EurJIC
European Journal of Inorganic Chemistry

Review
doi.org/10.1002/ejic.202100911

Chemistry Europe
European Chemical Societies Publishing

www.eurjic.org

Synthesis and Applications of Ferrocene-Fused Nitrogen Heterocycles

Olaya Bernardo,[a] Silvia González-Pelayo,[b] and Luis A. López*[a]

The marriage of heterocyclic compounds with ferrocene has proven to be an extremely fruitful field of research. In fact, in the last years, several ferrocene-embedded heterocyclic compounds have been reported. In some cases, the synergistic combination of the properties of the heterocyclic and metallacyclic motifs provides to the fused systems interesting applications. This Review summarizes the major advances in the synthesis of ferrocene-fused nitrogen heterocyclic compounds and their applications, particularly in asymmetric catalysis.

1. Introduction

Heterocyclic compounds are ubiquitous and essential to life because they are common structural motifs in numerous natural products and bioactive compounds. As a clear example of that, heterocyclic compounds are key components in nucleic acids, which, by controlling the protein biosynthesis, are the macromolecules responsible of the inherited traits of living beings. In addition to being part of multiple natural products, heterocyclic compounds also play a crucial role in modern societies because many synthetic heterocycles have a direct impact on human wellbeing. For example, it has been reported that about 70% of all agrochemicals that have been introduced to the market within the last 20 years bear at least one heterocyclic ring.[1] As an additional example, a study on the prevalence of nitrogen in U.S. FDA approved unique small-molecule pharmaceuticals published in 2020 revealed that 78% of small-molecule drugs contain a nitrogen heterocycle.[2] Interestingly, this proportion was 59% in a similar study published in 2014,[3] thus highlighting the ever-growing importance of nitrogen heterocycles in modern drug design (Figure 1A shows two representative prescribed drugs containing nitrogen heterocycles).[4] Additionally, heterocyclic compounds (particularly those featuring nitrogen) are extremely important in organic synthesis, coordination chemistry and homogeneous catalysis, including organocatalysis (some relevant examples are depicted in Figure 1B).

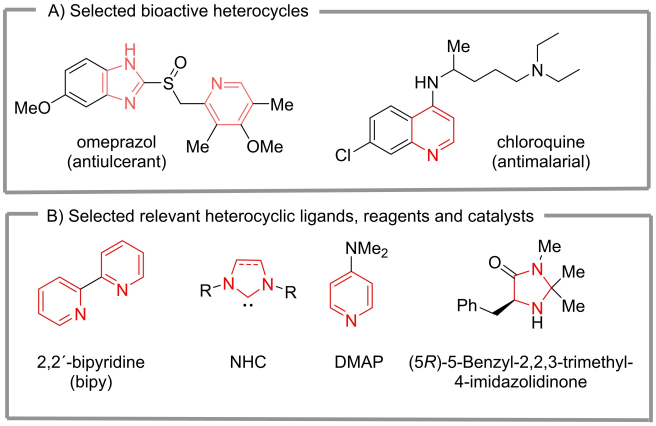


Figure 1. A) Representative drugs containing heterocyclic compounds. B) Selected relevant heterocyclic compounds in organic synthesis, coordination chemistry and catalysis.

Owing to their diverse applications, the development of efficient methodologies for the synthesis of new heterocyclic architectures represents always a worthwhile objective.

On the other hand, 70 years after its discovery,[5] the chemistry of ferrocene continues to attract intense attention. This lasting interest is due, in part, to the fact that many functionalized ferrocene derivatives display relevant applications in numerous aspects of chemical sciences.[6] For example, ferrocene derivatives are widely used as ligands in (asymmetric) catalysis, even on an industrial scale (some representative examples are provided in Figure 2A).[7] The most emblematic example in this field is xyliphos ligand, used in the synthesis of (*S*)-metolachlor, a popular herbicide with a production scale of over 10^4 tons/year since 1996.[8] Ferrocene derivatives are also of steadily importance in medicinal chemistry (one of the most relevant examples, the antimalarial ferroquine, is shown in Figure 2B).[9]

Classical methods for the functionalization of ferrocene include Friedel-Crafts acylation[10] and the use of a lithiation/

[a] *O. Bernardo, Prof. Dr. L. A. López*
Departamento de Química Orgánica e Inorgánica,
Instituto Universitario de Química Organometálica "Enrique Moles" and Centro de Innovación en Química Avanzada (ORFEO-CINQA),
Universidad de Oviedo
Julián Clavería 8, 33006-Oviedo, Spain
E-mail: lalg@uniovi.es
[b] *Dr. S. González-Pelayo*
Laboratorio de Química Orgánica y Farmacéutica,
Departamento de Ciencias Farmacéuticas,
Facultad de Farmacia,
Universidad de Salamanca
Campus Miguel de Unamuno, 37007-Salamanca, Spain

Part of the Ferrocene Chemistry Special Collection.

Review
doi.org/10.1002/ejic.202100911

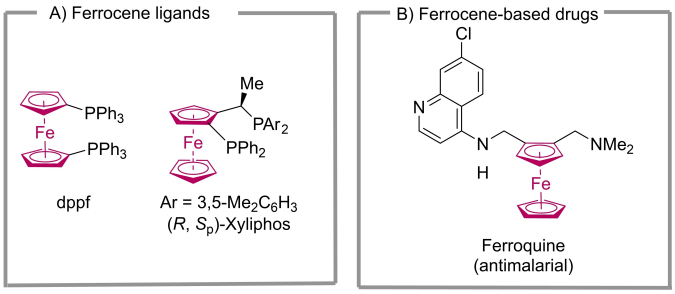


Figure 2. A) Selected widely used ferrocene-based ligands. B) Representative example of ferrocene-based organometallic drugs.

treatment with electrophilic reagent sequence.[11] However, recent developments in transition metal-catalyzed C–H bond functionalization have provided new approaches for the catalytic functionalization of ferrocene derivatives, thus greatly expanding the range of functionalized ferrocene derivatives available.[12]

In this context, it is hardly surprising that merging ferrocene with heterocyclic chemistry has become a very fruitful research topic. Both the synthesis of ferrocenes which contain heterocyclic systems and their applications have been intensively addressed during the last years. The main intention of this Review is to showcase the most representative advances in the synthesis and applications of ferrocene-fused heterocyclic compounds. Given the already discussed relevance of nitrogen heterocycles, we will focus exclusively on those ferrocene derivatives featuring nitrogen in the heterocyclic motif. On the other hand, although also important, those ferrocene derivatives containing heterocyclic systems as a substituent are beyond the scope of this Review.

It should be noted that in the fused system, the heterocyclic moiety will retain the main features of the heterocyclic nucleus. For example, the presence of nitrogen will be responsible of the nucleophilic/basic character or the ability to coordinate metals. On the other hand, the ferrocene moiety will preserve its characteristic redox properties. Interestingly, as a 1,2-disubstituted ferrocene derivative, the fused systems would exhibit planar chirality. Recent advances have demonstrated that interesting applications in different fields, particularly in asymmetric catalysis, can emerge from the synergistic combination of the properties of both structural motifs.

For the sake of simplicity, the contents of this Review will be arranged based on the nature of the heterocyclic nucleus fused to ferrocene. In general, we will focus on the synthesis and applications; however, a brief discussion of the most relevant mechanistic aspects will also be included in some representative examples. Although early applications in asymmetric catalysis of planar-chiral analogues of 4-(dimethylamino)pyridine have been thoroughly reviewed by Fu,[13] some of those initial efforts will be briefly discussed here in order to place more recent advances in context. Similarly, the synthesis and applications of planar-chiral ferrocene-based *N*-heterocyclic carbene ligands have been the subject of a recent excellent Review by Yoshida and Yasue and therefore this topic will not be deeply discussed in this Review.[14]

2. Synthesis and Applications of Pyridine-Fused Ferrocene Derivatives

Pyridine derivatives play a central role in diverse fields such as coordination chemistry and catalysis. As stated before, in pyridine-fused ferrocene derivatives, the ferrocene backbone would provide planar chirality while the pyridine moiety would preserve its nucleophilic and basic character (Figure 3). As a result, many efforts in this area have been devoted to the development of chiral versions of some of these widely used nucleophilic reagents/catalysts. In particular, because the widespread uses of 4-dimethylaminopyridine (DMAP) and related 4-

Olaya Bernardo studied chemistry at the Universidad de Oviedo. She obtained her master degree in 2019 working on the synthesis of functionalized ferrocene derivatives. She is currently pursuing her PhD studies under the supervision of Prof. L. A. López. Her work focuses on the development of new metal-catalyzed transformations involving carbene intermediates.

Silvia González-Pelayo graduated in chemistry at the Universidad de Oviedo in 2013. In 2014, she obtained her master degree from the Universidad Autónoma de Madrid. In 2020, she completed her PhD at the Universidad de Oviedo with a thesis on the synthesis of functionalized ferrocene derivatives under the supervision of Prof. L. A. López. Currently, she is a postdoctoral researcher at the Universidad de Salamanca working on a medicinal chemistry project.

