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Recent advances in transition metal-catalyzed C-H bond functionalization of ferrocene derivatives†

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Transition metal-catalyzed C-H bond functionalizations of ferrocene derivatives have emerged in the last few years as a versatile tool in synthetic organometallic chemistry. These protocols offer significant advantages over more traditional approaches for the synthesis of functionalized ferrocene derivatives in terms of both atom- and step-economy. In this Perspective, we aim to showcase the state of the art in this field, with special emphasis on recent asymmetric methodologies.

Introduction

Few other simple molecules can claim as fascinating a history as ferrocene's. It would be a mistake, however, to regard ferrocene as just a historically significant organometallic compound. In fact, more than 60 years after its discovery,¹ the chemistry of ferrocene still represents a very active research field.² The reasons for this long-lasting interest are manifold. First of all, ferrocene featured a nice, yet not trivial at that time, sandwich-type structure, whose understanding impelled the revision of conventional thinking about the nature of the metal-carbon bond. On the other hand, ferrocene and its derivatives display an unusual stability towards moisture, oxygen and many chemicals as well as possessing other unique electrochemical properties. Furthermore, functionalized ferrocenes have a huge number of applications in a diverse range of fields including material science and medicinal chemistry. In this regard, one of the most important applications of ferrocene derivatives is their use in catalysis. Particularly, planar chiral ferrocene-based ligands are extremely useful structural motifs in homogeneous asymmetric catalysis.³

In general, the high sensitivity of many metallocene complexes precludes the direct functionalization through conventional organic functional group conversions. Consequently, the synthesis of substituted metallocene derivatives requires the derivatization of the cyclopentadiene ring before the final transmetalation step. This synthetic route has been used for the preparation of numerous 1,1'-disubstituted metallocenes, including many ferrocene derivatives (Scheme 1, A).⁴ However, the above-mentioned stability of ferrocene towards reaction conditions of conventional organic functional group interconversion makes the direct functionalization of the coordinated cyclopentadienyl ligand also possible. In this regard, two strategies have mainly been used for accessing functionalized ferrocene derivatives (Scheme 1, B). The first one is based on the well-established aromatic nature of ferrocene and its consequent ability to undergo typical aromatic electrophilic substitution reactions.⁵ Particularly, a sequence involving initial Friedel-

Crafts acylation followed by subsequent transformations of the resulting acylferrocene has been successfully applied to the synthesis of many functionalized ferrocenes.

A second general strategy relies on initial treatment of ferrocene with alkyllithium reagents to afford ferrocenyl lithium which, in turns, would react in a second step with the corresponding electrophile. This methodology has proven particularly useful for the diastereo- and enantioselective synthesis of chiral 1,2-disubstituted ferrocenes using chiral auxiliary directed metalation groups⁶ or chiral ligands,⁷ respectively.

Scheme 1 Traditional approaches for the synthesis of functionalized ferrocene derivatives (X = halogen or OOCR; FG = functional group).

In spite of the unquestionable synthetic usefulness of these classical methodologies, their use entails several issues. Thus, in general, a multistep sequence of organic-group transformations is often required to install specific functionalities. Moreover, they require the use of a stoichiometric amount of a Bronsted or Lewis acid or of a highly basic (and nucleophilic) organolithium

reagent. Finally, these methodologies display a low functional group compatibility. For these reasons, the search for new and efficient methods for the synthesis of functionalized ferrocene derivatives is still a very active research topic. Particularly, the development of *catalytic* functionalization approaches, which overcome some of the mentioned shortcomings, would be very convenient.

