardía T. Calvet, *J. Organomet. Chem.* **2009**, *694*, 3633–3642; Some ferrocene-containing pyrazole derivatives exhibit relevant pharmacological properties. For selected examples, see: a) E. Guillén, A. González, C. López P. K. Basu, A. Ghosh, M. Font-Bardía, C. Calvis, R. Messeguer, *Eur. J. Inorg Chem.* **2015**, 3781–3790; b) W. C. M. Duivenvoorden, Y. Liu, G. Schatte H.-B. Kraatz, *Inorganica Chim. Acta* **2005**, *358*, 3183–3189.

[18] For the ring-opening of activated cyclopropane derivatives with pyrazole and related heteroaromatics, see: M. I. Uddin, A. Mimoto, K Kakano, Y. Ichikawa, H. Kotsuki, *Tetrahedron Lett.* **2008**, *49*, 5867–5870

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Part B.2. Synthesis of Aminofunctionalized Metallocene Derivatives

B.2.1. Introduction and Objective

As stated before, functionalized ferrocene derivatives have a large number of applications in several important fields. In this regard, ferrocene derivatives containing nitrogen display interesting applications in catalysis, polymer and material sciences and medicinal chemistry. Some of these nitrogen-containing ferrocene derivatives are readily available and have become suitable precursors for the synthesis of new ferrocene derivatives. This is the case of aminomethyl ferrocene derivatives such as Ugi´s amine (*N*,*N*-dimethylaminomethylferrocene, $R^1 = R^2 = R^3 = Me$) (Figure 1).[124]

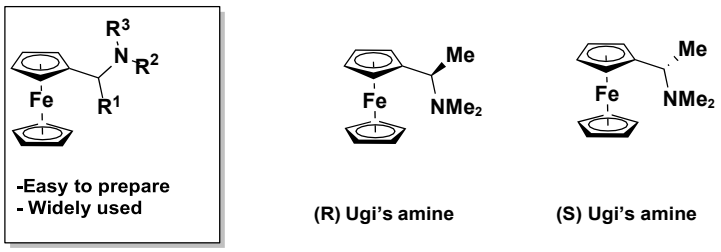


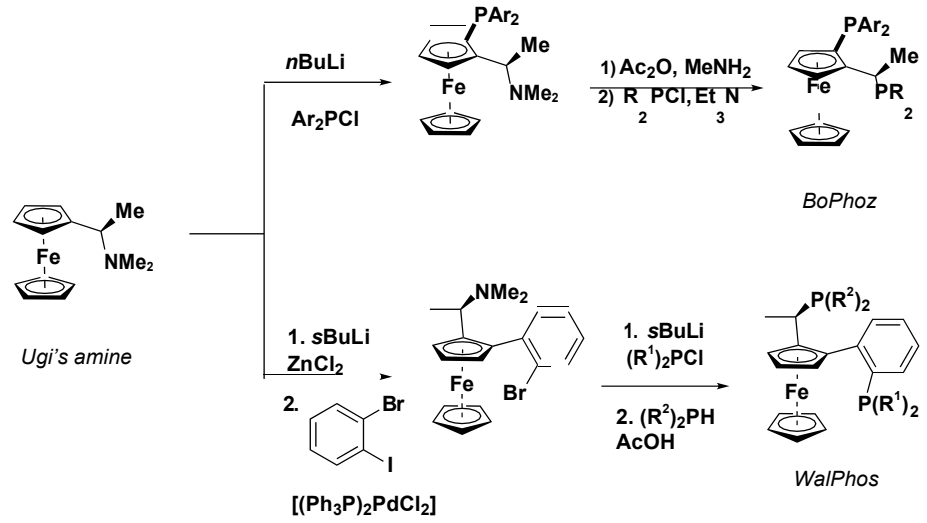
Figure 1: Ferrocenylmethylamine derivatives. (R)- and (S)-enantiomers of Ugi's amine.

Since its discovery in 1970, Ugi´s amine has been extensively used for the preparation of 1,2-disubstituted ferrocene derivatives through *ortho*-lithiation and subsequent reaction with an electrophilic reagent. In most cases the metalation process takes place in a highly diastereoselective way allowing the preparation of compounds with both planar and central chirality.[125] As illustrative examples of the potential of this approach, Scheme 1 shows the synthesis of two ferrocene ligands widely used in asymmetric catalysis: BoPhoz and Walphos.[126]

[124] Pionering study: D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389-5383.

[125] a) T. Hayashi, K. Yamamoto, M. Kumada, *Tetrahedron Lett*. **1974**, 4405 – 4408; b) D. Markarding, H. Klusacek, G. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc*. **1970**, *92*, 5389 – 5393; c) T. Hayashi, *VCH, Weinheim*,**1995**, pp. 105-142; d) H. B. Kagan, O. Riant, *Adv. Asymmetric Synth*. **1997**, *2*, 189 –235; e) C. F. Richards, A. J. Lock*, Tetrahedron: Asymmetry.* **1998**, *9* ,2377-2407; f) R. Gómez Arrayás, J. Adrio, J. C. Carretro, *Angew. Chem. Int. Ed*. **2006**,*45*, 7674-771.

[126] a) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc*.1994,116, 4062-4066; b) T. Sturm, W. Weissensteiner, F. Spindler, *Adv. Synth. Catal*. **2003**, *345*, 160-164; c) M. A. Fernandez-Rodríguez, Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc*. **2006**, *128*, 2180-2181; d) Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, *Angew. Chem*. **2005**, 117, 1395-1397*; Angew. Chem. Int. Ed*. **2005**, *44*, 1371-1375.



Scheme 1: Examples of synthesis of 1,2-disubstituted ferrocene ligands from Ugi´s amine.

Recent studies in this field have focused on using the 1-aminomethyl function as efficient coordinating directing group in transition metal-catalyzed C-H bond functionalization reactions.[127] Some of these catalytic transformations could be performed in an asymmetric way with excellent levels of enantiocontrol. Key breakthroughs in this field include the palladium-catalyzed asymmetric coupling of aminomethyl ferrocene derivatives with aryl boronic acids,[128] alkenes,[129] alkynes,[130] heteroarenes,[131] and azoles.[132]

As important example, selective monoraylation of (dimethylaminomethyl)ferrocene using arylboronic acids under palladium catalysis was already displayed in section II.1.3 (see scheme 7).

Another interesting example of C-H bond functionalization employing a similar strategy was described by Wu and co-workers (Scheme 2). They reported a new strategy of dehydrogenative Heck reaction controlled by redox process of ferrocene. Using readily

[127] For selected reviews on transition metal-catalyzed C-H bond functionalization reactions of ferrocene derivatives, see: a) L. A. López, E. López, *Dalton Trans.* **2015**, *44*, 10128-10135; b) D.-Y., Zhu, P. Chen, J.-B. Xia, *ChemCatChem.* **2016**, *8*, 68-73; c) D.-W. Gao, Q. Gu, C. Zheng, S.-L. You, *Acc. Chem. Res.* **2017**, *50*, 351−365.

[128] D.-W. Gao, Y. C. Shi, Q. Gu, Z.-L. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2012**, *135*, 86-89. For a recent related report on the diastereoselective Pd-catalyzed C-H arylation of ferrocenylmethanamines with arylboronic acids and pinacol esters, see: K. Plevová, B. Mudráková, E. Rakovský, R. Šebesta, *J. Org. Chem.* **2019**, *84*, 7312-7319.

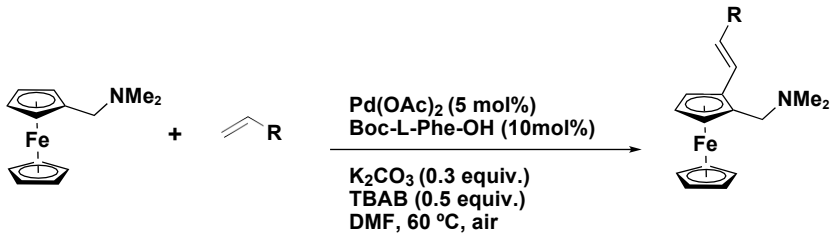
[129] C. Pi, Y. Li, X. Cui, H. Zhang, Y. Han, Y. Wu, *Chem. Sci.* **2013**, *4*, 2675-2679.

[130] Y.-C. Shi, R.-F. Yang, D.-W. Gao, S.-L. You, *Beilstein J. Org. Chem.*, **2013**, *9*, 1891-1896. For a previous racemic version of this reaction, see: H. Zhang, X. Cui, X. Yao, H. Wang, J. Zhang, Y. Wu, *Org. Lett.* **2012**, *14*, 3012-3015.

[131] D.-W. Gao, Q. Gu, S.-L. You, *J. Am. Chem. Soc.* **2016**, *138*, 2544-2547.

[132] Z.-J. Cai, C.-X. Liu, Q. Gu, C. Zheng, S.-L. You, *Angew. Chem.* **2019**, *131*, 2171-2175; *Angew. Chem. Int. Ed.* **2019**, *58*, 2149-2153.

available amino acids as ligands, they obtained planar-chiral ferrocene derivatives with excellent enantioselectivities and yields. [133]



Scheme 2: Palladium-catalyzed C-H bond activation through cross-coupling reaction with substituted olefins.

In contrast, the chemistry of β-aminoethyl ferrocene derivatives (Figure 2) remains much less developed very likely because of the lack of suitable efficient methodologies for their preparation. In fact, to the best of our knowledge, this type of aminofunctionalized ferrocene derivatives have not been used for the preparation of new functionalized disubstituted ferrocenes.

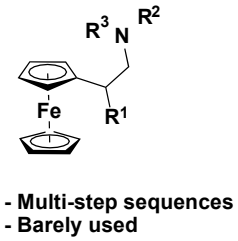


Figure 2: Ferrocenylethylamine derivatives.

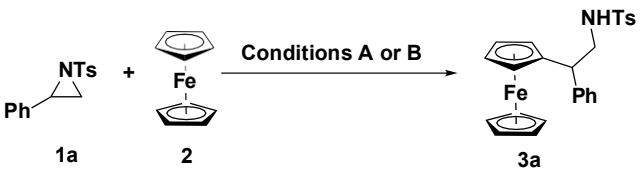
Based on our previous work involving TfOH-catalyzed ring-opening of D-A cyclopropanes and continuing with the interest of our group in the synthesis of ferrocene derivatives (see Section x), our goal in this chapter was to further expand the study to aziridine derivatives in order to provide a straightforward route to new amino substituted ferrocene derivatives.

[133] C. Pi, Y. Li, X. Cui, H. Zhang, Y. Han, Y. Wu, *Chem. Sci.* **2013**, *4*, 2675.

B.2.2. Results and Discussion

B.2.2.a Reaction of tosylaziridines and ferrocene: Screening of reactionconditions and scope

Based on our previous experience in the reaction of ferrocene with donor-acceptor cyclopropane derivatives, we tested racemic 2-phenyl-1-tosylaziridine **1a** as model substrate with ferrocene **2** in the presence of TfOH (10 mol%). At room temperature in 1,2-dichloroethane (DCE) we were able to isolate the desired ferrocene derivative **3a** in 68% yield. We have also studied the reaction with different Lewis and Brønsted acids. Boron trifluoride etherate in catalytic amounts (10 mol%) was shown to be also competent catalyst for this ring-opening reaction providing **3a** in similar yield. Unfortunately, other Brønsted and Lewis acids proved ineffective in the present ring-opening transformation. It should be noted that this ring-opening reaction takes place with complete regioselectivity.