Luis A. López studied chemistry at the Universidad de Oviedo, where he also earned his PhD degree in 1990 for a thesis on heterocyclic chemistry under the supervision of Prof. J. Barluenga and M. Tomás. After a two-year postdoctoral position with Prof. G. Erker at the Universität Münster (Germany) as an Alexander von Humboldt postdoctoral fellowship, he took a possition as a Research Associate at the Universidad de Oviedo, where he was promoted to Associate Professor in 2000 and Full Professor in 2019. His current research interests include the development of new transtion metal-catalyzed synthetic methodologies, heterocyclic chemistry and metallocene functionalization.

Review
doi.org/10.1002/ejic.202100911

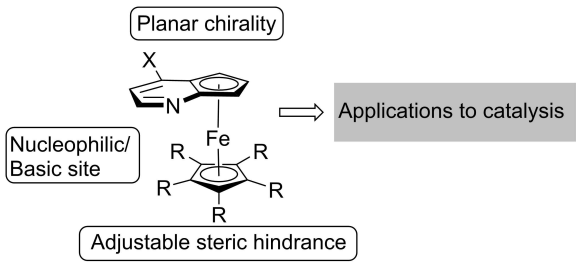
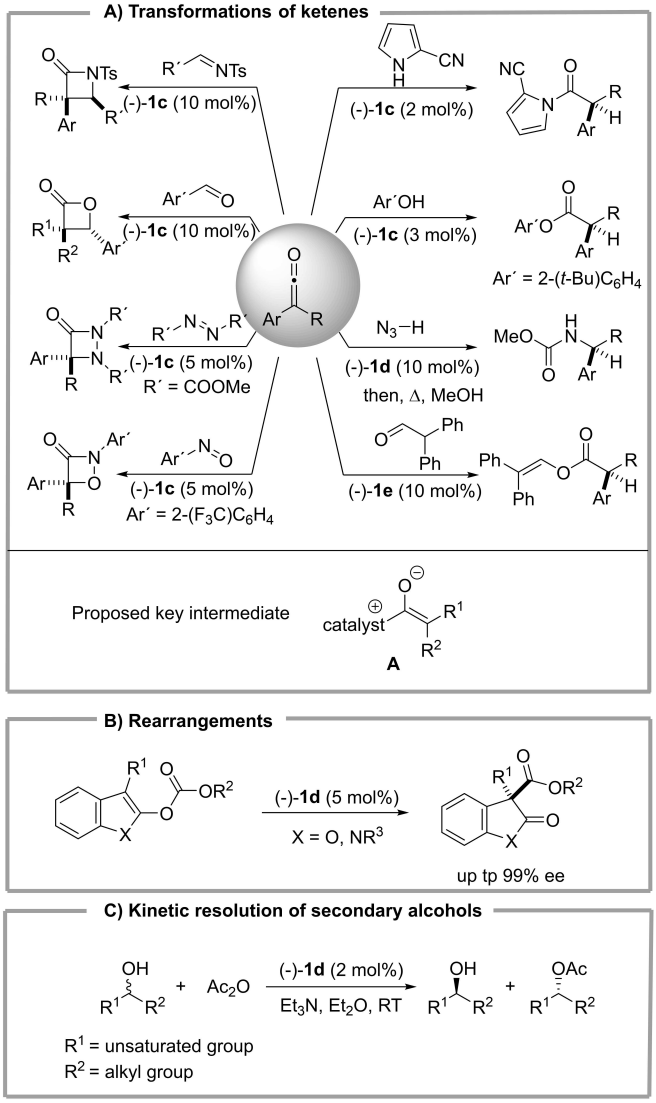


Figure 3. Pyridine-fused ferrocene derivatives: General structure.

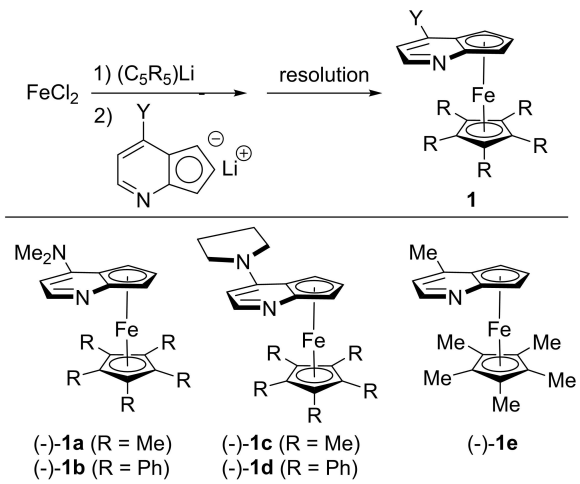
dialkylaminopyridine derivatives,[15] the synthesis of planar chiral analogues of DMAP has been extensively studied.

A significant breakthrough in this field was achieved by Fu and co-workers, who, in 1996, reported the synthesis of the most popular chiral analogues of DMAP, namely the planar-chiral ferrocene-fused pyridine derivatives **1**.[16] The original protocol for the synthesis of planar-chiral ferrocene-fused pyridine derivatives **1** is outlined in Scheme 1. It involves initial reaction of $FeCl_2$ with $(C_5R_5)Li$ (R = Me, Ph) and subsequent treatment with the corresponding 4-substituted pyridine-fused cyclopentadienyl lithium to deliver racemic complexes **1**. In most cases, final resolution through chiral HPLC provided compounds **1** as single enantiomers.[17]

DMAP analogues **1** have been reported to efficiently catalyze a wide range of asymmetric transformations (Scheme 2). In particular, complexes **1** have proved to be extremely useful catalysts for enantioselective transformations of ketenes (Scheme 2A). For example, ferrocene derivatives **1** serve as effective catalysts for [2 + 2] cycloadditions of ketenes with imines,[18] aldehydes,[19] azo compounds,[20] and nitroso compounds.[21] DMAP equivalents **1** can also catalyze the addition of 2-cyanopyrrole,[22] 2-tert-butylphenol, [23] hydrazoic acid,[24] and enolates[25] to ketenes. These transformations are proposed to proceed through a stepwise pathway with initial



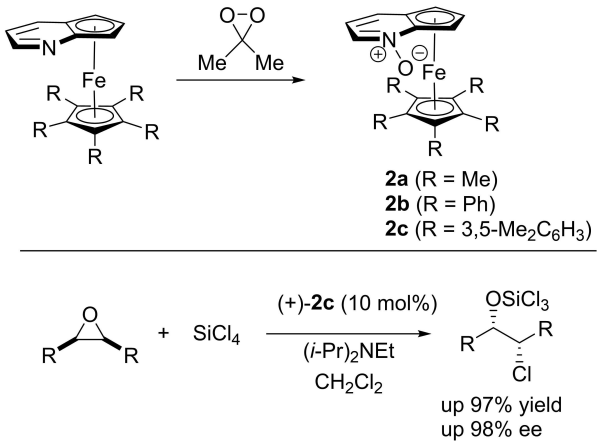
Scheme 2. Selected Catalytic Applications of DMAP analogues **1**.



Scheme 1. Synthesis of planar-chiral ferrocene-fused pyridines **1** and representative examples.

addition of the nucleophilic catalyst to the ketene to generate the corresponding zwitterionic intermediate **A**, which would be subsequently intercepted with an electrophile. Compounds **1** are also efficient and selective catalysts in the enantioselective rearrangement of *O*-acylated azlactones[26] and benzofuranones and oxindoles to furnish protected α-alkylated α-aminoacids and oxindoles and benzofuranones bearing a quaternary center, respectively (Scheme 2B).[27] Finally, the nonenzymatic kinetic resolution of alcohols[28] and amines[29] via enantioselective acylation has also been achieved by using conveniently substituted DMAP analogues **1** (Scheme 2C).

Fu and co-workers also reported the synthesis of planar-chiral pyridine *N*-oxides through oxidation with dimethyloxirane and subsequent resolution by chiral HPLC.[30] These planar-chiral pyridine *N*-oxides demonstrated to be efficient catalysts for the enantioselective ring-opening of meso epoxides with $SiCl_4$ (Scheme 3). The authors found that the increased steric demand

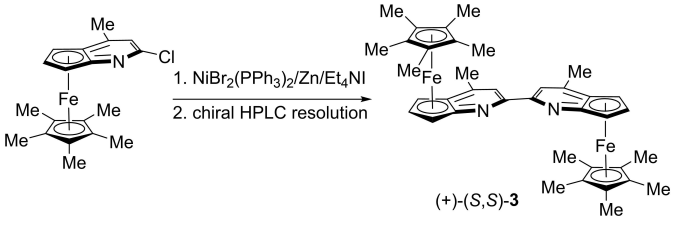


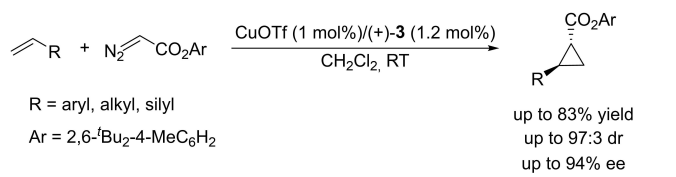
Scheme 3. Synthesis of planar-chiral pyridine *N*-oxides and their application in the catalytic enantioselective desymmetrization of meso epoxides.

provided by meta-substituted aryl groups resulted crucial to achieve high enantioselectivity.