In recent years transition metal-catalyzed C-H bond functionalization has emerged as an important and powerful tool in organic synthesis.⁸ These strategies have become extremely popular because they enable the transformation of non-activated C-H bonds into C-C and C-heteroatom bonds in an atom- and step-economical way starting from simple and available precursors, offering significant advantages over more traditional approaches. In particular, direct functionalization of arenes via metal-catalyzed C(sp²)-H activation has undergone rapid growth in the last years. These C-H bond activation methodologies appear particularly well-suited for the preparation of functionalized ferrocene derivatives. Surprisingly, only in a limited number of cases these well-established methodologies for the functionalization of benzene derivatives have been transferred to ferrocene derivatives. It is the aim of this Perspective to showcase these recent advances in the emerging field of homogeneous transition metal-catalyzed C-H bond functionalization of ferrocene derivatives (Scheme 2). Taking into account the well-known importance of planar chiral ferrocenes in asymmetric catalysis, special focus is given in this review to recent asymmetric metal-catalyzed methodologies for direct functionalization of ferrocene derivatives. We have decided to arrange the contents of this review according to the structure of the involved ferrocene precursor. Thus, it is divided into three parts: 1) intermolecular directing group assisted metal-catalyzed C-H bond functionalization of ferrocene derivatives, 2) intramolecular metal-catalyzed C-H bond functionalizations of ferrocene derivatives and 3) intermolecular metal-catalyzed C-H bond functionalizations of ferrocene. In general, we will focus mainly on the synthetic utility of the processes; however, a brief discussion of the reaction pathways will also be included in some selected cases.

Scheme 2 Metal-catalyzed C-H bond activation approaches for the synthesis of functionalized ferrocene derivatives.

1. Intermolecular directing group assisted metal-catalyzed C-H bond functionalization of ferrocene derivatives

In most cases the transition metal-catalyzed C-H bond functionalization of ferrocene derivatives requires the use of preinstalled directing groups. In this approach, the presence of a strongly coordinating atom favors the regioselective cleavage of neighboring C-H bonds (usually the C-H bonds *ortho* to the

directing group) with formation of metallacycle intermediates. Nitrogen-based directing groups proved particularly useful in the C-H bond functionalization of ferrocene derivatives. Regarding the catalyst, although this field has been amply dominated by the use of palladium-based catalysts, successful transformations involving alternative catalysts have also been documented.

1.1 Transition metal-catalyzed intermolecular C-H bond functionalizations of ferrocene derivatives bearing nitrogen heterocycles as directing groups

In 2007, taking advantage of the well-documented coordination ability of the oxazoline moiety, You and co-workers reported the palladium-mediated cross-dehydrogenative coupling of ferrocenyl oxazolines with simple arenes (Scheme 3).⁹ Several arenes including benzene, toluene, fluorobenzene, *tert*-butylbenzene, and 1,4-dimethoxybenzene can participate in this double C-H activation process. Moderated yields are obtained when a non-chiral oxazoline auxiliary ($R^1 = R^2 = \text{Me}$) was used as the directing group. Under appropriate reaction conditions, a dimeric palladium complex intermediate (**I** in Scheme 3) resulting from an *ortho*-palladation reaction could be isolated.

Interestingly, when an enantiopure ferrocenyl oxazoline ($R^1 = \text{H}$; $R^2 = i\text{Pr}$) was employed, the corresponding planar chiral ferrocene derivative was isolated in modest yield (24%) but as a single stereoisomer.

Although the use of a catalytic amount of the palladium source in combination with several oxidants and additives was also attempted, it proved much less successful.

Scheme 3 Palladium-mediated cross-coupling reactions of ferrocenyl oxazolines with arenes.

The use of an oxazoline auxiliary as both directing group and chirality source has also been investigated by Shibata and co-workers, who reported the rhodium(III)-catalyzed reaction of a chiral oxazolyl ferrocene derived from valinol with isocyanates (Scheme 4).¹⁰ The best results were obtained when a combination of [RhCp*(OAc)₂(H₂O)] (5 mol%) and HBF₄·OEt₂ (10 mol%) was used as the catalytic system. Under these conditions, the corresponding amidation products were isolated as single diastereoisomers in moderated yields (24–69%).

Scheme 4 Rhodium-catalyzed amidation of ferrocene derivatives with isocyanates (Cy = cyclohexyl).