Conditions A: TfOH (10mol%), DCE, RT 66%
Conditions B: $BF_3 \cdot OEt_2$ (10mol%), DCE, RT 68%

Scheme 3: Reaction of aziridine **1a** and ferrocene; Initial findings.

The structure of ferrocene derivative **3a** was determined using NMR experiments. As shown in the ^{1}H-NMR spectrum, the signals at 3.28 and 3.82 ppm integrating for 1H belong to the diastereotopic protons of the methylene group. At 3.57 ppm appears the proton that is attached to the phenyl and the ferrocenyl group. Attending to the ferrocene moiety, there is one multiplet between 4.14-3.93 ppm for 9 H where one intense singlet correspond to the 5 protons to the unsubstituted Cp ligand, while the other four protons belong for the monosubstituted ring. The N-H gives a signal at 4.58 ppm.

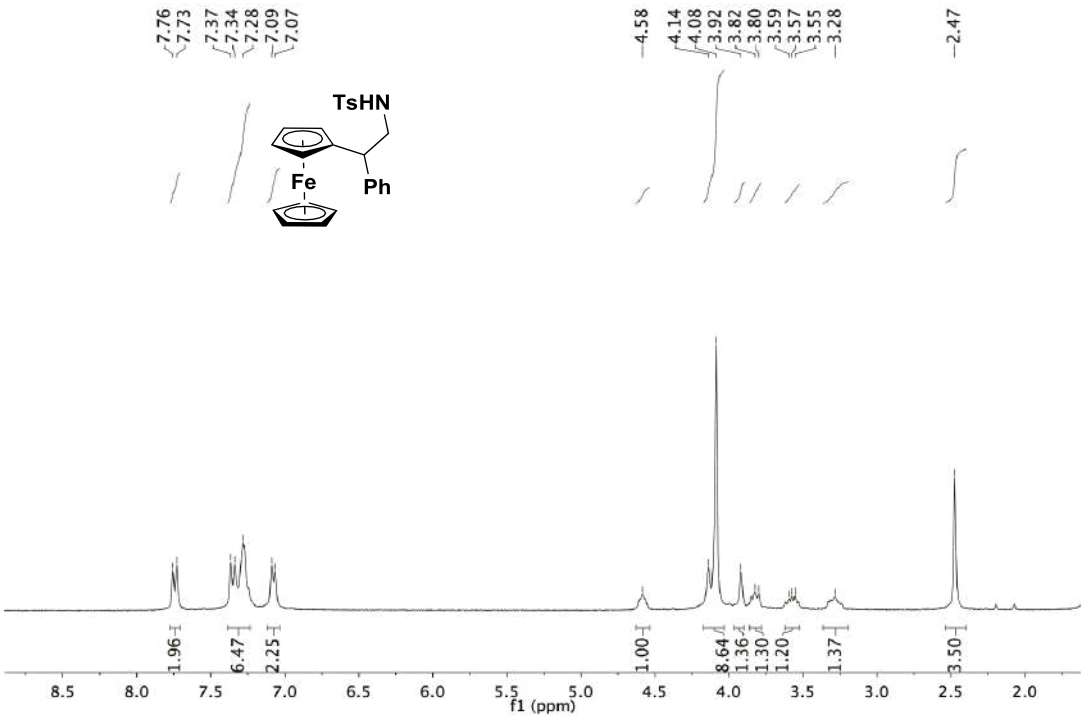


Figure 3: ^{1}H-NMR ($CDCl_3$, 300 MHz) of compound **3a**.

According to the ^{13}C-NMR spectrum, there is one intense signal at 68.8 ppm for the five equivalent carbon atoms of the unsubstituted Cp ligand, while the substituted one give rises to four different CH signals at 68.0, 67.7, 67.4 and 66.5 ppm. The C_{ipso} of the ferrocene appears at 89.3 ppm. The signals at 48.4 and 45.6 ppm belong to the CH_2 and CH, respectively.

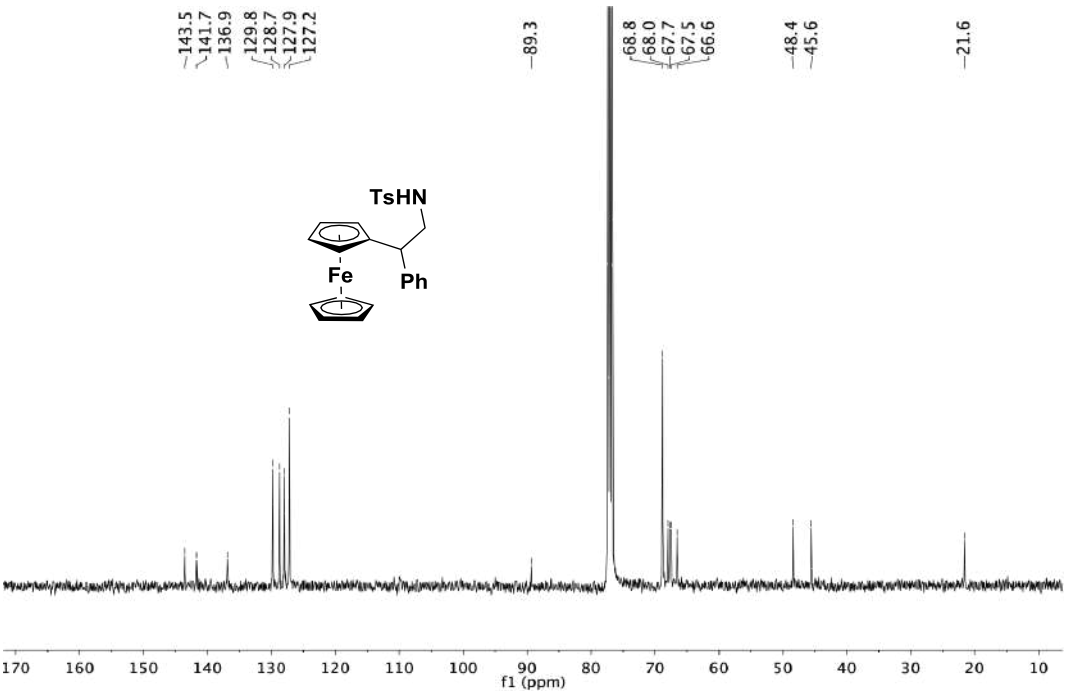
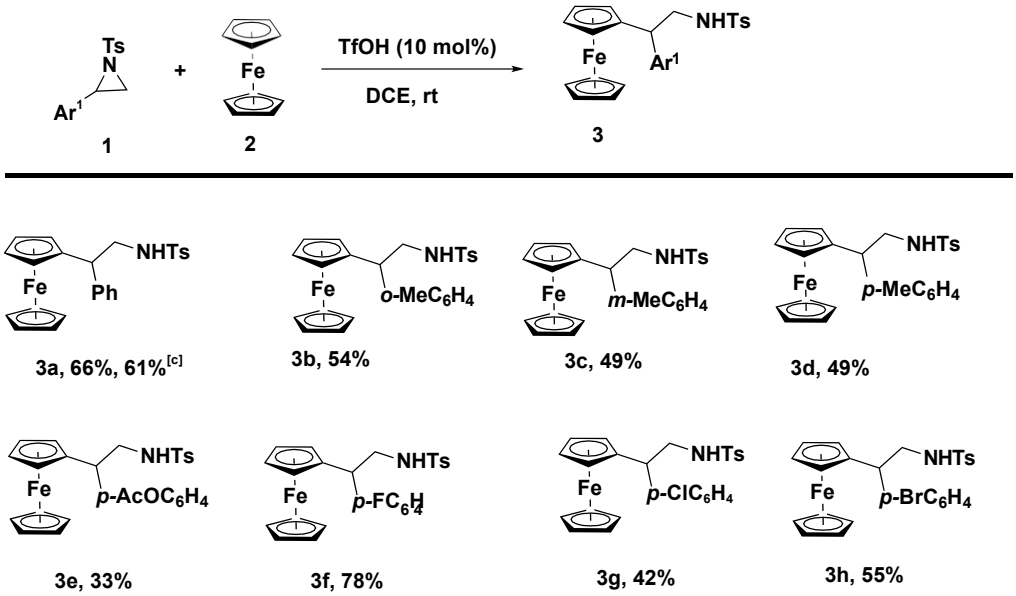


Figure 4: ^{13}C-NMR ($CDCl_3$, 75MHz) of ferrocene derivative **3a.**

With optimal conditions in hand, we first demonstrated that running the model reaction under conditions A on a 1 mmol scale had no detrimental effect in the yield affording compound **3a** in almost the same yield.

Concerning the reaction scope, a range of sterically and electronically differentiated aryl-substituted aziridines **1** smoothly reacted with ferrocene **2** to produce the desired functionalized ferrocene derivatives **3** (Table 1). For example, methyl substituents in the *ortho*, *meta* or *para* positions were well tolerated and furnished the desired ferrocene derivatives **3b**-**d** with comparable yields. An aziridine substrate bearing a *p*-$AcOC_6H_4$ group was also transformed into the desired ferrocene derivative **3e** in moderate yield (42%). Halogenated aziridines also undergo this ring-opening reaction delivering the corresponding ferrocene derivatives **3f**-**h** in synthetically useful yields.

Table 1: Scope of the reaction of aziridines and ferrocenes.[a,b]



[a] Reaction conditions: **1** (0.1 mmol), (0.2 mmol), **2** (0.1 mmol), TfOH (10 mol%), DCE, RT. [b] The reported yields refer to isolated products **3** after column chromatographic purification. [c] Reaction performed on a 1.0 mmol scale.

Of note, substrates bearing strong electron-withdrawing groups failed to undergo this ring-opening reaction (Figure 5). Moreover, unsubustituted 1-tosyl aziridine did not react at all under the standard conditions and the starting materials were recovered unchanged.[134]

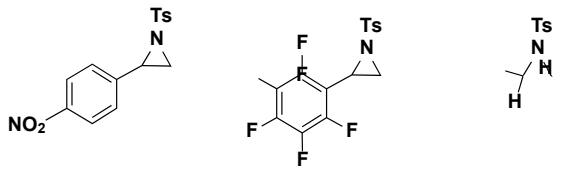
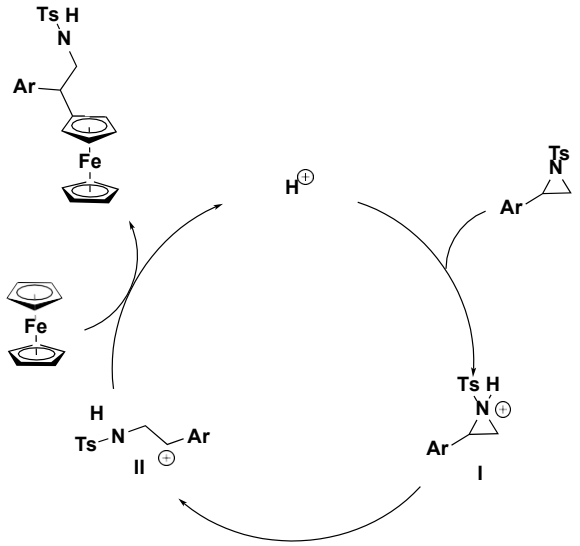


Figure 5: Unsuitable substrates.