The synthesis of a planar-chiral analogue of the widely used 2,2'-bipyridine ligand (bipy) was also accomplished by Fu and co-workers (Scheme 4).[31] In the same work, the authors demonstrated that the combination of this chiral bipy analogue with CuOTf was an efficient and selective catalytic system for the cyclopropanation of monosubstituted olefins using 2,6-di-*tert*-butyl-4-methylphenyl ester of diazoacetic acid as the carbene source. The corresponding cyclopropane derivatives were obtained in good yields with excellent diastereo- and enantioselectivity.

Although a milestone in asymmetric catalysis, the use of DMAP analogues **1** has been hampered in part by their limited availability. In particular, the late-stage chiral resolution of the racemic mixture required for their synthesis represents an important limitation. To partially overcome this drawback, alternative entries into these planar-chiral DMAP analogues have been recently established.



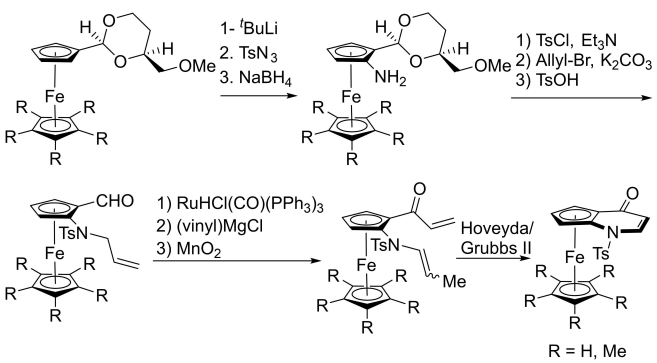


Scheme 4. Synthesis of a planar-chiral bipyridine ligand and its application in the enantioselective Cu-catalyzed cyclopropanation of olefins.

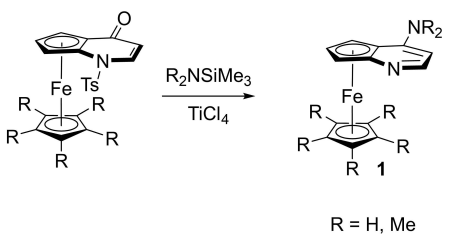
In 2015, Takahashi, Yoshida and co-workers reported an enantioselective synthesis of planar-chiral ferrocene-fused 4-pyridones, which were subsequently converted into enantiomerically pure ferrocene-fused pyridine derivatives.[32] The developed sequence to planar-chiral 4-pyridone-fused ferrocenes is shown in Scheme 5. Initially, an adaptation of Kagan's method for preparing enaniomerically enriched 2-substituted ferrocenecarboxaldehydes[33] allowed the authors to access amino-substituted ferrocene derivatives, which were subjected to a conventional three-step tosylation/allylation/deprotection of the acetal function sequence delivering the corresponding *N*-allyl-*N*-tosylaminoferrocenecarbaldehyde derivatives. Subsequent Ru-catalyzed olefin isomerization provided the corresponding enamide-containing aldehydes, which were subjected to a vinylation/oxidation sequence to give the respective substituted acroleine derivatives. Finally, ring-closing methateis (RCM) using the Hoveyda/Grubss II catalyst provided the corresponding ferrocene-fused 4-pyridones in enantiomerically pure form. Noteworthy, this protocol could be accomplished on a multigram scale.

The resulting planar-chiral ferrocene-fused 4-pyridones could be converted into various enantiomerically pure ferrocene-fused pyridine derivatives. In particular, the reaction with *N*-trimethylsilylamines in the presence of titanium tetrachloride delivered the corresponding planar-chiral DMAP analogues (Scheme 6). This detosylative amination proceeded smoothly, leading to the corresponding products in good yields as single enantiomers.

The planar-chiral DMAP analogues available by this methodology exhibited good catalytic activity in the addition of 2-*tert*-



Scheme 5. Synthesis of enantiomerically pure ferrocene-fused 4-pyridones.



Scheme 6. Detosylative amination of 4-pyridones: Synthesis of planar-chiral DMAP analogues.

butylphenol to ethyl(*p*-tolyl)ketene providing the corresponding ester in excellent yield (up to 92%) and with high ee (up to 92%). Moreover, moderate enantioselectivity with s-factors ranging from 4.2 to 6.7 was also observed in the enantioselective acylation of racemic 2,2-dimethyl-1-phenylpropan-1-ol.

Although a series of enantiomerically pure pyridine based organocatalysts became available through the developed protocol, several issues remain unresolved. First, the reported sequence comprised a considerable number of synthetic steps, thus compromising the overall yield. Moreover, one of the key steps (the ring-closing metathesis reaction) required the use of an expensive catalyst (Hoveyda/Grubbs-II catalyst). Finally, some steps in the developed sequence were very sensitive to steric hindrance and, as a result, some of the most selective catalysts, namely those featuring a sterically demanding (η^5-C_5Ph_5)Fe substructure, were not available by this methodology.

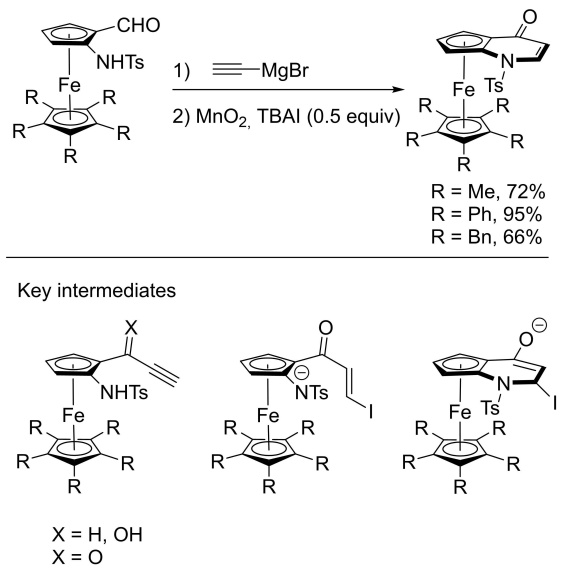
In 2020, the same group developed an alternative approach to ferrocene-fused 4-pyridone derivatives that, at least in part, overcomes those limitations.[34] The key step in this improved sequence is a tetrabutylammonium iodide (TBAI)-catalyzed cyclization of propynoyl-*N*-tosylaminoferrocenes, generated in situ by manganese dioxide oxidation of the corresponding propargylic alcohols, which in turn are easily available by treatment of the respective optically active aldehydes with ethynylmagnesium bromide (Scheme 7). This sequence afforded the corresponding ferrocene-fused 4-pyridone derivatives as single enantiomers in good overall yield even for substrates featuring sterically demanding (η^5-C_5Ph_5)Fe and (η^5-C_5Bn_5)Fe substructures.

The key iodide-catalyzed cyclization of propynoyl-*N*-tosylaminoferrocenes is proposed to occur through initial attack of the iodide anion to the β-carbon atom of the ynone intermediate with formation of a β-iodo-substituted enone species. Subsequent intramolecular vinylogous nucleophilic substitution of the iodide would close the catalytic cycle and account for the formation of the ferrocene-fused 4-pyridone derivative.

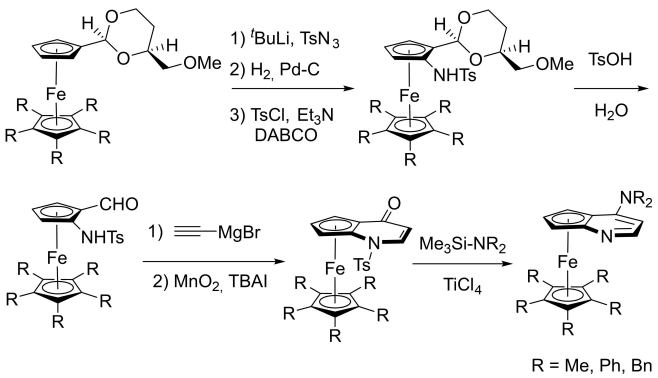
The whole improved sequence for the synthesis of planar-chiral ferrocene-fused pyridines from the respective chiral acetals is outlined in Scheme 8. It involves initial diastereoselective lithiation using ^{t}BuLi followed by reaction with tosylazide to afford the corresponding ferrocenyl azide, which is converted into the ferrocenylamine by catalytic hydrogenation. This amine was immediately tosylated without purification to provide the corresponding *N*-tosylaminoferrocenyl acetal. *p*-TsOH-catalyzed hydrolysis of the acetal furnished the corresponding aldehydes in almost quantitative yields, which were subjected to the above discussed iodine-catalyzed cyclization to produce the pyridone derivatives. As reported before (see Scheme 6), conversion of the pyridone derivatives into the corresponding 4-dialkylaminopyridine derivatives was achieved in good to excellent yields by treatment with the appropriate *N*-trimetylsilylamine in the presence of $TiCl_4$.