In 2012, Shibata and co-workers reported the $[\text{Ir}(\text{cod})_2]\text{BARF}$ [cod = cycloocta-1,5-diene; BARF = tetrakis(3,5-trifluoromethylphenyl)borate] catalyzed reaction of ferrocene derivatives bearing directing groups with alkenes to give products resulting from a C-H bond alkylation.¹¹ Good yields of the corresponding dialkylated products were obtained in the reaction of 2-ferrocenylpyridine with a broad range of olefin coupling partners, including those bearing functional groups such as ester, ketone, boronic ester, etc.

Based on these results, the same group reported in 2014 the enantioselective version of this process.¹² A catalytic system comprising $[\{\text{Ir}(\text{coe})_2\text{Cl}\}_2]$ (coe: cyclooctene), sodium tetrakis[3,5-bis(trifluoromethylphenyl)]borate (NaBARF), and a chiral diene ligand proved highly proficient when an isoquinolyl directing group was used (Scheme 5). Under the optimized reaction conditions monoalkylated products were obtained with good yields (up to 96%) and enantioselectivities (up to 93%). As in the achiral version, this transformation is compatible with a wide range of alkenes.

Scheme 5 Iridium-catalyzed enantioselective C-H alkylation of (isoquinol-1-yl)ferrocene [NaBARF = sodium tetrakis[3,5-bis(trifluoromethylphenyl)]borate].

1.2 Transition metal-catalyzed intermolecular C-H bond functionalizations of dimethylaminomethyl-substituted ferrocene derivatives

The use of a dimethylaminomethyl directing group has been particularly fruitful in a number of palladium-catalyzed

processes. Thus, following seminal work by Yu and co-workers on the use of chiral monoprotected amino acids as efficient ligands for enantioselective C-H activation of prochiral substrates,¹³ the group of You accomplished the palladium-catalyzed asymmetric coupling of aminomethyl ferrocene derivatives with arylboronic acids with air as terminal oxidant (Scheme 6, Method A).¹⁴ After extensive screening of amino acids, Boc-L-Valine-OH (Boc-L-Val-OH) turned out to be the optimal ligand in terms of enantioselectivity and reactivity. When this ligand was employed, an array of arylboronic acids bearing either an electron-donating group as an electron-withdrawing group were converted into the corresponding monoarylated ferrocene derivatives in excellent chemical yields (up to 81%) and enantioselectivities (up to 99% ee). Aside from its remarkable efficiency and selectivity, the affordability of the required ligand (commercially available) along with the possibility of performing the reaction on a relatively large scale with no significant detrimental effect are, from a practical point of view, additional features of this catalytic coupling process.

In a related approach, Wu and co-workers demonstrated the feasibility of a palladium-catalyzed asymmetric dehydrogenative cross-coupling between *N,N*-dimethylaminomethylferrocene and a variety of alkenes, leading to the corresponding alkenylated ferrocene derivatives in excellent enantioselectivities (up to 99%) and yields (up to 98%) when monoprotected amino acid Boc-L-Phe-OH was employed as a chiral ligand (Scheme 6, Method B).¹⁵ Acrylates, acrylamides, phosphate esters, styrenes and aliphatic olefins were suitable reaction partners in this dehydrogenative cross-coupling process.

Scheme 6 Synthesis of planar chiral ferrocenes by palladium/amino acid-catalyzed enantioselective arylation (Method A) and alkenylation (Method B) of *N,N*-dimethylaminomethylferrocene (TBAB = tetrabutylammonium bromide; DMA = *N,N*-dimethylacetamide; DMF = *N,N*-dimethylformamide).

Interestingly, these palladium-catalyzed transformations did

not require the addition of an external oxidant to regenerate the active palladium(II) species. In this regard, some experimental evidences support a dual role (as substrate and oxidant) of the starting ferrocene. Indeed, Pd(0) would be oxidized by *N,N*-dimethylaminomethylferrocenium, generated in situ by reaction of *N,N*-dimethylaminomethylferrocene and air, regenerating the catalytically active Pd(II) species (Scheme 7). In full agreement with this proposal, when these palladium-catalyzed reactions were performed under a N₂ atmosphere only a trace amount of the desired coupling product was obtained.