A mechanistic proposal for the present ring-opening process consistent with these experimental observations is depicted Scheme 4. Initial protonation of the aziridine nitrogen and subsequent ring-opening reaction would generate intermediates **I** and **II**, respectively.[135] Then, carbocationic intermediate **II** would be trapped by ferrocene through a Friedel-Crafts type electrophilic aromatic substitution giving rise to the corresponding product. In line with this mechanism, a cationic stabilizing substituent on the aziridine is paramount to reaction success. The unsuccessful result with aziridines bearing strong electron-withdrawing groups or unsubstituted aziridine could be ascribed to the low stability of the proposed carbocationic species.

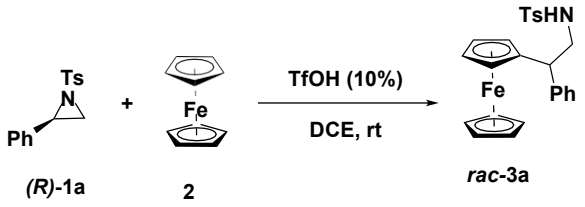


Scheme 4: Proposed mechanism for the reaction of aziridines with ferrocene.

[134] 2-phenyl-1-acetylaziridine also failed to undergo this ring-opening reaction.

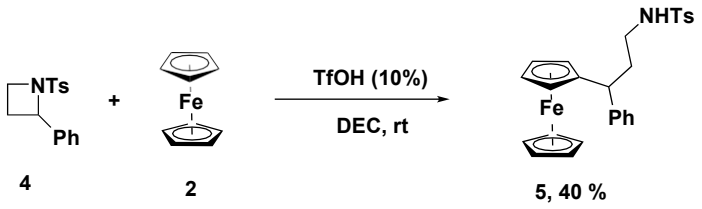
[135] For selected transformations of activated aziridines involving carbocationic intermediates, see: a) H. Liu, H. Jia, W. Shi, C. Wang, C. Zhang, H. Guo, *Org. Lett.* **2018**, *20*, 3570-3573; b) S. Fang, Y. Zhao, H. Li, Y. Zheng, P. Lian, X. Wan, *Org. Lett.* **2019**, *1*, 2356-2359; c) S. Teranishi, K. Maeda, T. Kurahashi, S. Matsubara, *Org. Lett.* **2019**, *21*, 2593-2598

To further support this mechanistic assumption, we studied the reaction of enantiopure aziridine (*R*)-**1a**. Under the developed conditions, (*R*)-**1a** underwent the ring-opening reaction to produce racemic **3a** with complete loss of stereochemical information (Scheme 5). This result would provide support for the mechanism depicted in Scheme 4 involving a carbocation intermediate.



Scheme 5: Reaction of optically active aziridine (*R*)-**1a** and ferrocene **2.**

Interestingly, the present TfOH-catalyzed ring-opening process could be extended to azetidine derivatives. Thus, reaction of 2-phenyl-1-tosylazetidine (**4**) with ferrocene (**2**, 2 equiv.) under conditions A (TfOH 10 mol%, DCE, RT) afforded the aminofunctionalized ferrocene derivative **5** in moderate yield (40%). As in the case of the reaction with aziridines, this ring-opening process took place with complete regioselectivity.



Scheme 6: Reaction of 2-phenyl-1-tosylazetidine with ferrocene.

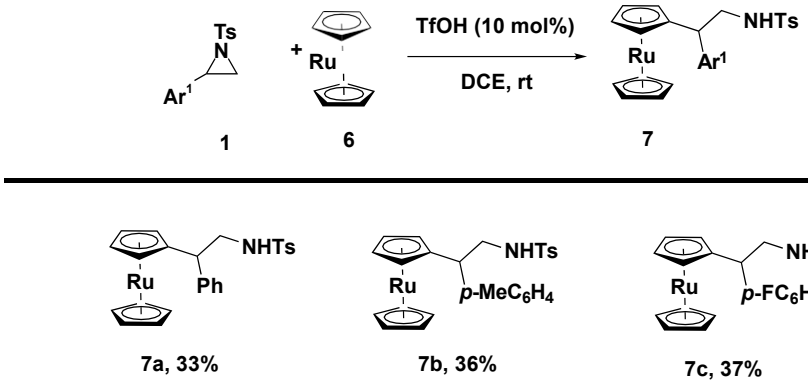
B.2.2.b Reaction of N-tosyl aziridines with ruthenocene

We found that this acid-catalyzed ring opening reaction was not limited to ferrocene. Indeed, ruthenocene **6** was likewise identified as viable substrate yielding the corresponding functionalized ruthenocene derivatives **7** (Table 2).

Thus, a representative aryl-substituted aziridines **1** and ruthenocene **6** were subjected to the previously developed reaction conditions A (TfOH 10 mol%, room temperature) providing the corresponding functionalized ruthenocene derivatives **7** in moderate yields. Both electron-rich and electron-deficient substituents could be accommodated in the aryl moiety.

As shown, the reaction of aziridines **1** with ruthenocene **6** exhibited consistently lower yields than those involving ferrocene, which might be related to the well documented diminished ability of ruthenocene to engage in electrophilic substitution reactions.[136]

Table 2: Reaction of aziridines **1** with rutenocene.



[a] Reaction conditions: **1** (0.1 mmol), (0.2 mmol), **4** (0.1 mmol), TfOH (10 mol%), DCE, rt. [b] The reported yields refer to isolated products **5** after column chromatographic purification.

B.2.2.c Synthesis of metallocene analogues of the relevant tetrahydroisoquinolines scaffold: proof of concept

To evaluate the synthetic potential of the new aminofunctionalized metallocenes derivatives we planned the synthesis of metallocene analogues of the privileged tetrahydroisoquinoline scaffold, which is a valuable and highly sought-after framework in medicinal chemistry.[137]

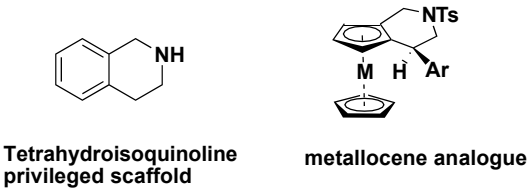
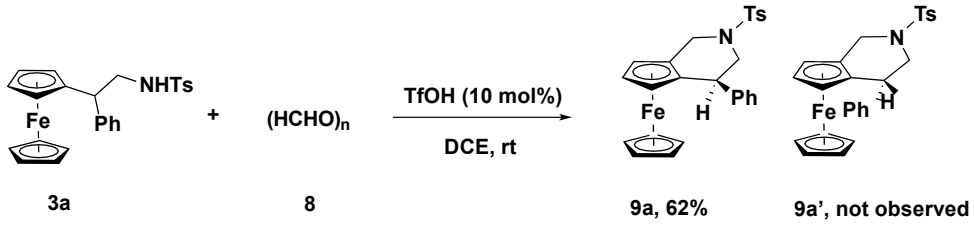


Figure 6: Metallocene analogues of tetrahydroisoquinoline.

We realized that a Pictet-Spengler type reaction could provide the target tetrahydroisoquinoline metallocene analogues. [138] To test this hypothesis, functionalized

[136] a) E. A. Hill, J. H. Richards, *J. Am. Chem. Soc.***1961**, *83*, 3840-3846; b) E. O. Fischer, M. von Foerster, C. G. Kreiter, K. Schwarzhans, *J. Organomet. Chem.***1967**, *7*, 113.
[137] M. E. Welsch, S. A. Snyder, B. R. Stockwell. **2010**. *Current Opinion in Chemical Biology, 14,* 347–361.
[138] (a) A. Pictet, T. B. Spengler. *Dtsch. Chem. Ges*. **1911**, *44*, 2030-2036. (b) G. J. Tatsui, *Pharm. Soc. Jpn*. **1928**, *48*, 92. For reviews: (a) E. D. Cox, J. M. Cook, *Chem. ReV*. **1995**, *95*, 1797-1842. (b) M. Chrzanowska, M. D. Rozwadowska. *Chem. Rev*. **2004***, 104*, 3341-337.

ferrocene **3a** was reacted with paraformaldehyde **8** in the presence of a catalytic amount (10 mol%) of different Lewis and Brønsted acids. Pleasingly, we found that the use of TfOH allowed the isolation of the corresponding ferrocene derivative **9a** in moderate yield after column chromatography (Scheme 7). Interestingly, compound **9a** featuring both central and planar chirality is formed as a single diastereoisomer.



Scheme 7: TfOH-catalyzed type reaction of ferrocene **3a** and paraformaldehyde.

The structure of compound **9a** was deduced from NMR experiments. In the ^{1}H-NMR spectrum, the two diastereotopic protons of the methylene appears at 3.55 and 4.63 ppm. The signal at 2.52 ppm belongs to the H in the benzylic position. The five protons of the unsubstituted Cp ligand appear at 4.23 ppm as a singlet. The other three protons for the monosubsituted ring appear between 4.02 and 4.23 ppm.

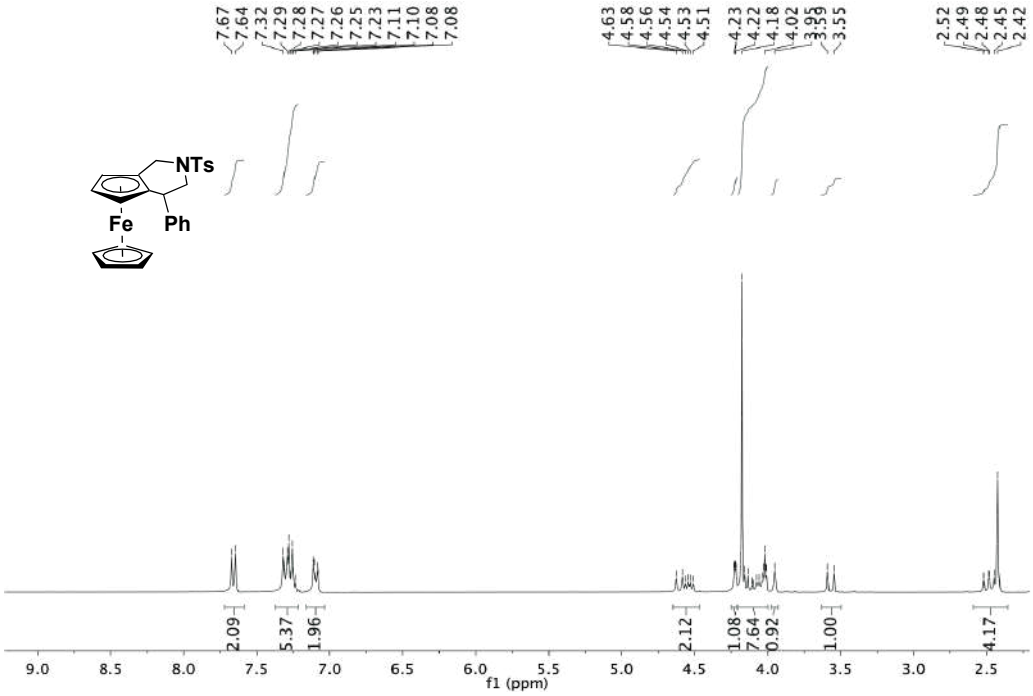


Figure 7: ^{1}H-NMR ($CDCl_3$, 300 MHz) of compound **9a.**

Representative signals in the ^{13}C-NMR spectrum are those at 81.6 and 85.1 ppm which belong to the C_{ipso} of the ferrocene. For the five equivalents carbon atoms of the unsubstituted ring, there is one signal at 63.8 ppm. The signal at 43.3 ppm corresponds to the benzylic carbon.