Compared with the previous one, this improved reaction sequence is shorter, simpler and higher-yielding. For example, the synthesis of the pyridone featuring a (η^5-C_5Me_5) ligand was accomplished in 35% overall yield from the corresponding chiral acetal according to the sequence depicted in Scheme 5, while the synthesis of the same pyridone proceeded in 50% overall yield following the improved procedure (Scheme 8). Furthermore, sterically demanding ferrocene derivatives featuring the (η^5-C_5Ph_5)Fe substructure are now accessible. Notably, some previously unreported planar-chiral pyridine derivatives (for example, those that own a η^5-pentabenzylcyclopentadienide ligand) became available by this improved protocol.

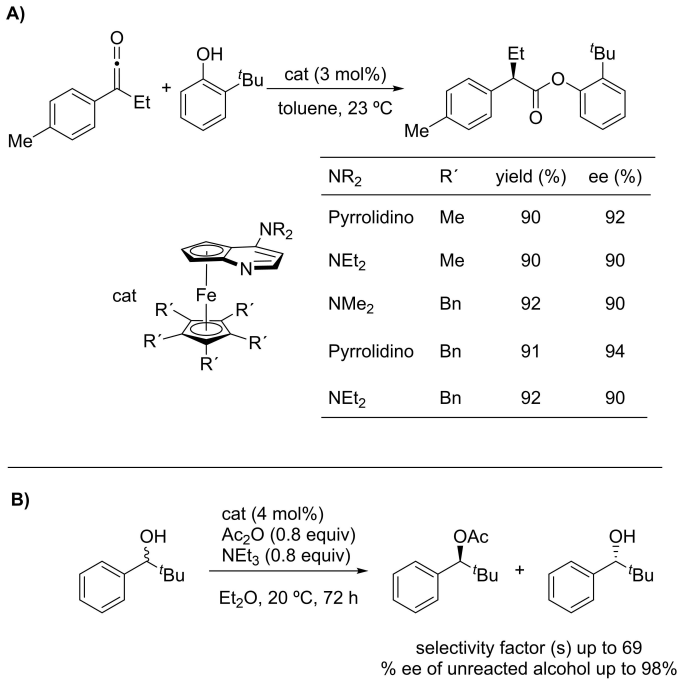
The catalytic performance of these new organocatalysts was evaluated in two representative asymmetric reactions previously investigated by Fu and co-workers. First, the authors effected the addition of 2-*tert*-butylphenol to ethyl(*p*-tolyl)ketene (Scheme 9A). In this regard, the newly developed catalysts featuring a bulkier and electron-donating η^5-pentabenzylcyclopentadienide fragment outperformed other organocatalysts providing excellent yield and the highest enantioselectivity (up to 94% ee). Besides, some of the newly available organocatalysts displayed also remarkable selectivity (with selectivity



Scheme 7. Iodine-catalyzed cyclization of propynoyl-*N*-tosylamino ferrocenes.



Scheme 8. Improved enantioselective synthesis of planar-chiral ferrocene-fused pyridines through iodide-catalyzed cyclization of propynoyl-*N*-tosylaminoferrocenes.

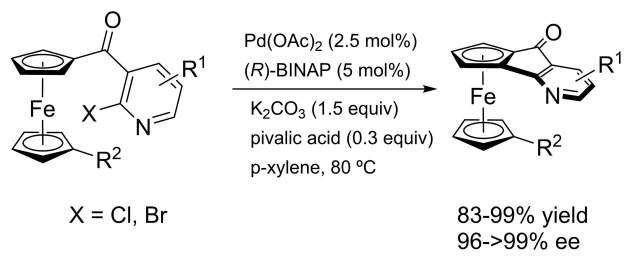


NR_2	R´	yield (%)	ee (%)
Pyrrolidino	Me	90	92
NEt_2	Me	90	90
NMe_2	Bn	92	90
Pyrrolidino	Bn	91	94
NEt_2	Bn	92	90

Scheme 9. Applications of the new DMAP analogues: A) Enantioselective addition of 2-*tert*-butylphenol to ethyl(*p*-tolyl)ketene; B) Kinetic resolution of racemic 2,2-dimethyl-1-phenylpropan-1-ol.

factors up to 69) in the kinetic resolution of racemic 2,2-dimethyl-1-phenylpropan-1-ol via enantioselective acylation with acetic anhydride (Scheme 9B).

As an extension of their previous work on the enantioselective synthesis of indenone-fused ferrocene derivatives via Pd-catalyzed intramolecular C–H bond arylation,[35] You and co-workers accomplished the synthesis of new planar chiral ferrocene derivatives featuring a pyridine motif (Scheme 10).[36] Good yields (up to 99%) and excellent enantioselectivities (up to 99% ee) for the coupling products could be obtained when using commercially available (*R*)-2,2′-bis(diphenylphosphino-1,1′-binaphthyl (BINAP) as chiral ligand. Other bis-phosphine ligands also promoted the arylation reaction in good yields and selectivities. Broad substrate scope, easy scale-up and low catalyst loading are additional features of this coupling reaction. Treatment of these pyridine derivatives with dimethyldioxirane efficiently produced the corresponding planar chiral pyridine *N*-



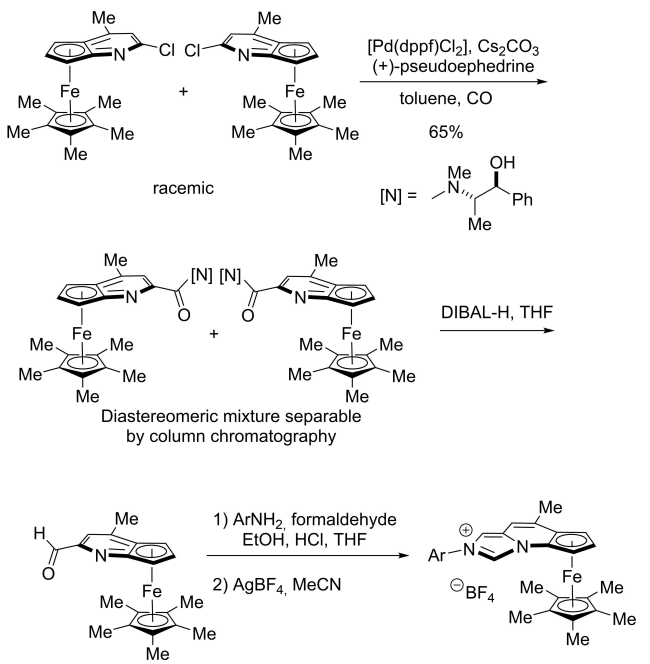
Scheme 10. Pd-catalyzed asymmetric C–H bond arylation entry to planar chiral ferrocenylpyridine derivatives.

oxides, which were tested as catalysts in the asymmetric opening of *cis*-stilbene oxide with $SiCl_4$ providing the corresponding chlorohydrin in good yield and moderate enantioselectivity (up to 66% ee).

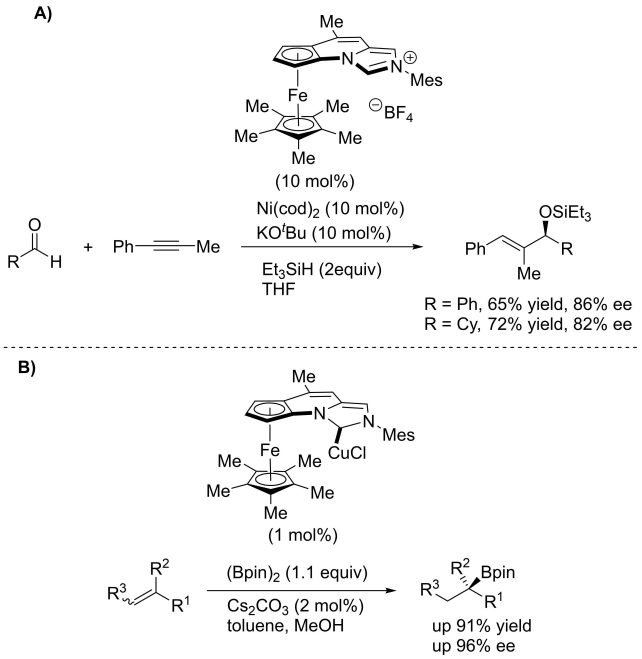
A relevant and direct application of the ferrocene-fused pyridine derivatives available by the Fu's original protocol is the synthesis of planar-chiral ferrocene-based *N*-heterocyclic carbene (NHC) ligands. In spite of recent impressive advances, asymmetric catalysis by using chiral NHC ligands is still a relatively underdeveloped field. In this regard, the great success achieved with ferrocene-fused pyridine catalysts has paved the way for the development of new chiral fused ring type ligands.