Scheme 7 *N,N*-dimethylaminomethylferrocenium as terminal oxidant in palladium-catalyzed C-H bond functionalizations of *N,N*-dimethylaminomethylferrocene.

The palladium-catalyzed dehydrogenative annulation of *N,N*-dimethylaminomethyl ferrocene and diarylalkynes under external oxidant-free conditions has been reported by Cui, Wu and co-workers in 2012 (Scheme 8).¹⁶

Scheme 8 Palladium-catalyzed dehydrogenative annulations of *N,N*-dimethylaminomethyl ferrocene with diarylalkynes (TBAB = tetrabutylammonium bromide; DMA = *N,N*-dimethylacetamide).

Shortly after the Cui's and Wu's report, You and co-workers developed the enantioselective version of this process.¹⁷ Even though yields of this transformation were only moderate (28-45%), excellent enantioselectivities (up to 99%) were achieved again when the monoprotected amino acid Boc-L-Val-OH was used as the chiral ligand.

1.3 Transition metal-catalyzed intermolecular C-H bond functionalizations of acylferrocene derivatives

In 2012 Sing and Dixneuf reported the ruthenium(II)-catalyzed alkenylation of ferrocenyl ketones via directed C-H bond activation (Scheme 9).¹⁸ This dehydrogenative coupling is limited to the use of alkyl substituted ketones (R¹ = alkyl group). Even though the reported yields are in all the cases modest (14-26%), this process represents the unique ruthenium-catalyzed C-H bond functionalization of ferrocene derivatives reported to date.

Scheme 9 Ruthenium(II)-catalyzed alkenylation of ferrocenyl ketones via C-H bond activation.

2. Intramolecular metal-catalyzed C-H bond functionalizations of ferrocene derivatives

A pioneering contribution in this field was made by Siegel and Schmalz, who in 1997 reported the intramolecular carbene insertion into Cp-H bonds of ferrocene derivatives.¹⁹ Thus, the decomposition of diazoketones in the presence of both rhodium and copper catalysts allowed the preparation of the cyclization products resulting from the insertion of the corresponding electrophilic metal-carbene intermediate into the Cp-H bond. Moreover, this cyclization could be conducted in an enantioselective way when copper(I) triflate (5 mol%) was used in combination with a chiral bis-oxazoline ligand (Scheme 10).

Scheme 10 Intramolecular insertion of carbenoids into Cp-H bonds of ferrocene.

In 2014, three research groups concurrently reported the enantioselective synthesis of planar chiral ferrocenes via palladium(0)-catalyzed intermolecular direct C-H bond arylation.²⁰⁻²² Thus, Kang, Gu and co-workers reported the palladium-catalyzed intramolecular cyclization reaction of 2-iodobenzoyl substituted ferrocenes to form indenone-fused derivatives (Scheme 11, Method A).²⁰ Screening of different ligands allowed the authors to identify diphosphines as the most convenient ligands for this coupling process. Among them, BINAP was finally chosen because it offers an optimal balance between efficiency and accessibility. Further optimization studies revealed that toluene at elevated temperature (100 °C) was the best solvent for this reaction. Notably, a range of functional groups, including aldehyde, ketone, ester, and amide, were perfectly tolerated under the reaction conditions. Even substrates containing terminal carbon-carbon double bonds and α,β -unsaturated esters, usually reactive functionalities in palladium-catalyzed reactions, were also competent reactants in this intramolecular coupling. Under standard conditions the reaction with ruthenocenes proceeded with good yields and selectivities.