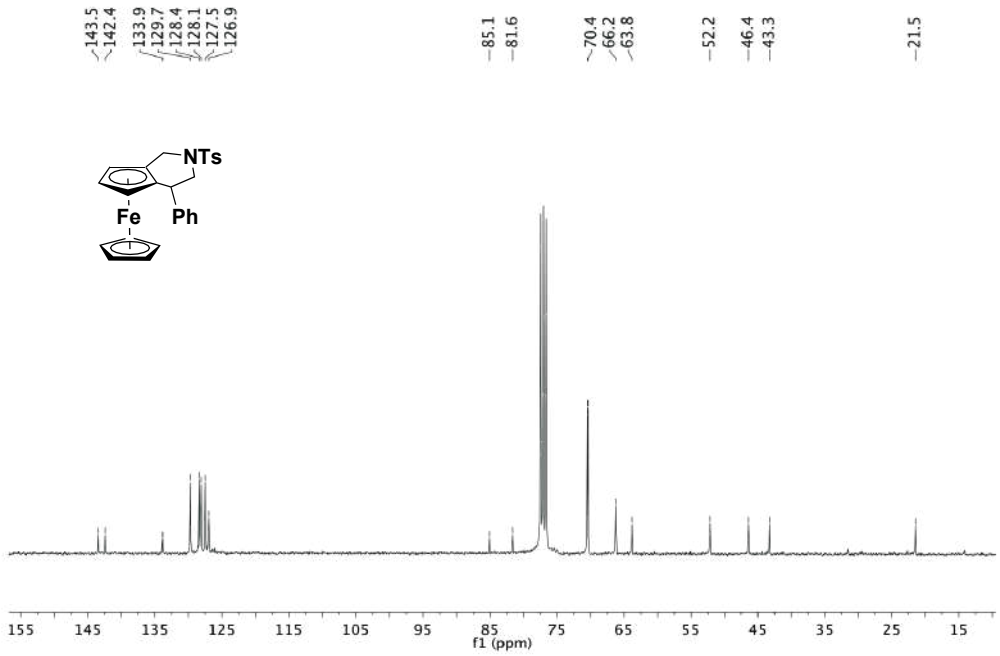
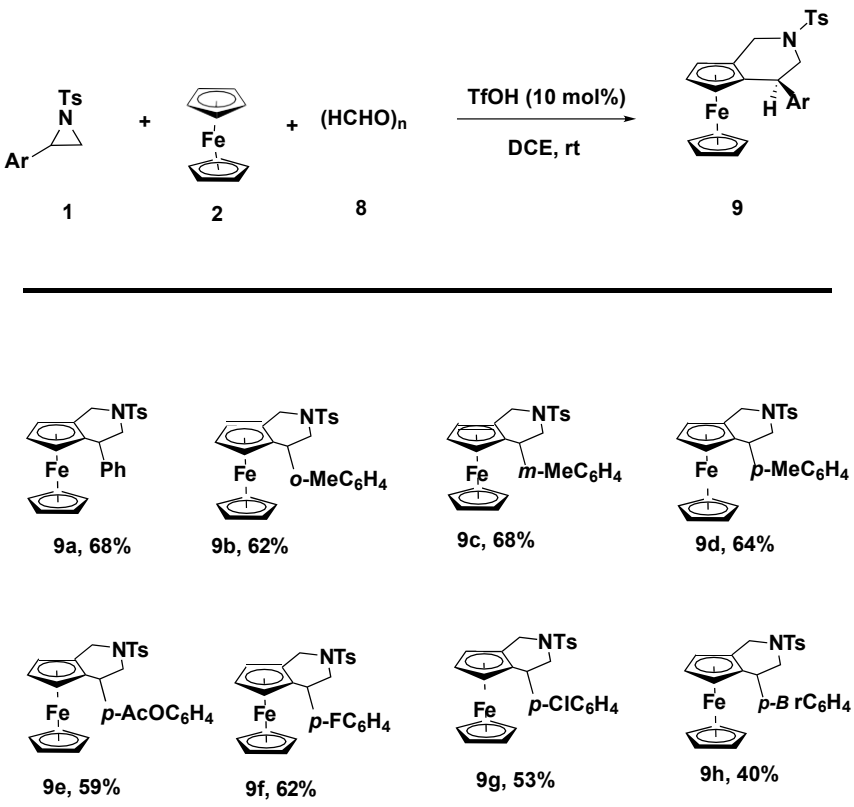


Figure 8: ^{13}C-NMR ($CDCl_3$, 75 MHz) of ferrocene derivative **9a.**

B.2.2.d Development of a multicomponent approach to metallocene analogues of tetrahydroisoquinolines

After establishing a suitable stepwise method to access ferrocene **9a**, and considering the ability of TfOH to catalyze the ring-opening reaction of *N*-sulfonyl aziridines **1** by ferrocene (Scheme 3, Conditions A), we decided to investigate the feasibility of preparing compound **9a** and structurally related ferrocene derivatives in a straightforward manner through a multicomponent reaction. Indeed, we were pleased to find that stirring ferrocene (**2**), the corresponding aziridine **1** and paraformaldehyde **8** in the presence of TfOH (10 mol%) in DCE at room temperature afforded the desired heterocyclic compounds **9** in synthetically useful yields (40-68%, Table 3). In all the cases investigated, compounds **9** are formed as single diastereoisomers.

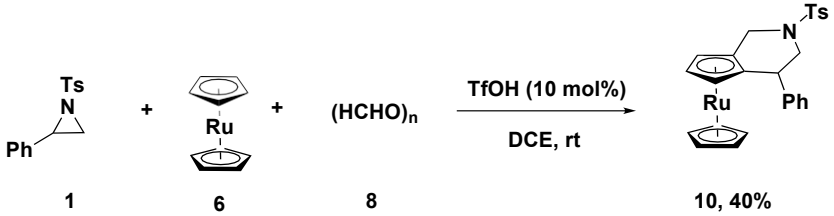
Table 3: Three-component approach to disubstittuted ferrocene derivatives **9.**



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), **8** (0.5 mmol), TfOH (10 mol%), DCE, RT. [b] The reported yields refer to isolated products after column chromatographic purification

Unfortunately, under the above reaction conditions, substituted aldehydes (e.g. benzaldehyde, acrolein) were found to be unreactive. The reaction stops after the ring-opening reaction of aziridine forming the corresponding derivatives **3**.

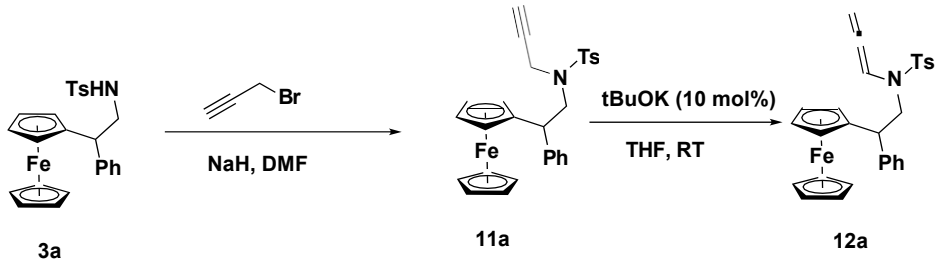
On the other hand, we carried out the 3-component coupling of 2-phenyl-1-tosylaziridine **1a**, ruthenocene **6** and paraformaldehyde **8**. Consistent with the results previously seem for the ring-opening of *N*-sulfonyl aziridines by ruthenocene (see Table 2), this transformation proceeded sluggishly delivering the desired functionalized ruthenocene derivative **10a** in moderate yield (40%).



Scheme 8: Three-component approach to disubstituted ruthenocene.

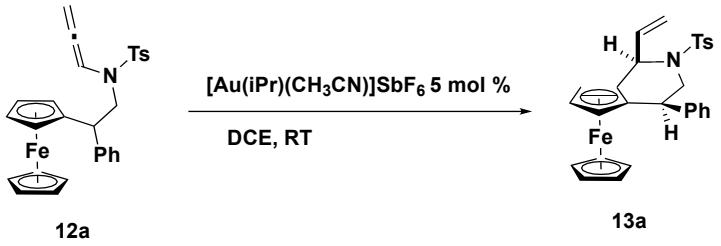
B.2.2.e. Gold-catalyzed intramolecular cyclization of allenamides

To partially overcome the limitation of the three-component reaction, we envisioned an alternative pathway to vinyl substituted derivatives based on the gold-catalyzed intramolecular cyclization of allenamides.[139] Thus, starting from aminosubstituted ferrocene derivative **3a** and using a conventional two-step sequence consisting of initial propargylation and subsequent *t*-BuOK-catalyzed isomerization, *N*-tosylallenamide **11a** was prepared in good overall yield (Scheme 9).



Scheme 9: Syntheis of allenamide **12a**.

Pleasingly, exposure of allenamide **12a** to 5 mol% of $[Au(IPr)(CH_3CN)]SbF_6$ in dichloromethane at room temperature resulted in the formation of ferrocene derivative **13a** in excellent isolated yield (88%) as a single stereoisomer.



Scheme 10: Isomerization of allenamide **12a** to ferrocene derivative **13a**.

The structure of compound **12a** was ascertained by mono and bidimensional NMR experiments. Furthermore, an X-ray diffraction study of ferrocene **12a** confirmed the proposed structure (Figure 9).

[139] For selected examples of gold(I)-catalyzed intramolecular hydroarylation of allenes, see: a) C. Liu, R. A. Widenhofer, *Org. Lett.* **2007**, *9*, 1935-1938; b) J. Barluenga, M. Piedrafita, A. Ballesteros, A. L. Suárez-Sobrino, J. M. González, *Chem. Eur. J*. **2010**, *16*, 11827-11831; c) Y. Wang, P. Zhang, X. Di, Q. Dai, Z.-M. Zhang, J. Zhang, *Angew. Chem*. **2017**, *129*, 16121-16125; *Angew. Chem. Int. Ed*. **2017**, *56*, 15905-15909.