In 2015, Scheidt and co-workers disclosed the synthesis of planar-chiral ferrocene-fused *N*-heterocyclic carbene ligands.[37] As shown in Scheme 11, the synthetic sequence to such as NHC ligands started from racemic chloro-substituted ferrocene-fused pyridine previously reported by Fu and co-workers, which can be prepared on a multigram scale starting from readily available precursors. This racemic mixture was transformed into pseudoephedrine amides through a Pd-catalyzed aminocarbonylation reaction. Interestingly, the resulting diastereoisomeric amides could be separated by column chromatography. Subsequent reduction with DIBAL–H yielded the enantiopure aldehyde. Final annulation with the corresponding aniline and formaldehyde led to enantiomerically pure ferrocene-based azolium salts, precursors of the corresponding NHC ligands.

In the same work, the authors also disclosed preliminary studies on the potential of these NHCs precursors in asymmetric catalysis demonstrating that they are suitable ligands for the Ni-catalyzed reductive coupling of 1-phenyl-1-propyne with aldehydes using triethylsilane as the reducing agent (Scheme 12A) and for the copper-catalyzed borylation of olefins

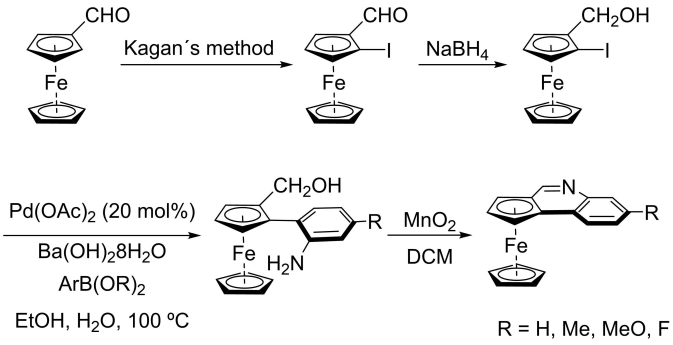


Scheme 11. Synthesis of enantiopure ferrocene-based NHC precursors.

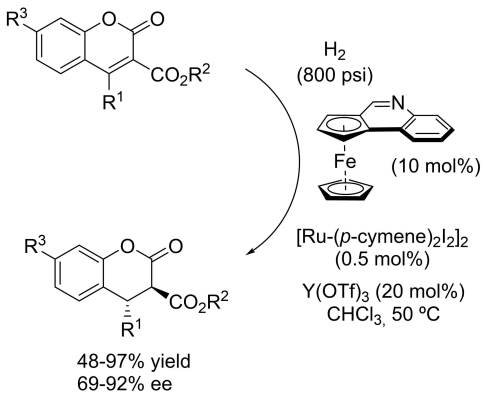


Scheme 12. Applications of planar-chiral ferrocene-fused *N*-heterocyclic carbene ligands in transition metal-catalyzed transformations.

(Scheme 12B). In both transformations, the ferrocene-based NHC ligand outperformed in terms of enantioselectivity other ligands previously reported in the literature.



Scheme 13. Synthesis of enantiomerically pure quinoline-fused ferrocene derivatives.



Scheme 14. Quinoline-fused ferrocene-catalyzed biomimetic asymmetric reduction of tetrasubstituted alkenes

3. Synthesis and Applications of Quinoline-Fused Ferrocene Derivatives

As compared with pyridine-fused ferrocene derivatives discussed in the previous section, the synthesis of the analogues quinoline-fused derivatives has been much less developed.

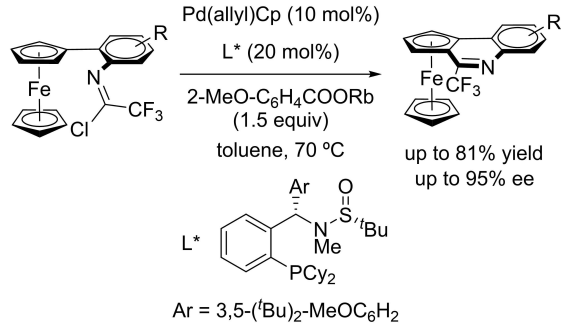
In 2019, Zhou and co-workers reported the synthesis of planar-chiral quinoline-fused ferrocene derivatives.[38] Starting from (*S*)-2-iodoferrocenecarboxaldehyde, readily available in enantiopure form from ferrocenecarboxaldehyde via the Kagan's method,[33] a three-step sequence consisting of initial reduction of the aldehyde function to the corresponding alcohol, subsequent Suzuki coupling with the corresponding 2-aminoarylboronic acid or 2-aminoarylboronic acid pinacolate ester and final oxidative cyclization delivered the corresponding enantiomerically pure quinoline-fused ferrocene derivatives in moderate overall yields (Scheme 13).

These compounds were used as chiral and regenerable NAD(P)H synthetic models in biomimetic asymmetric reduction reactions using hydrogen gas as terminal reductant. This strategy was suitable for the reduction of a number of electron-deficient tetrasubstituted alkenes, challenging substrates in asymmetric hydrogenation, with excellent yields and levels of enantioselectivity (Scheme 14).[38,39] This methodology proved also highly efficient for the asymmetric reduction of heterocyclic compounds featuring iminic substructures such as benzoxazinones, quinoxalinones and quinazolinones.[38–41] The mechanism of these biomimetic reductions has been elucidated by a combination of experimental and theoretical studies.

Building upon previous work by Cramer and Grosheva on the enantioselective synthesis of 1*H*-isoindoles through Pd-catalyzed C–H functionalization using trifluoroacetimidoyl chlorides as electrophilic components,[42] very recently, Liu and co-workers reported the catalytic enantioselective synthesis of planar chiral 2-(trifluoromethyl)quinoline fused ferrocenes through Pd-catalyzed intramolecular C–H imidoylation (Scheme 15).[43] Chiral sulfonamide phosphine ligands proved to be critical, providing high yields and enantioselectivities (up to 95 % ee).

4. Synthesis and Applications of Pyridinone-Fused Ferrocene Derivatives

As shown in Section 2 of this Review, some 4-pyridinone-fused ferrocene derivatives have been synthesized and found application as precursors for the preparation of new pyridine-fused derivatives (see Scheme 6 and Scheme 8). Some complementary approaches to pyridone-fused ferrocenes are based on tran-



Scheme 15. Synthesis of planar quiral 2-(trifluoromethyl)quinoline-fused ferrocenes.

sition metal-catalyzed C–H bond functionalization of properly substituted ferrocene derivatives.

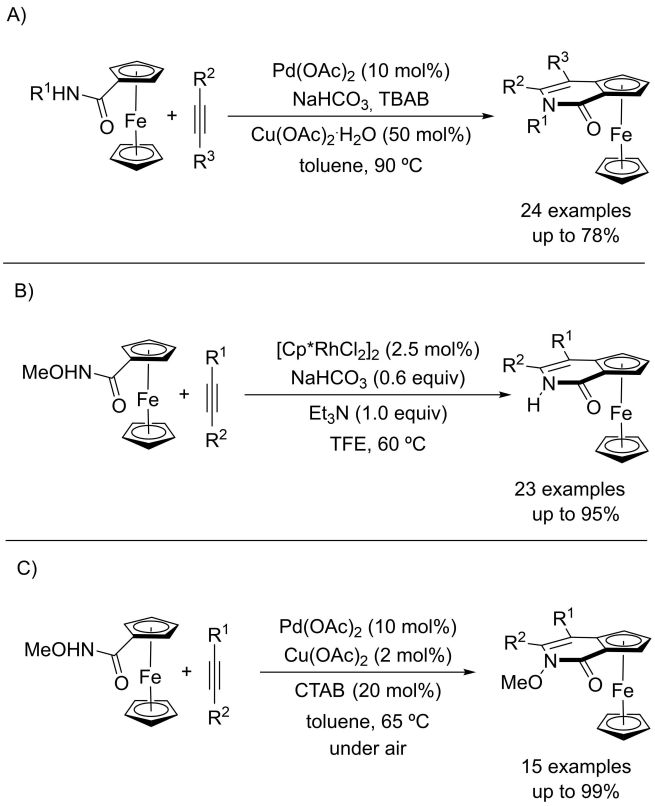
In 2014, Wang and co-workers reported the efficient synthesis of racemic ferrocene[1,2,*c*]pyridine-3(4*H*)-ones through Pd-catalyzed dehydrogenative annulation of ferrocenecarboxamides with internal alkynes using stoichiometric copper acetate and air as the terminal oxidants (Scheme 16A).[44]

Afterwards, You and co-workers described the synthesis of *N*-unprotected pyridinones through Rh(III)-catalyzed annulation of *N*-methoxy ferrocenecarboxamides with internal alkynes using a directing group as an internal oxidant (Scheme 16B).[45]