Independently, Gu, You and coworkers reported a similar palladium-catalyzed intramolecular asymmetric C-H bond

arylation starting from 2-chlorobenzoyl substituted ferrocenes (Scheme 11. Method B).²¹ As in the previous study, good chemical yields and excellent enantioselectivities for the coupling products could be obtained when using BINAP as the chiral ligand. Under the optimized reaction conditions (2.5 mol% of Pd(OAc)₂, 5 mol% of the biphosphine ligand, 30 mol% of pivalic acid, and 1.5 equiv of Cs₂CO₃ in *p*-xylene at 60 °C) the coupling process showed a broad substrate scope. Moreover, this intramolecular C-H bond arylation was carried out on a gram-scale without any detrimental effect on both yield and enantioselectivity.

Scheme 11 Enantioselective synthesis of indenone-fused ferrocene derivatives via palladium-catalyzed intramolecular direct C-H arylation.

A related process, namely the palladium-catalyzed intramolecular C-H arylation reaction of *N*-(2-bromoaryl)ferrocenecarboxamides, was reported by Liu, Zhao and co-workers (Scheme 12).²² The resulting quinolinone-fused ferrocene derivatives were obtained in good chemical yields (up to 91%) and enantioselectivities (up to 96%) when a TADDOL-derived phosphoramidite was used as a chiral ligand.

Scheme 12 Enantioselective synthesis of quinolinone-fused ferrocene derivatives via palladium-catalyzed intramolecular direct C-H arylation.

A simplified catalytic cycle for these palladium-catalyzed intramolecular direct C-H bond arylations is outlined in Scheme 13. It would involve initial oxidative addition of the haloarene moiety to palladium(0) ligated to the chiral ligand to afford the corresponding palladium(II) intermediate **I**. Subsequent *ortho*-C-H palladation would afford a palladacycle intermediate **III**, which would evolve to the final arylated ferrocene derivatives via reductive elimination. According with this mechanistic proposal, the induction of the axial chirality would take place during the metalation step, in which the chiral palladium complex **I** would be able to discriminate between the two enantiotopic *ortho*-C-H bonds of the cyclopentadienyl ligand.

Scheme 13 Proposed catalytic cycle for the palladium-catalyzed intramolecular direct C-H bond arylation.

Very recently, Shibata and co-workers developed an efficient rhodium-catalyzed asymmetric intramolecular cross dehydrogenative coupling of ferrocene with silanes (Scheme 14).²³ Screening of different chiral ligands showed that chiral dienes are superior in terms of selectivity. Interestingly, the use of an alkene as a hydrogen acceptor was essential to reach high enantioselectivities with 3,3-dimethylbut-1-ene providing the best results. Under the optimized conditions a range of 2-(dimethylhydrosilyl)phenylferrocene substrates bearing both electron-donating and electron-withdrawing substituents on the phenyl ring were converted into the corresponding products in good yields and selectivities. In contrast, poorer yield and selectivity were observed when substrates bearing bulky substituents at the silicon were subjected to the standard conditions. A similar situation was found for the germanium analogues.

Independently, He and coworkers reported a similar rhodium-catalyzed enantioselective intramolecular C-H bond silylation of Cp rings in ferrocene and ruthenocene derivatives.²⁴

Selected examples

- R = H, 67% yield, 85% ee
- R = 4-Me, 56% yield, 74% ee
- R = 4-CF₃, 55% yield, 78% ee
- R = 5-Me, 44% yield, 86% ee
- R = 5-CF₃, 53% yield, 80% ee
- R = 5-OCF₃, 55% yield, 76% ee

Scheme 14 Enantioselective synthesis of planar chiral ferrocenes via rhodium-catalyzed intramolecular direct C-H silylation (coe = cyclooctene).

3. Intermolecular metal-catalyzed C-H bond functionalizations of ferrocene

As stated before, the development of transition-metal-catalyzed C-H bond functionalizations of ferrocene derivatives that do not contain a coordinating directing group has remained challenging.

Plenio and co-workers reported in 2004 the iridium-catalyzed regioselective borylation of ferrocene derivatives with a stoichiometric amount of B₂pin₂ (pin = pinacolato) (Scheme 15).²⁵ Ferrocene and a range of mono- and disubstituted ferrocene derivatives were successfully used in this process. The borylated ferrocene derivatives available by this methodology are suitable for further transformations.