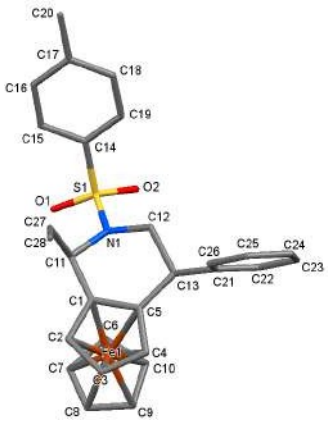


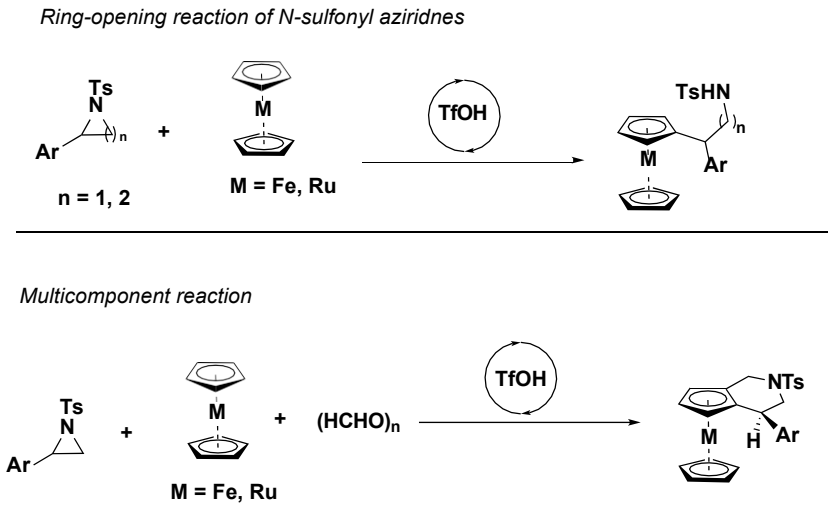
Figure 9: X-ray structure for ferrocene derivative **12a**.

B.2.3 General Conclusions

- We have devised a convenient synthesis of aminofunctionalized metallocene derivatives based on the regioselective ring-opening *N*-sulfonyl aziridines. Both ferrocene and ruthenocene proved to be suitable substrates for this ring-opening reaction.

- These aminofunctionalized metallocene were transformed into heterocyclic compounds through a Pictet-Splenger type reaction. Furthermore, three-component reactions between ferrocene, aziridine and formaldehyde have also demonstrated to represent a rapid and efficient means to access these metallocene analogues of the medicinally relevant tetrahydroisoquinoline motiv. Both stepwise and multicomponent fashions proceed with complete stereolectivity.

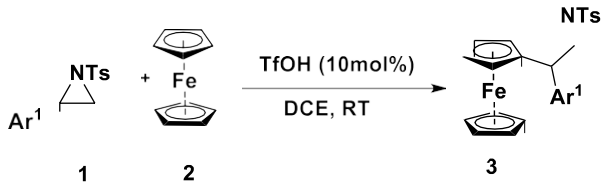
Graphical Summary



B.2.4 Experimental Section

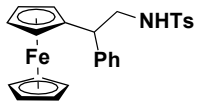
General Procedure for the synthesis of compounds 3

To a solution of aziridines **1** (0.1 mmol) and ferrocene **2** (0.2 mmol) in DCE (1 mL) was added TfOH (10 mol %). The resulting mixture was stirred at room temperature until disappearance of the starting material (monitored by TLC). The solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography (silica gel, mixtures of hexane/ethyl acetate 10:1) to yield compounds **3a-i.**



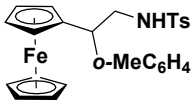
***N*-(2-phenyl-2ferrocenylethyl)-4-methyllbencenesulfonamide (3a):** The general procedure was followed using phenyl-aziridine **1a** (0.1 mmol), ferrocene **2** (0.2 mmol). Final chromatographic purification afforded compound **3a** (51%) as orange solid m.p = 160.3-163.9 ^{o}C

^{1}H RMN (300 MHz, $CDCl_3$): 7.74 (d, *J* = 8.0 Hz, 2H), 7.38-7.26 (m, 5H), 7.08 (d, *J* = 6.6 Hz, 2H), 4.59 (s, 1H), 4.16-3.90 (s + m, 9H), 3.81 (dd, *J* = 8.8 and 6.0 Hz, 1H), 3.63-3.50 (m, 1H), 3.29 (dd, *J* = 15.2 and 6.3 Hz, 1H), 2.47 (s, 3H). **^{13}C RMN** (75 MHz, $CDCl_3$): 143.5 (C), 141.7 (C), 136.8 (C), 129.8 (CH), 128.7 (CH), 127.9 (CH), 127.2 (CH), 89.3 (C) 68.8 (CH), 68.0 (CH), 67.7 (CH), 66.6 (CH), 48.4 (CH_2), 45.6 (CH), 21.6 (CH_3); **HRMS** (EI) calculated for [$C_{25}H_{25}FeNNaO_2S$] $[M+Na]^+$: 482.0848, found 482.0833.



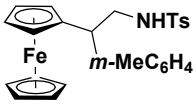
***N*-(2-*o*-methylphenyl-2ferrocenylethyl)-4-methyllbencenesulfonamide (3b):** The general procedure was followed using aziridine **1b** (0.1 mmol), ferrocene **2** (0.2 mmol). Final chromatographic purification afforded compound **3b** (54%) as orange solid m.p = 112.9-115.3 ^{o}C.

^{1}H RMN (300 MHz, $CDCl_3$): 7.75 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.19-7.04 (m, 3H), 6.92-6.86 (m, 1H), 4.77 (d, *J* = 6.0 Hz, 1H), 4.27-4.02 (s + m, 9H), 3.98 (d, *J* = 1.2 Hz, 1H), 3.53 (dd, *J* = 12.6 and 6.0 Hz, 1H), 3.41-3.27 (m, 1H), 2.47 (s, 3H), 2.38 (s, 3H). **^{13}C RMN** (75 MHz, $CDCl_3$): 143.5 (C), 140.3 (C), 136.7 (C), 135.9 (C), 130.7 (CH), 129.8 (CH), 127.2 (CH), 126.7 (CH), 126.4 (CH), 89.8 (C), 68.9 (CH), 68.1 (CH), 67.5 (CH), 67.1 (CH), 66.8 (CH), 65.9 (C), 47.8 (CH_2), 40.3 (CH), 21.6 (CH_3), 19.9 (CH_3). **HRMS** (EI) calculated for [$C_{26}H_{27}FeNNaO_2S$] $[M+Na]^+$: 496.1004, found 496.0994.



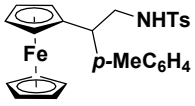
***N*-(2-*m*-methylphenyl-2ferrocenylethyl)-4-methyllbencenesulfonamide (3c):** The general procedure was followed using aziridine **1c** (0.1 mmol), ferrocene **2** (0.2 mmol). Final chromatographic purification afforded compound **3c** (49%) as orange solid m. p = 134.1-137.8 ^{o}C.

^{1}H RMN (300 MHz, $CDCl_3$): 7.74 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.23-7.00 (m, 2H), 6.86 (s, 2H), 4.64-4.46 (m, 1H), 4.12 (s + m, 8H), 3.94 (s, 1H), 3.76 (dd, *J* = 9.3 and 5.8 Hz, 1H), 3.67-3.51 (m, 1H), 3.35-3.23 (m, 1H), 2.47 (s, 3H), 2.32 (s, 3H). **^{13}C RMN** (75 MHz, $CDCl_3$): 143.5 (C), 141.6 (C), 138.3 (C), 136.9 (C), 129.7 (CH), 128.6 (CH), 128.0 (CH), 127.2 (CH), 124.9 (CH), 89.7 (C), 69.0 (CH), 68.1 (CH), 67.9 (CH), 67.5 (CH), 66.7 (CH), 48.3 (CH_2), 45.4 (CH), 21.6 (CH_3), 21.5 (CH_3). **HRMS (EI)**: calculated for $[C_{26}H_{27}FeNNaO_2S]$ $[M+Na]^+$: 496.1004, found 496.0999.



***N*-(2-*p*-methylphenyl-2ferrocenylethyl)-4-methyllbencenesulfonamide (3d):** The general procedure was followed using aziridine **1d** (0.1 mmol), ferrocene **2** (0.2 mmol). Final chromatographic purification afforded compound **3d** (49%) as orange solid m. p = 137.8-139.8 ^{o}C.

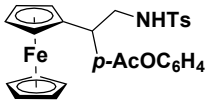
^{1}H RMN (300 MHz, $CDCl_3$): 7.73 (d, *J* = 8.2 Hz, 2H), 7.38-7.23 (m, 3H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 4.59 (d, *J* = 5.6 Hz, 1H), 4.16-4.12 (s + m, 8H), 3.94 (s, 1H), 3.75 (dd, *J* = 9.2 and 5.7 Hz, 1H), 3.54 (dd, *J* = 12.9 and 5.6 Hz, 1H), 3.34-3.18 (m, 1H), 2.47 (s, 3H), 2.33 (s, 3H). **^{13}C RMN** (75 MHz, $CDCl_3$): 143.9 (C), 139.0 (C), 137.2 (C), 130.2 (C), 129.8 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 90.3 (C), 69.4 (CH), 68.5 (CH), 68.2 (CH), 68.0 (CH), 67.1 (CH), 48.8 (CH_2), 45.5 (CH), 22.0 (CH_3), 21.5 (CH_3). **HRMS** (EI) calculated for $[C_{26}H_{27}FeNNaO_2S]$ $[M+Na]^+$: 496.1004, found 496.0984.



***N*-(2-*p*-acetoxylphenyl-2ferrocenylethyl)-4-methyllbencenesulfonamide (3e):** The general procedure was followed using aziridine **1e** (0.1 mmol), ferrocene **2** (0.2 mmol). Final chromatographic purification afforded compound **3e** (33%) as orange solid m. p = 152.5-155.5 ^{o}C.

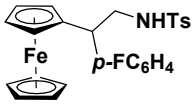
^{1}H RMN (300 MHz, $CDCl_3$): 7.73 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 4.58 (s, 1H), 4.23 (s, 8H), 4.04 (s, 1H), 3.75 (d, *J* = 7.7 Hz, 1H), 3.56 (dt, *J* = 12.7 and 6.5 Hz, 1H), 3.30-3.14 (m, 1H), 2.46 (s, 3H), 2.31 (s, 3H). **^{13}C RMN** (75 MHz, $CDCl_3$): 169.4 (C), 149.6 (C), 143.5 (C), 139.4 (C), 136.8 (C), 129.8 (CH), 128.9 (CH),

127.2 (CH), 121.7 (CH), 90.7 (C), 70.1 (CH), 69.1 (CH), 68.6 (CH), 68.3 (CH), 48.3 (CH_2), 45.1 (CH), 21.6 (CH_3), 21.2 (CH_3). **HRMS (EI):** calculated for [$C_{27}H_{27}FeNaNO_4S$] $[M+Na]^+$: 540.0902, found 540.0889.



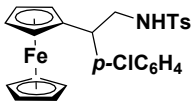
***N*-(2-*p*-fluorolphenyl-2ferrocenylethyl)-4-methyllbencenesulfonamide (3f):** The general three-component procedure was followed using aziridine **1f** (0.1 mmol), ferrocene **2** (0.2 mmol). Final chromatographic purification afforded compound **3f**(78%) as orange solid m. p = 135.8-139.2 ^oC.