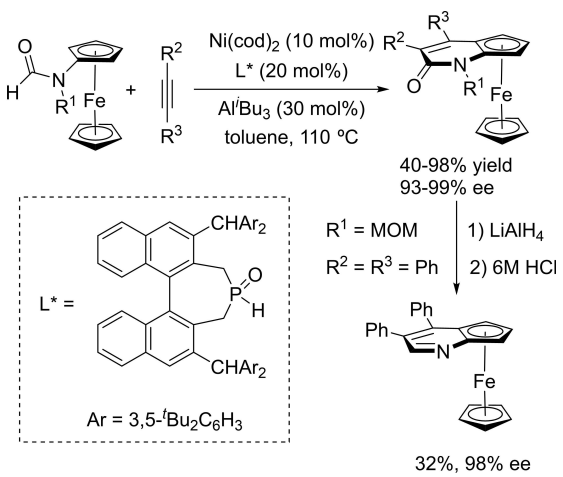
In the case of unsymmetrical alkynes, this coupling reaction was found to proceed with complete regioselectivity. Moreover, this transformation could be scaled-up without any erosion of its efficiency and selectivity. A preliminary study on the asymmetric version of this transformation using a chiral Rh catalyst resulted in moderate yield and enantioselectivity.

A completely different reaction outcome was achieved when the same *N*-methoxy ferrocenecarboxamides were reacted with internal alkynes in the presence of a catalytic system comprising $Pd(OAc)_2$ (10 mol%), NaOAc (1 equiv), cetyl trimethylammonium bromide (CTAB, 20 mol%) in toluene at 70 °C (Scheme 16C).[46] Surprisingly, the methoxy group remained in the final pyridinone-fused ferrocene showing that, in contrast with the Rh(III)-catalyzed transformation, now the *N*-methoxy amide group does not act as an internal oxidant.

In 2020, Ye and coworkers developed a highly enantioselective approach to planar-chiral 2-pyridinone-fused ferrocene derivatives.[47] Based on a previous work by Nakao, Hiyama and co-workers on the dehydrogenative [4 + 2] cycloaddition of formamides with alkynes through twofold C–H activation,[48] they reported the asymmetric annulation of ferrocene-substituted formamides and alkynes (Scheme 17). A bimetallic catalytic system comprising $Ni(cod)_2$ (10 mol%) and Al^tBu_3 (30 mol%) in combination with a bulky BINOL-derived chiral secondary phosphine oxide ligand (20 mol%) proved critical to a successful outcome. Under the developed conditions, chiral ferrocene-fused 2-pyridone derivatives were obtained in excellent yield (up to 98%) and enantioselectivity (up to 99% ee). Furthermore, the reaction could be scaled up without any noticeable erosion of yield. Lithium aluminum hydride (LAH) reduction of a methoxymethyl (MOM) *N*-protected derivative followed by hydrolysis provided the corresponding chiral pyridine in moderate overall yield (32%) but retaining the excellent ee (98%).



Scheme 16. Metal-catalyzed approaches to ferrocene-based pyridinones through metal-catalyzed dehydrogenative annulation of ferrocenecarboxamides with alkynes.



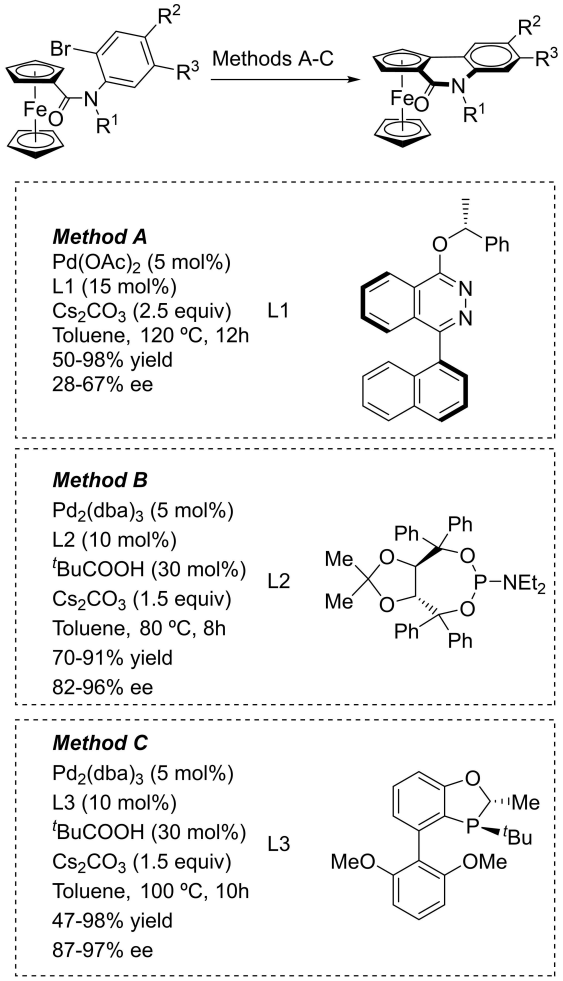
Scheme 17. Synthesis of planar-chiral 2-pyridinone-fused ferrocene derivatives through enantioselective twofold C–H annulation of formamides and alkynes.

5. Synthesis of Quinolinone- and Isoquinolinone-Fused Ferrocene Derivatives

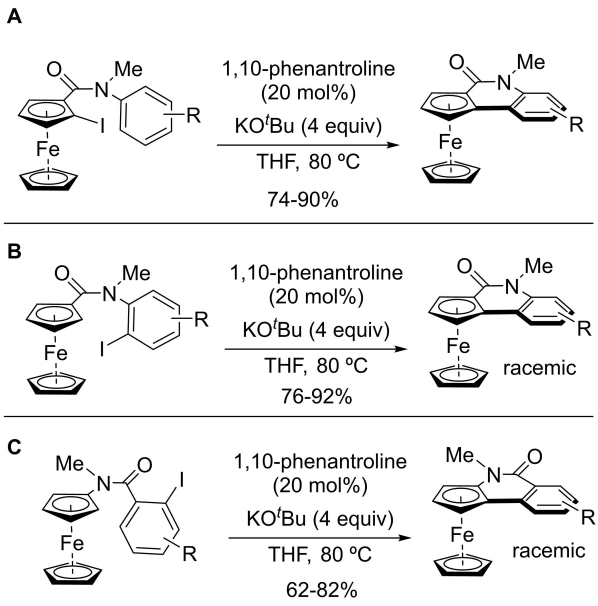
Several strategies have been put forward for the intramolecular C–H arylation of appropriately substituted ferrocene derivatives, leading to quinolinone- and isoquinolinone fused ferrocene derivatives.

In 2014, Ma and Gu showed that under palladium catalysis *N*-(2-bromoaryl)ferrocenecarboxamides undergo an intramolecular C–H arylation reaction, providing the corresponding quinolinone-fused ferrocene derivatives (Scheme 18, Method A).[49] In this study, the use of Carreira's PINAP ligand L1 delivered the coupling products in good yields and moderate enantioselectivity (up to 67% ee).

Soon after, Liu, Zhao and co-workers envisioned the asymmetric synthesis of quinolinone-fused ferrocene derivatives through a similar palladium-catalyzed intramolecular asymmetric C–H bond arylation (Scheme 18, Method B).[50] The resulting planar chiral lactam-fused ferrocenes were obtained in good chemical yields (up to 91%) and enantioselectivities (up to 96%) when a TADDOL-derived phosphoramidite L2 was used as a chiral ligand.



Scheme 18. Asymmetric synthesis of quinolinone-fused ferrocene derivatives by enantioselective intramolecular C–H bond arylation.



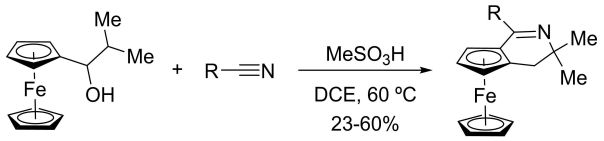
Scheme 19. Metal-free approaches to quinolinone- and isoquinolinone-fused ferrocene derivatives.

In 2021, Liu, Mao and co-workers reported a similar palladium-catalyzed approach to planar chiral isoquinolinone-fused ferrocene derivatives from *N*-ferrocenyl *o*-bromobenzanilides (Scheme 18, Method C).[51] Screening of different ligands allowed the authors to identify the P-chiral biaryl phosphine (*S*,*S*)-Me-BI-DIME L3 as the most convenient ligand for this coupling reaction delivering the corresponding products with up to 97% ee.