Scheme 15 Iridium-catalyzed borylation of ferrocene (pin = pinacolato, dtbp = 4,4'-di-*tert*-butyl-2,2'-bipyridine).

In 2010, while studying the iron-catalyzed direct arylation of unactivated arenes with aryl halides, Lei and co-workers reported the reaction of ferrocene with bromobenzene to give the monoarylated product in moderate yield (54%) (Scheme 16).²⁶

Scheme 16 Iron-catalyzed direct arylation of ferrocene with bromobenzene (DMEDA = *N,N*'-dimethylethane-1,2-diamine; HMDS = hexamethyldisilazane).

Rooted in stoichiometric work on alkenylation of ferrocene by Fujiwara and co-workers,²⁷ the palladium-catalyzed aerobic

dehydrogenative Heck reaction of ferrocene was recently demonstrated by Zakrzewski and co-workers (Scheme 17).²⁸ In this process, the use of 4,5-diazafluoren-9-one (DAF) as additive resulted essential to boost product formation. It is also worth noting that the reaction required molecular oxygen as the sole oxidant. This coupling process was compatible with a variety of olefins containing electron-withdrawing groups such as ketone, aldehyde, ester, and phosphonate. In contrast, alkenes that bear aryl or alkoxy groups are not reactive under these conditions. Notably, the process took place with complete *E*-stereoselectivity.

Scheme 17 Palladium-catalyzed dehydrogenative Heck reaction of ferrocene with alkenes (DAF = 4,5-diazafluoren-9-one).

In 2014, López et al reported the synthesis of functionalized ferrocenes via gold(I)-catalyzed coupling of stabilized vinyl diazo derivatives and ferrocene.²⁹ Indeed, treatment of vinyl diazo compounds with a slight excess of ferrocene in the presence of a catalytic amount (5 mol%) of [Au(IPr)(CH₃CN)]SbF₆ [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene] in dichloromethane at room temperature afforded the corresponding functionalized ferrocene derivatives in moderate yields (Scheme 18). This functionalization of ferrocene is believed to proceed by means of a gold-vinyl carbenoid intermediate **IV** with a high electrophilic character at the terminal position. Based on isotopic labelling and competition experiments the authors proposed an electrophilic aromatic substitution mechanism, in which the gold-vinyl carbenoid intermediate would act as the electrophilic partner. The synthesis of the corresponding ruthenocene derivatives has been also reported.

Scheme 18 Synthesis of functionalized ferrocene derivatives via gold(I)-catalyzed reaction of ferrocene and vinyl diazo compounds [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene].

Conclusions

In this Perspective, we have summarized some relevant developments in the synthesis of functionalized ferrocene derivatives by means of transition metal-catalyzed C-H bond functionalization reactions. This field has experienced an extraordinary growth in the last few years, resulting in the discovery of powerful transformations otherwise difficult to achieve. For some specific reactions, impressive advances have been made. This is the case for example of the directed asymmetric Pd-catalyzed C-H functionalization of ferrocene derivatives where both high reactivity and excellent enantioselectivity have been accomplished in a number of cases.

In spite of these relevant recent contributions, a critical lecture of the current state of the art allows identifying some pending issues on which further work is required. For example, with a few exceptions, most of the reported processes require the presence of a directing group attached to the ferrocene and the metal-catalyzed C-H bond functionalization of ferrocene itself remains particularly challenging. Most of the developed transformations resorted to the use of precious metals as catalysts (mainly palladium), whose availability is far from ideal. In this regard, further developments need to focus on implementing new and more sustainable C-H bond functionalization methodologies based on widely available metals. Finally, the transition metal-catalyzed C-H bond functionalization of ferrocene derivatives involving C-heteroatom bond formation remains clearly underdeveloped.

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† This Perspective article is dedicated to Professor José Barluenga on the occasion of his 75th birthday.

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