^{1}H RMN (300 MHz, $CDCl_3$): 7.77-7.68 (m, 2H), 7.37-7.26 (m, 2H), 7.01 (ddd, *J* = 28.2, 13.1 and 7.1 Hz, 4H), 4.72 (t, *J* = 5.9 Hz, 1H), 4.17-3.99 (s + m, 8H), 3.93-3.88 (m, 1H), 3.84 (dd, *J* = 9.4 and 5.8 Hz, 1H), 3.56 (dt, *J* = 12.7 and 6.4 Hz, 1H), 3.24 (ddd, *J* = 12.7, 9.4 and 5.2 Hz, 1H), 2.47 (s, 3H). **^{13}C RMN** (75 MHz, $CDCl_3$): 161.8 (C, d, J_{C-F} = 244.1 Hz), 143.6 (C), 137.7 (C, d, J_{C-F} = 3.1 Hz), 129.8 (CH), 129.4 (CH, d, J_{C-F} = 7.9 Hz), 128.2 (C), 127.1 (CH), 115.5 (CH, d, J_{C-F} = 21.1 Hz), 89.2 (C), 68.8 (CH), 68.1 (CH), 67.6 (CH), 67.5 (CH), 66.4 (CH), 48.5 (CH_2), 45.5 (CH), 21.6 (CH_3). **^{19}F RMN** (282 MHz, $CDCl_3$): 115.4. **HRMS (EI)**: calculated [$C_{25}H_{24}FFeKNO_2S$] $[M+K]^+$: 516.0493, found 516.0496.



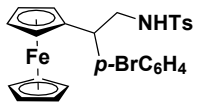
***N*-(2-*p*-chlorophenyl-2ferrocenylethyl)-4-methyllbencenesulfonamide (3g):** The general three-component procedure was followed using aziridine **1g** (0.1 mmol), ferrocene **2** (0.2 mmol). Final chromatographic purification afforded compound **3g** (42%) as orange solid m. p = 157.3-160.2 ^oC.

^{1}H RMN (300 MHz, $CDCl_3$): 7.71 (d, *J* = 8.2 Hz, 2H), 7.35 (s, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 4.68 (t, *J* = 6.0 Hz, 1H), 4.15 (s + m, 9H), 3.81 (dd, *J* = 9.2 and 5.8 Hz, 1H), 3.55 (dd, *J* = 12.6 and 6.2 Hz, 1H), 3.24 (ddd, *J* = 12.7, 9.4 and 5.7 Hz, 1H), 2.47 (s, 3H).**^{13}C RMN** (75 MHz, $CDCl_3$): 143.6 (C), 140.4 (C), 136.7 (C), 132.8 (C), 129.8 (CH), 129.3 (CH), 128.8 (CH), 127.1 (CH), 89.1 (C), 69.1 (CH), 68.3 (CH), 67.8 (CH), 66.6 (CH), 48.3 (CH_2), 45.1 (CH), 21.6 (CH_3). **HRMS (EI)**: calculated for [$C_{25}H_{24}ClFeNO_2S$] $[M+Na]^+$: 516.0458, found 516.0437.



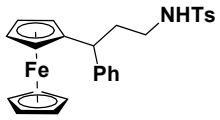
***N*-(2-*p*-bromophenyl-2ferrocenylethyl)-4-methyllbencenesulfonamide (3h):** The general three-component procedure was followed using aziridine **1g** (0.1 mmol), ferrocene **2** (0.2 mmol). Final chromatographic purification afforded compound **3h** (55%) as orange solid m. p = 168.5-171.1 ^oC.

^{1}H RMN (300 MHz, $CDCl_3$): 7.71 (d, *J* = 8.2 Hz, 2H), 7.35 (dd, *J* = 11.0 and 8.3 Hz, 4H), 6.95 (d, *J* = 8.3 Hz, 2H), 4.78 (t, *J* = 6.2 Hz, 1H), 4.18-4.05 (s + m, 8H), 3.90 (s, 1H), 3.82 (dd, *J* = 9.4 and 5.7 Hz, 1H), 3.57 (dt, *J* = 12.6 and 6.3 Hz, 1H), 3.24 (ddd, *J* = 12.7, 9.5 and 5.8 Hz, 1H), 2.47 (s, 3H).**^{13}C RMN** (75 MHz, $CDCl_3$): 143.6 (C), 141.0 (C), 136.7 (C), 131.7 (CH), 129.8 (CH), 129.7 (CH), 127.1 (CH), 120.9 (C), 88.9 (C), 68.9 (CH), 68.2 (CH), 67.7(CH), 66.4 (CH), 48.3 (CH_2), 45.2 (CH), 21.6 (CH_3). **HRMS (EI):** calculated for $[C_{25}H_{24}BrFeNO_2S]$ $[M+Na]^+$: 559.9953, found 559.9953.



***N*-(3-phenyl-2ferrocenylethyl)-4-methyllbencenesulfonamide (5):** The general three-component procedure was followed using phenyl-azetidine **4** (0.1 mmol), ferrocene **2** (0.2 mmol). Final chromatographic purification afforded compound **5** (40%) as orange solid m.p = 167.5-168.4 ^oC.

^{1}H-NMR (300 MHz, $CDCl_3$): 1.91-2.06 (m, 1H), 2.20-2.27 (m, 1H), 2.44 (s, 3H), 2.83-2.91 (m, 2H), 3.61 (dd, *J*=10.7 and 4.6 Hz, 1H), 3.96 (br, 1H), 4.06 (s, 1H), 4.09-4.12 (m, 8H), 4.21-4.25 (m, 1H), 7.11-7.14 (m, 2H), 7.21-7.32 (m, 4H), 7.68-7.70 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.5 (CH_3), 36.8 (CH_2), 41.7 (CH_2), 43,3 (CH), 67.2 (CH_2), 67.5 (CH), 67.9(CH), 68.8 (CH), 94.32 (C), 126.6 (CH), 127.1 (CH), 127.7 (CH), 128.5 (CH), 129.7 (CH), 136.9 (C), 143,4 (C), 144.0 (C); **HRMS** (EI) calculated for $[C_{26}H_{27}FeNO_2S]^+$ (M^+): 473.1119, found :



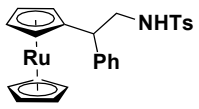
General Procedure for the synthesis of compounds 7

To a solution of aziridines **1** (0.1 mmol) and ruthenocene **6** (0.2 mmol) in DCE (1 mL) was added TfOH (10 mol %). The resulting mixture was stirred at room temperature until disappearance of the starting material (monitored by TLC). The solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography (silica gel, mixtures of hexane/ethyl acetate 10:1) to yield compounds **7a-c**

***N*-(2-phenyl-2-ruthenocenilethyl)-4-methyllbencenesulfonamide (7a):** The general three-component procedure was followed using phenyl-aziridine **1a** (0.1 mmol), ruthenocene **6** (0.2 mmol). Final chromatographic purification afforded compound **7a** (33%) as yellow solid m.p = 163.2-166.9 ^oC

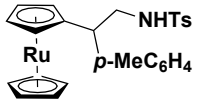
^{1}H RMN (300 MHz, $CDCl_3$): 7.75 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.26 (dd, *J* = 10.9 and 3.5 Hz, 3H), 7.04 (dd, *J* = 7.8 and 1.5 Hz, 2H), 5.64-5.54 (m, 1H), 4.62 (s, 5H), 4.52-4.50(m, 2H), 4.42-4.39 (m, 2H), 3.79-3.65 (m, 1H), 3.33-3.15 (m, 2H), 2.47 (s, 3H); **^{13}C RMN** (75 MHz, $CDCl_3$): 143.5 (C), 142.5 (C), 136.6 (C), 129.8 (CH), 128.6

(CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 92.0 (C), 71.5 (CH), 70.6 (CH), 70.4 (CH), 69.9 (CH), 69.1 (CH), 48.3 (CH_2), 44.3 (CH), 21.6 (CH_3). **HRMS (EI):** calculated for $[C_{25}H_{25}RuNO_2S]$ $[M+Na]^+$: 528.0646, found 528.0604.



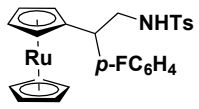
***N*-(2-*p*-methylphenyl-2-ruthenocenilethyl)-4-methyllbencenesulfonamide (7b):** The general three-component procedure was followed using p-methoxyphenyl-aziridine **1** (0.1 mmol), ruthenocene **6** (0.2 mmol). Final chromatographic purification afforded compound **7b** (36%) as yellow solid m.p = 163.5-167.1 ^oC

^{1}H RMN (300 MHz, $CDCl_3$): 7.75 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 5.56 (t, *J* = 5.8 Hz, 1H), 4.62 (s, 5H), 4.56-4.43 (m, 2H), 4.44-4.35 (m, 2H), 3.66 (t, *J* = 7.7 Hz, 1H), 3.29-3.14 (m, 2H), 2.47 (s, 3H), 2.31 (s, 3H);**^{13}C RMN** (75 MHz, $CDCl_3$): 143.4 (C), 139.4 (C), 136.7 (C), 136.6 (C), 129.7 (CH), 129.3 (CH), 127.4 (CH), 127.2 (CH), 92.2 (C), 71.4 (CH), 70.6 (CH), 70.4 (CH), 69.8 (CH), 69.0 (CH), 48.4 (CH_2), 43.9 (CH), 21.6 (CH_3), 21.0 (CH_3); **HRMS (EI)**: calculated $[C_{26}H_{27}RuNaNO_2S]$ $[M+Na]^+$: 516.0493, found 516.0493.

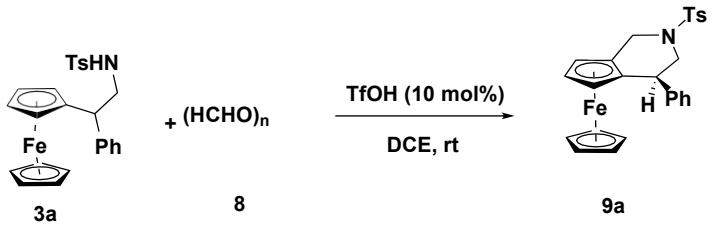


***N*-(2-*p*-Fluorophenyl-2-ruthenocenilethyl)-4-methyllbencenesulfonamide (7c):** The general three-component procedure was followed using p-fluorophenyl-aziridine **1** (0.1 mmol), ruthenocene **6** (0.2 mmol). Final chromatographic purification afforded compound **7c** (37%) as yellow solid m.p = 179.2-181.6 ^oC.

^{1}H RMN (300 MHz, $CDCl_3$): 7.75 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.99 (ddd, *J* = 24.5, 13.0 and 7.2 Hz, 4H), 5.64-5.56 (m, 1H), 4.62 (s, 5H), 4.51 (d, *J* = 1.1 Hz, 2H), 4.40-4.35 (m, 2H), 3.72 (dd, *J* = 14.5 and 6.8 Hz, 1H), 3.29-3.12 (m, 2H), 2.47 (s, 3H); **^{13}C RMN** (75 MHz, $CDCl_3$): 161.8 (C, d, J_{C-F} = 244.1 Hz), 143.5 (C), 138.3 (C, d, J_{C-F} = 3.1 Hz), 129.8 (CH), 129.1 (CH, d, J_{C-F} = 7.9 Hz), 127.2 (CH), 115.4 (CH, d, J_{C-F} = 21.3 Hz), 91.8 (C), 71.5 (CH), 70.5 (CH), 69.9 (CH), 69.0 (CH), 48.4 (CH_2), 43.5 (CH), 21.6 (CH_3). **HRMS (EI)**: calculated $[C_{25}H_{24}RuFNaNO_2S]$ $[M+Na]^+$: 546.0553, found 546.0493.