In a completely different approach, Xu, Jin and co-workers effected the intramolecular direct C–H arylation of chiral iodoferrocenocarboxamides under transition-metal-free conditions (Scheme 19A).[52] This transformation was promoted by a catalytic amount of 1,10-phenantroline and is proposed to proceed by single electron transfer (SET) initiation with generation of a planar-chiral ferrocenyl radical. Under the optimized reaction conditions, an array of quinolinone-fused ferrocene derivatives were available in good to excellent yields and with complete retention of configuration. The same products but in racemic form were also available by intramolecular coupling of *o*-haloaniline-derived amides (Scheme 19B). In the same work, the authors succeeded in extending this metal-free protocol to the intramolecular arylation of aminosubstituted ferrocenes, leading to isoquinolinone-fused ferrocene derivatives (Scheme 19C).

6. Synthesis of Dihydro- and Tetrahydro-Pyridine-Fused Ferrocenes

In 2019, Rozhkova and co-workers accomplished the synthesis of racemic 3,4-dihydroferroceno[c]pyridines via methansulfonic acid-promoted Ritter reaction of 2-methyl-1-ferrocenylpropan-1-ol with nitriles (Scheme 20).[53] A wide range of nitriles are compatible with this protocol affording the corresponding

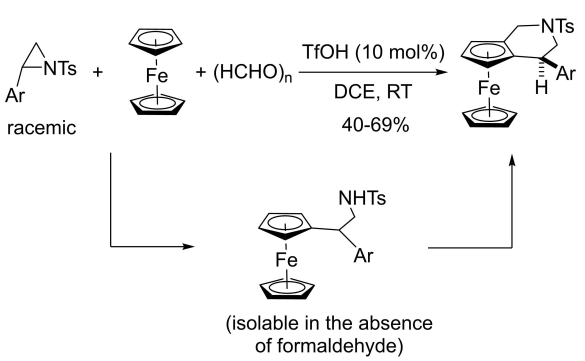


Scheme 20. Synthesis of dihydropyridine fused ferrocenes through the Ritter reacton.

heterocycle-fused ferrocene derivatives in moderate yields. In selected examples, chiral HPLC resolution of the racemic products followed by crystallization provided access to both enantiomers.

In a subsequent study, 1-alkyl-3,4-dihydroferroceno[c]pyridines were reacted with 1-nitro-1-(2,2,2-trifluroethylidene)alkanes or 3-nitro-2-(trifluoromethyl)-2*H*-chromenes in 2-propanol at reflux to give ferrocene derivatives featuring a trifluromethyindolizine substructure.[54]

In 2021, López and co-workers developed the regio- and stereoselective synthesis of tetrahydropyridine-fused ferrocene derivatives through a trifluoromethanesulfonic acid-catalyzed three-component reaction of racemic 2-aryl-*N*-sulfonyl aziridines, ferrocene, and formaldehyde (Scheme 21).[55] This multicomponent reaction proceeds through initial regioselective ring opening of the aziridine to furnish the corresponding β-aminoethyl ferrocene derivatives (isolable in the absence of formaldehyde). Subsequent stereoselective Pictet-Spengler type cyclization furnishes the final ferrocene fused heterocyclic products. The formation of racemic products when starting from enantiopure aziridines would point to the participation of a benzylic carbocation intermediate in the ring-opening of the aziridine. Besides ferrocene, ruthenocene also serves as suitable substrate for this multicomponent reaction.



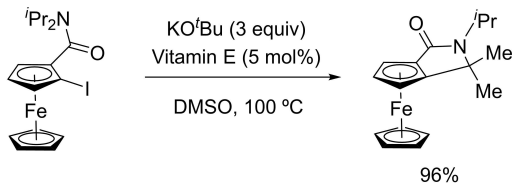
Scheme 21. Three-component approach to tetrahydropyridine-fused ferrocene derivatives.

7. Synthesis of Pyrrolo-Fused Ferrocene Derivatives

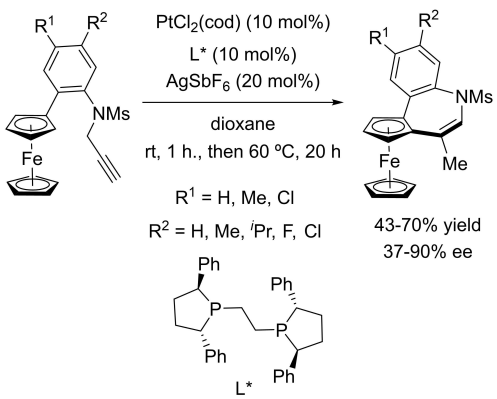
As compared with six-membered ferrocene-fused nitrogen heterocycles, the synthesis of five-membered systems remains almost unexplored. In 2014, Kumar and co-workers reported the KO^{t}Bu-mediated synthesis of dimethylisoindolin-1-ones from 2-halo-*N*-isopropyl-*N*-alkylbenzamides.[56] While exploring the substrate scope, they found that *N*,*N*-diisopropyl-2-iodoferrocenecarboxamide was also a suitable substrate for this transformation providing the corresponding fused ferrocene derivative in excellent yield (Scheme 22). This metal-free C–C coupling is proposed to proceed through a radical pathway.

8. Synthesis of Azepine-Fused Ferrocene Derivatives

The synthesis of azepine-fused ferrocene derivatives has been scarcely explored. In 2019, Ito, Shibata and co-workers reported the synthesis of azepine-fused planar-chiral ferrocenes through a Pt-catalyzed cycloisomerization of *N*-propargyl-2-ferrocenylanilines (Scheme 23).[57] Enantioselectivities ranging from 37 to 90% ee were obtained when 1,2-bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane was used as a chiral ligand. This cycloisomerization reaction is proposed to proceed through initial 7-*exo*-*dig* cyclization and subsequent isomerization of the resulting exocyclic olefin.



Scheme 22. KO^{t}Bu-mediated C–C coupling in *N*,*N*-diisopropyl-2-iodoferrocenecarboxamide.



Scheme 23. Synthesis of azepine-fused ferrocene derivatives through Pt-catalyzed cycloisomerization of *N*-propargyl-2-ferrocenylanilines.

9. Summary and Outlook

In this Review, we have summarized some relevant developments in the synthesis of ferrocene fused heterocyclic compounds. Since Fu's seminal work in the late 1990s, this field has become extremely active, resulting in the synthesis of a wide variety of fused systems. Because of their planar chirality, some of these fused ferrocenes served as organocatalysts in diverse transformations providing excellent levels of enantioselection. As demonstrated in this Review, initial asymmetric approaches to these fused systems relied on stoichiometric transformations, mainly based on the Kagan's protocol for the synthesis of enantiomerically enriched 1,2-disubstituted ferrocenes. More recently, the introduction of transition metal-catalyzed C–H bond functionalization protocols has had a tremendous impact in this field, allowing the synthesis of fused ferrocenes in a much more efficient and sustainable way. The huge variety of heterocyclic scaffolds can anticipate new and interesting fused architectures with potential applications in different areas of science. Further advances in this direction are highly desirable and we hope that the selected examples provided in this Review can contribute to this purpose.

Acknowledgements

We are extremely grateful to the co-workers who contributed to this research. Support for our investigation in this topic has been provided by Ministerio de Economía y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER) (Grants CTQ2016-76840-R and PID2019-107469RB-I00). SG-P thanks the Principado de Asturias for a predoctoral grant (Severo Ochoa Program).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Ferrocene · Nitrogen heterocycles · Fused ring systems · Planar chirality · Asymmetric catalysis