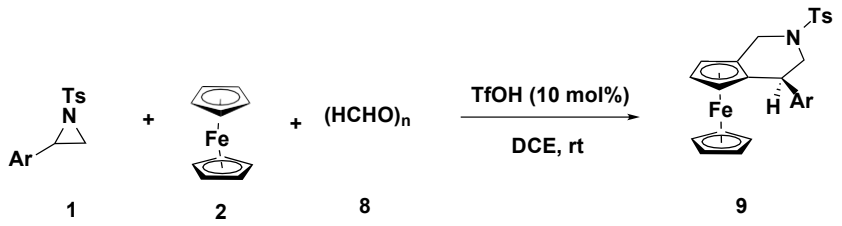


General Procedure for the synthesis of compounds 9



To a solution of ferrocene derivative **3a** (0.1 mmol), paraformaldehyde **8** (0.5 mmol) in DCE (1 mL) was added TfOH (10 mol %). The resulting mixture was stirred at room temperature until disappearance of the starting material (monitored by TLC). The solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography (silica gel, mixtures of hexane/ethyl acetate 10:1) to yield compound **9a.**

Multicomponent syntheisis of derivatives 7



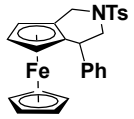
To a solution of aziridines **1** (0.1 mmol), ferrocene **2** (0.2 mmol), paraformaldehyde **8** (1 mmol) in DCE (1 mL) was added TfOH (10 mol %). The resulting mixture was stirred at room temperature until disappearance of the starting material (monitored by TLC). The solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography (silica gel, mixtures of hexane/ethyl acetate 10:1) to yield compounds **9a-h**.

Characterization Data of compunds

9a

The general three-component procedure was followed using phenyl-aziridine **1a** (0.1 mmol), ferrocene **2** (0.2 mmol), paraformaldehyde **8** (1 mmol). Final chromatographic purification afforded compound **9a** (68%) as orange solid m.p = 155.6-157.2 ^{o}C.

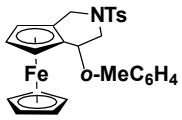
^{1}**H-NMR** (300 MHz, $CDCl_3$): 2.42 (s, 3H), 2.42-2.52 (m, 1H), 3.56 (d, *J*= 13.1 Hz, 1H), 3.95 (br, 1H), 4.02-4.18 (s, 7H), 4.22 (br, 1H), 4.52 (dd, *J*= 9.6 and 5.7 Hz, 1H), 4.60 (d, *J*= 13.1, 1H), 7.08-7.11 (m, 2H), 7.25-7.32 (m, 5H), 7.65 (d, *J*=8.0 Hz, 2H); ^{13}**C-NMR** (75 MHz, $CDCl_3$): 21.5 (CH_3), 43.3 (CH), 46.4 (CH_2), 52.2 (CH_2), 3.8 (CH), 66.2 (CH), 70.4 (CH), 81.6 (C), 85.1(C), 126.9 (CH), 127.5 (CH), 128.1 (CH), 128.4 (CH), 129.7 (CH), 133.9 (C), 142.4 (C), 143.5 (C); **HRMS** (EI) calculated for $[C_{26}H_{25}FeNO_2S]^+$ (M^+): 471.09554, found 494. 2957



9b

The general three-component procedure was followed using aziridine **1b** (0.1 mmol), ferrocene **2** (0.2 mmol), paraformaldehyde **8** (1 mmol). Final chromatographic purification afforded compound **9b** (62%) as orange solid.

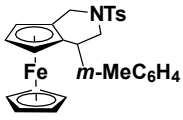
^{1}H-NMR (300 MHz, $CDCl_3$): 2-40-2.43 (m+s, 4H), 2.48 (s, 3H), 3.57 (d, *J*= 13.1 Hz, 1H), 3.92 (br, 1H), 4.09 (t, *J*= 2.2 Hz, 1H), 4.03-4.07 (m, 1H), 4.19 (s, 5H), 4.22 (br, 1H), 4.66 (d, *J*= 13.2 Hz, 1H), 4.79-4.84 (m, 1H), 6.80 (d, *J*= 7.44 Hz, 1H), 7.05-7.40 (m, 5H), 7.67 (d, *J*=8.2 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 20.2 (CH_3), 22.0 (CH_3), 39.8 (CH), 46.8 (CH_2), 51.0 (CH_2), 64.2 (CH), 66.4 (CH), 66.5 (CH), 70.8 (CH), 82.1 (C), 86.0(C), 126.5 (CH), 127.2 (CH), 127.9 (CH), 128.5 (CH), 130.2 (CH), 130.8 (CH), 134.3 (CH), 136.2 (CH), 140.7 (C), 143.9 (C); **HRMS** (EI) calculated for $[C_{27}H_{27}FeNO_2S]^+$ (M^++Na): 508.1004, found 508.0986.



9c

The general three-component procedure was followed using aziridine **1c** (0.1 mmol), ferrocene **2** (0.2 mmol), paraformaldehyde **8** (1 mmol). Final chromatographic purification afforded compound **9c** (68%) as orange solid.

^{1}H-NMR (300 MHz, $CDCl_3$): 2.31 (s, 3H), 2-41-2.48 (m+s, 4H), 3.54 (d, *J*= 13.1 Hz, 1H), 3.97 (br, 1H), 4.01-4.08(m, 2H), 4.18 (s, 5H), 4.22 (br, 1H), 4.51 (dd, *J*= 9.8 and 5.7 Hz, 1H), 4.62 (d, *J*= 13.1 Hz, 1H), 6.88-6.92 (m, 2H), 7.04-7.07 (m, 1H), 7.14-7.19 (m, 1H), 7.28-7.32 (m, 2H), 7.65-7.68 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.8 (CH_3), 21.9 (CH_3), 43.7 (CH), 46.9 (CH_2), 52.7 (CH_2), 64.2 (CH), 66.6 (CH), 66.7 (CH), 70.8 (CH), 82.0 (C), 85.5 (C), 125.6 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 129.3 (CH), 130.1 (CH), 134.1 (CH), 138.5 (CH), 142.7 (C), 143.9 (C); **HRMS** (EI) calculated for $[C_{27}H_{27}FeNO_2S]^+$ (M^++ Na): 508.1004, found 508.1004.

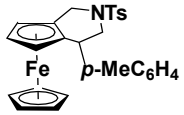


9d

The general three-component procedure was followed using aziridine **1d** (0.1 mmol), ferrocene **2** (0.2 mmol), paraformaldehyde **8** (1 mmol). Final chromatographic purification afforded compound **9d** (64%) as orange solid.

^{1}H-NMR (300 MHz, $CDCl_3$): 2.33 (s, 3H), 2.43 (s, 3H), 2.43-2.51 (m, 1), 3.57 (d, *J*= 13.1, 1H), 4.00 (br, 1H), 4.01-4.06 (m, 2H), 4.17 (s, 5H), 4.21 (br, 1H), 4.49 (dd, *J*= 9.5 and 5.3 Hz, 1H), 4.60 (d, *J*= 13.1 Hz, 1H), 6.97-7.08 (m, 4H), 7.28-7.31 (m, 2H), 7.65 (d, *J*=8.3 Hz, 2H); **^{13}C-NMR**

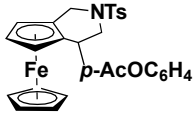
(75 MHz, $CDCl_3$): 21.0 (CH_3), 21.5 (CH_3), 42.8 (CH), 46.4 (CH_2), 52.3 (CH_2), 63.7 (CH), 66.1 (CH), 70.4 (CH), 81.6 (C), 85.2(C), 127.5 (C), 128.0 (CH), 129.1 (CH), 129.7 (CH), 133.9 (CH), 136.6 (C), 139.4 (C), 143.4 (C); **HRMS** (EI) calculated for $[C_{27}H_{27}FeNO_2S]^+$ (M^++ Na): 508.1004, found 508.0986.



9e

The general three-component procedure was followed using aziridine **1e** (0.1 mmol), ferrocene **2** (0.2 mmol), paraformaldehyde **8** (1 mmol). Final chromatographic purification afforded compound **9e** (59%) as orange solid.

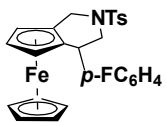
^{1}H-NMR (300 MHz, $CDCl_3$): 2.31 (s, 3H), 2.43-2.50 (m, 4H), 3.56 (d, *J*= 13.1, 1H), 3.96-4.03 (m, 3H), 4.18 (s, 6H), 4.22 (br, 1H), 4.54 (dd, *J*= 9.5 and 5.3 Hz, 1H), 4.62 (d, *J*= 13.1 Hz, 1H), 6.97 (d, *J*= 8.6 Hz, 2H), 7.08 (d, *J*= 8.6 Hz, 2H), 7.30 (d, *J*= 7.9 Hz, 2H), 7.65 (d, *J*=8.3 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.2 (CH_3), 21.5 (CH_3), 42.7 (CH), 46.4 (CH_2), 52.4 (CH_2), 63.9 (CH), 66.2 (CH), 66.3 (CH_2), 70.4 (CH), 81.6 (C), 84.7 (C), 121.5 (CH), 127.5 (CH), 129.1 (CH), 129.8 (CH), 133.7 (CH), 139.9 (C), 143.6 (C), 149.5 (C), 169.6 (C); **HRMS** (EI) calculated for $[C_{28}H_{27}FeNO_4S]^+$ (M^++ Na): 552.0902, found 552.0888.



9f

The general three-component procedure was followed using aziridine **1f** (0.1 mmol), ferrocene **2** (0.2 mmol), paraformaldehyde **8**(1 mmol). Final chromatographic purification afforded compound **9f** (62%) as orange solid.

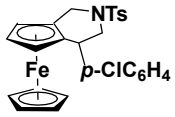
^{1}H-NMR (300 MHz, $CDCl_3$): 2.43 (s, 3H), 2.51-2.58 (m, 1), 3.63 (d, *J*= 13.2 Hz, 1H), 3.93-4.03 (m, 3H), 4.15 (s, 5H), 4.22 (br, 1H), 4.48 (dd, *J*= 9.1 and 5.6 Hz, 1H), 4.55 (d, *J*= 13.2 Hz, 1H), 6.91-7.04 (m, 4H), 7.31 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 22.0 (CH_3), 42.8 (CH), 46.7 (CH_2), 52.5 (CH_2), 64.3 (CH), 66.4 (CH), 66.7 (CH), 70.8 (CH), 81.9 (C), 85.3 (C), 115.6 (CH, $J_{C\text{-}F}$= 21.0 Hz), 128.9 (CH), 129.99-130.0 (CH, $J_{C\text{-}F}$= 7.6 Hz), 133.9 (CH), 134.1 (C), 138.6 (C), 144.0 (C), 162.2 (C, $J_{C\text{-}F}$= 2.44 Hz); **HRMS** (EI) calculated for $[C_{26}H_{24}FFeNO_2S]^+$ (M^++Na): 512.0753, found 512.0742.



9g

The general three-component procedure was followed using aziridine **9g** (0.1 mmol), ferrocene **2** (0.2 mmol), paraformaldehyde **8** (1 mmol). Final chromatographic purification afforded compound **9g** (53%) as orange solid.

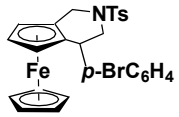
^{1}H-NMR (300 MHz, $CDCl_3$): 2.43 (s, 3H), 2.54-2.61 (m, 1H), 3.65 (d, *J*= 13.2 Hz, 1H), 3.94-4.03 (m, 3H), 4.15 (m, 5H), 4.23 (br, 1H), 4.42-4.46 (m, 1H), 4.54 (d, *J*= 13.2 Hz, 1H), 6.94 (d, *J*= 8.4 Hz, 2H), 7.33(d, *J*=8.4 Hz, 2H), 7.36 (d, *J*= 9.4 Hz, 2H), 7.62 (d, *J*=8.2 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.5 (CH_3), 42.6 (CH), 46.2 (CH_2), 51.8 (CH_2), 63.9 (CH), 66.0 (CH), 66.4 (CH), 70.4 (CH), 81.5 (C), 84.5 (C), 120.9 (CH), 127.4 (CH), 129.7 (C), 129.8 (CH), 131.4 (CH), 133.8 (C), 141.5 (C), 143.6 (C); (EI) calculated for $[C_{26}H_{24}ClFeNO_2S]^+$ (M^++ Na): 528.0567, found 528.0458.



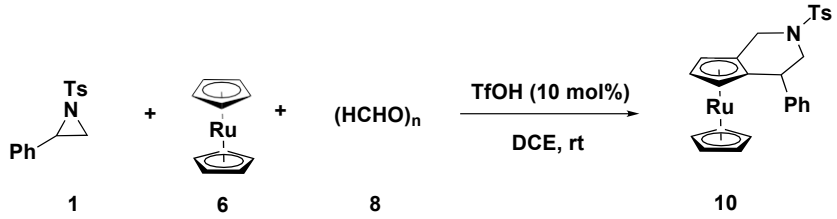
9h

The general three-component procedure was followed using aziridine **1h** (0.1 mmol), ferrocene **2** (0.2 mmol), paraformaldehyde **8** (1 mmol). Final chromatographic purification afforded compound **9h** (40%) as orange solid.

^{1}H-NMR (300 MHz, $CDCl_3$): 2.43 (s, 3H), 2.55-2.62 (m, 1H), 3.65 (d, *J*= 13.2 Hz, 1H), 3.94-4.04 (m, 3H), 4.16 (m, 5H), 4.22 (br, 1H), 4.46 (dd, *J*= 8.6 and 5.4 Hz 1H), 4.55 (d, *J*= 13.2 Hz, 1H), 7.00 (d, *J*= 8.4 Hz, 2H), 7.21 (d, *J*=8.4 Hz, 2H), 7.29 (d, *J*= 9.4 Hz, 2H), 7.65 (d, *J*=8.2 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 22.0 (CH_3), 42.9 (CH), 46.7 (CH_2), 52.4 (CH_2), 64.3 (CH), 66.4 (CH), 66.8 (CH), 70.8 (CH), 81.9 (C), 85.0 (C), 127.9 (CH), 128.9 (CH), 129.8 (C), 130.1 (CH), 133.1 (CH), 134.0 (C), 1414 (C), 144.0 (C); **HRMS** (EI) calculated for $[C_{26}H_{24}BrFeNO_2S]^+$ (M^++ Na): 571.9958, found 571.9458.



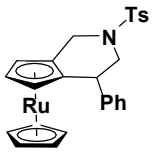
General Procedure for the synthesis of compund 10



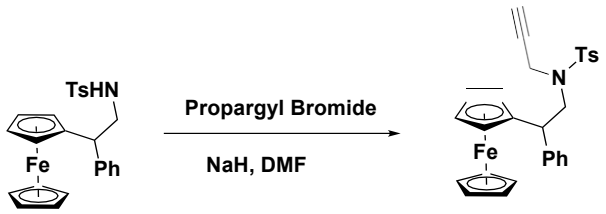
To a solution of aziridines **1** (0.1 mmol), ruthenocene **6** (0.2 mmol), paraformaldehyde **8** (1 mmol) in DCE (1 mL) was added TfOH (10 mol %). The resulting mixture was stirred at room temperature until disappearance of the starting material (monitored by TLC). The solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography (silica gel, mixtures of hexane/ethyl acetate 10:1) to yield compound **10**.

The general three-component procedure was followed using phenyl-aziridine **1a** (0.1 mmol), ruthenocene **6** (0.2 mmol) and paraformaldehyde **8** (1 mmol). Final chromatographic purification afforded compound **10** (53%) as orange solid.

^{1}H-NMR (300 MHz, $CDCl_3$): 2.41-2.51 (s+m, 4H), 3.55 (d, *J*= 13.2 Hz, 1H), 3.95 (br, 1H), 4.01-4.07 (m, 2H), 4.17 (s, 5H), 4.22 (br, 1H), 4.54 (dd, *J*= 9.6 and 5.7 Hz, 1H), 4.60 (d, *J*= 13.1 Hz, 1H), 7.08-7.11 (m, 2H), 7.25-7.31 (m, 5H), 7.65 (d, *J*=8.2 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 22.0 (CH_3), 43.1 (CH), 46.6 (CH_2), 52.43(CH_2), 67.2 (CH), 69.3 (CH), 69.6 (CH), 70.8 (CH), 72.6 (CH), 85.5 (C), 89.6 (C), 127.3 (C), 127.8 (CH), 128.4 (CH), 128.8 (CH), 130.1 (CH), 134.4 (C), 143.0 (C), 143.8; **HRMS** (EI) calculated for $[C_{26}H_{25}RuNO_2S]^+$ (M^+): 517.0650, found x.



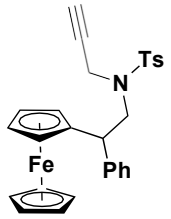
General Procedure for the synthesis of compund 12



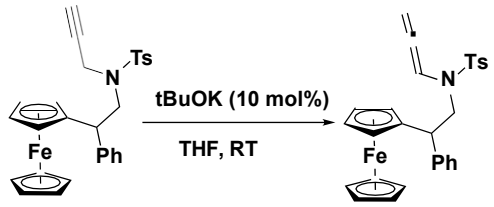
To a solution of ferrocene derivative **3a** (0.5 mmol) was dissolved in DMF (10 mL). The mixture was cooled to 0 ºC and NaH (1.2 equiv.) was added. The reaction mixture was stirring. Then, it was warmed to room temperature and propargyl bromide (1.4 equiv.) was added and it was stirred at room temperature 8 hours. The mixture was washed with H_2O (5 X 15 ml) and extracted with diethyl ether (3 x 15 ml). The combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography (silica gel, mixtures of hexane/ethyl acetate 20:1) to yield compound **11.**

Characterization Data of Compund 11

^{1}H-NMR (300 MHz, $CDCl_3$): 2.06 (t, *J*= 2.2 Hz, 1H), 2.44 (s, 3H), 2.97-3.03 (d, *J*= 16.7 Hz, 1H), 3.29-3.03 (m, 1H), 3.53-3.57 (m, 1H), 3.61-4.20 (m, 11H), 7.28-7.31 (m, 7H), 7.77 (d, *J*= 8.4 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.6 (CH_3), 37.6 (CH_2), 45.6 (CH_2), 51,5 (CH), 66.7 (CH), 67.4 (CH), 67.8 (CH), 67.9 (CH), 68.8(CH), 73.6(CH), 90.0 (C), 126.9 (CH), 127.8 (CH), 128.1(CH), 129.4(CH), 136.0 (C), 142.5 (C), 143.5 (C); **HRMS** (EI) calculated for $[C_{28}H_{27}FeNO_2S]^+$ (M^+): 497.1112, found 497.1087.



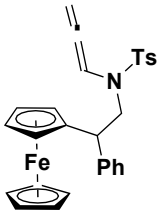
General Procedure for the synthesis of compund 12



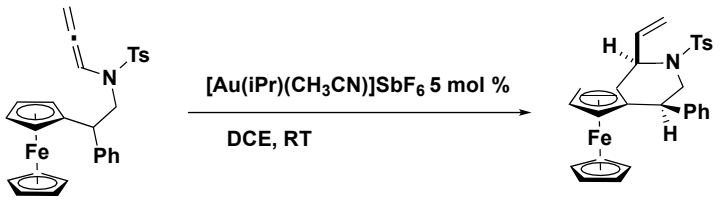
To a solution of compound **11** (0.2 mmol) in THF (6 ml) was added tBuOK (10 mol%) and it was stirred a room temperature. The resulting mixture was stirred at room temperature until disappearance of the starting material (monitored by TLC). The mixture extracted with diethyl ether (3 x 15 ml) and was washed with H_2O (3 X 15 ml). The combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography (silica gel, mixtures of hexane/ethyl acetate 5:1) to yield compound **12a.**

Characterization Data of Compund 12a

^{1}H-NMR (300 MHz, $CDCl_3$): 2.43 (s, 3H), 3.44 (dd, *J*= 13.7 and 9.7 Hz, 1H), 3.67 (dd, *J*= 13.6 and 6.1 Hz, 1H), 3.99 (br, 1H), 4.10-4.18 (m, 8H), 4.20 (br, 1H), 5.13 (dd, *J*= 9.6 and 6.2 Hz, 1H), 5.23 (dd, *J*= 9.7 and 6.4 Hz, 1H), 6.62 (t, *J*= 7.05 Hz, 1H), 7.21-7.32 (m, 7H), 7.67 (d, *J*=6.6 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 22.0 (CH_3), 45.1 (CH_2), 52.1 (CH_2), 67.5 (CH_2), 67.6 (CH), 68.2(CH), 69.1 (CH), 88.4 (CH_2), 99.1 (C), 101.1, 127.1 (CH), 127.7 (CH), 128.4 (CH), 129.0 (CH), 130.1 (CH), 135.3 (C), 142.6 (C), 144.2 (C), 202.1 (C); **HRMS** (EI) calculated for $[C_{28}H_{27}FeNO_2S]^+$ (M^+): 491.1112, found :



General Procedure for the synthesis of compound 13a



To a solution of compound **12** (0.1 mmol) in DCE (1 ml) was added tBuOK (10 mol%) and it was stirred a room temperature. Then was added [Au(iPr)(CH_3CN)]SbF_6 (5 mol%) and the resulting mixture was stirred at room temperature 8 hours. The solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography (silica gel, mixtures of hexane/ethyl acetate 20:1) to yield compound **13a**.

Characterization Data of Compund 13a

^{1}H-NMR (300 MHz, $CDCl_3$): 2.41 (s, 3H) 2.69-2.72 (m, 2H), 3.84-3.86 (m, 2H), 4.04 (t, *J*=2.1 Hz, 1H), 4.20 (br, 1H), 4.19-4.25 (m, 6H), 4.51-4.62 (m, 2H), 7.10-7.13 (m, 2H), 7.23-7.29 (m, 6H), 7.74 (d, *J*=8.5 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.9 (CH_3), 43.7 (CH_2), 47.4 (CH), 57.4 (CH), 65.2 (CH), 66.4 (CH), 66.8 (CH), 70.9 (CH), 85.4 (C), 86.0 (C), 118.2 (CH_2), 127.4 (CH), 128.6 (CH), 128.9 (CH), 130.0 (CH), 136.4 (C), 138.9 (C), 142.9 (C), 143.5; **HRMS** (EI) calculated for $[C_{28}H_{27}FeNO_2S]^+$ $(M)^+$ 497.1119, found 497.1121.