[1] For a review on heterocyclic chemistry in crop protection, see: C. Lamberth, *Pest Manage. Sci.* **2013**, *69*, 1106–1114.
[2] *Novel Drug Approvals for 2020*, https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020.
[3] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
[4] For a recent review on the synthesis, pharmacological properties and medical applications of top prescribed drugs containing nitrogen heterocycles, see: M. M. Heravi, V. Zadsirjan, *RSC Adv.* **2020**, *10*, 44247–44311.
[5] a) T. J. Kealy, P. L. Pauson, *Nature* **1951**, *168*, 1039–1040; b) S. A. Miller, J. A. Tebboth, J. F. Tremaine, *J. Chem. Soc.* **1952**, 632–635.
[6] Selected revisions on properties and applications of ferrocene derivatives: a) D. Astruc, *Eur. J. Inorg. Chem.* **2017**, 6–29; 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*, 59315986; f) D. R. Van Staveren, N. Metzler-Nolte, *Chem. Rev.* **2004**, *104*, 5931–5986.
[7] Selected reviews: a) R. G. Arrayás, J. Adrio, J. C. Carretero, *Angew. Chem.* **2006**, *118*, 7836–7878; *Angew. Chem. Int. Ed.* **2006**, *45*, 7674–7715; b) *Chiral Ferrocenes in Asymmetric Catalysis*, (Eds.: L.-X. Dai, X.-L. Hou), Wiley-VCH, Weinheim, **2009**; c) J.-C. Zhu, D.-X. Cui, Y.-D. li, R. Jiang, W.-P. Chen, P.-A. Wang, *ChemCatChem* **2018**, *10*, 907–919; d) L. Cunningham, A. Benson, P. J. Guiry, *Org. Biomol. Chem.* **2020**,*18*, 9329–9370.
[8] For an interesting discussion about the development of xyliphos, see: H.-U. Blasser, *Adv. Synth. Catal.* **2002**, *344*, 17–31.
[9] Selected reviews: a) M. Patra, G. Gasser, *Nat. Chem. Rev.* **2017**, *1*, No. 0066; b) S. S. Braga, A. M. S. Silva, *Organometallics* **2013**, *32*, 5626–5639; c) M. Patra, G. Gasser, N. Metzler-Nolte, *Dalton Trans.* **2012**, *41*, 6350–6358.
[10] For a seminal contribution on the Friedel-Crafts reactivity of ferrocene, see: R. B. Woodward, M. Rosenblum, M. C. Whiting, *J. Am. Chem. Soc.* **1952**, *74*, 3458–3459.
[11] For pioneering work on this topic, see: D. Marquanding, H. Klusacek, G. Gokel, O. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389–5393. 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*, 685–686.
[12] 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*, 351–365; b) D.-Y. Zhu, P. Chen, J.-B. Xia, *ChemCatChem* **2016**, *8*, 68–73; c) L. A. López, E. López, *Dalton Trans.* **2015**, *44*, 10128–10135.
[13] a) G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412–420; b) G. C. Fu, *Acc. Chem. Res.* **2004**, *37*, 542–547; c) G. C. Fu, *Acc. Chem. Res.* **2006**, *39*, 853–860.
[14] K. Yoshida, R. Yasue, *Chem. Eur. J.* **2018**, *24*, 18575–18586.
[15] For selected reviews on the uses of DMAP and related pyridines, see: a) G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602–615; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569–583; b) E. F. V. Scriven, *Chem. Soc. Rev.* **1983**, *12*, 129–161; c) A. Hassner, in *Encyclopedia of Reagents for Organic Synthesis*, Wiley, Chichester, **1995**, pp. 2022–2024; d) U. Ragnarsson, L. Grehn, *Acc. Chem. Res.* **1998**, *31*, 494–501; e) D. J. Berry, C. V. Digiovanna, S. S. Metrick, R. Murugan, *Arkivoc* **2001**, 201–226; f) A. C. Spivey, S. Arseniyadis, *Angew. Chem.* **2004**, *116*, 5552–5557; *Angew. Chem. Int. Ed.* **2004**, *43*, 5436–5441.
[16] J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1996**, *61*, 7230–7231.
[17] For a posterior and more efficient synthesis and resolution of planar-chiral DMAP derivatives, see: R. P. Wurz, E. C. Lee, J. C. Ruble, G. C. Fu, *Adv. Synth. Catal.* **2007**, *349*, 2345–2352.
[18] B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579.
[19] J. E. Wilson, G. C. Fu, *Angew. Chem.* **2004**, *116*, 6518–6520; *Angew. Chem. Int. Ed.* **2004**, *43*, 6358–6360.
[20] J. M. Berlin, G. C. Fu, *Angew. Chem.* **2008**, *120*, 7156–7158; *Angew. Chem. Int. Ed.* **2008**, *47*, 7048–7050.
[21] M. Dochnahl, G. C. Fu, *Angew. Chem.* **2009**, *121*, 2427–2429; *Angew. Chem. Int. Ed.* **2009**, *48*, 2391–2393.
[22] B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 10006–10007.
[23] S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176–6177.
[24] X. Dai, T. Nakai, J. A. C. Romero, G. C. Fu, *Angew. Chem.* **2007**, *119*, 4445–4447; *Angew. Chem. Int. Ed.* **2007**, *46*, 4367–4369.
[25] C. Schaefer, G. C. Fu, *Angew. Chem.* **2005**, *117*, 4682–4684; *Angew. Chem. Int. Ed.* **2005**, *44*, 4606–4608.
[26] J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.
[27] I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051–4054; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921–3924.
[28] a) J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492–1493; b) B. Tao, J. C. Ruble, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 5091–5092; c) S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling, G. C. Fu, *Chem. Commun.* **2000**, 1009–1010; d) S. Y. Lee, J. M. Murphy, A. Ukai, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 15149–15153.
[29] S. Arai, S. Bellemin-Laponnaz, G. C. Fu, *Angew. Chem.* **2001**, *113*, 240–242; *Angew. Chem. Int. Ed.* **2001**, *40*, 234–236.
[30] B. Tao, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 353–354.
[31] R. Rios, J. Liang, M. M.-C. Lo, G. C. Fu, *Chem. Commun.* **2000**, 377–378.
[32] M. Ogasawara, S. Wada, E. Isshiki, T. Kamimura, A. Yanagisawa, T. Takahashi, K. Yoshida, *Org. Lett.* **2015**, *17*, 2286–2289.
[33] O. Riant, O. Samuel, H. B. Kagan, *J. Am. Chem. Soc.* **1993**, *115*, 5835–5836.

[34] K. Yoshida, Q. Liu, R. Yasue, S. Wada, R. kimura, T. Konishi, M. Ogasawara, *ACS Catal.* **2020**, *10*, 292–301.
[35] D. W. Gao, Q. Yin, Q. Gu, S.-L. You, *J. Am. Chem. Soc.* **2014**, *136*, 4841–4844.
[36] D.-W. Gao, C. Zheng, S.-L. You, *Organometallics* **2015**, *34*, 4618–4625.
[37] C. T. Check, K. P. Jong, C. B. Schwamb, A. S. Wong, M. H. Wang, K. A. Scheidt, *Angew. Chem.* **2015**, *127*, 4338–4342; *Angew. Chem. Int. Ed.* **2015**, *54*, 4264–4268.
[38] J. Wang, Z.-H. Zhu, M.-W. Chen, Q.-A- Chen, Y.-G. Zhou, *Angew. Chem.* **2019**, *131*, 1827–1831; *Angew. Chem. Int. Ed.* **2019**, *58*, 1813–1817.
[39] J. Wang, Z.-B. Zhao, Y. Zhao, G. Luo, Z.-H. Zhu, Y. Luo, Y.-G. Zhou, *J. Org. Chem.* **2020**, *85*, 2355–2368.
[40] Z.-B. Zhao, X. Li, M.-W. Chen, Z. K. Zhao, Y.-G. Zhou, *Chem. Commun.* **2020**, *56*, 7309–7312.
[41] Z.-B. Zhao, X. Li, B. Wu, Y.-G. Zhou, *Chin. J. Chem.* **2020**, *38*, 714–718.
[42] D. Grosheva, N. Cramer, *Angew. Chem.* **2018**, *130*, 13832–13835; *Angew. Chem. Int. Ed.* **2018**, *57*, 13644–13647.
[43] A.-A. Zhang, C. Chen, Y. Gao, M. Mo, R.-Z. Shen, Y.-H. Zhang, N. Ishida, M. Murakami, L. Liu, *Green Synth. Catal.* **2021**, *2*, 311–314.
[44] W. Xie, B. Li, S. Xu, H. Song, B. Wang, *Organometallics* **2014**, *33*, 2138–2141.
[45] S.-B. Wang, J. Zheng, S.-L. You, *Organometallics* **2016**, *35*, 1420–1425.
[46] H.-Y. Liu, R.-Q. Mou, C.-Z. Sun, S.-Y. Zhang, D.-S. Guo, *Tetrahedron Lett.* **2016**, *57*,4676–4679.
[47] H. Chen, Y.-X. Wang, Y.-X. Luan, M. Ye, *Angew. Chem.* **2020**, *132*, 9514–9518; *Angew. Chem. Int. Ed.* **2020**, *59*, 9428–9432.
[48] Y. Nakao, E. Morita, H. Idei, T. Hiyama, *J. Am. Chem. Soc.* **2011**, *133*, 3264–3267.
[49] X. Ma, Z. Gu, *RSC Adv.* **2014**, *4*, 36241–35244.
[50] L. Liu, A.-A. Zhang, R.-J. Zhao, F. Li, T.-J. Meng, N. Ishida, M. Murakami, W.-X. Zhao, *Org. Lett.* **2014**, *16*, 5336–5338.
[51] L. Liu, H. Liu, Z. Zuo, A.-A. Zhang, Z. Li, T. Meng, W. Wu, Y. Hua, G. Mao, *Chin. Chem. Lett.* **2021**, *32*, 239–242.
[52] Y. Liu, J. Xu, J. Zhang, X. Xu, Z. Jin, *Org. Lett.* **2017**, *19*, 5709–5712.
[53] Y. S. Rozhkova, I. V. Plekhanova, A. A. Gorbunov, O. G. Stryapunina, E. N. Chulakov, V. P. Krasnov, M. A. Ezhikova, M. I. Kodess, P. A. Slepukhin, Y. V. Shklyaev, *Tetrahedron Lett.* **2019**, *60*, 768–772.
[54] V. K. Korotaev, I. B. Kutyashev, A. Y. Barkov, Y. S. Rozhkova, I. V. Plekhanova, Y. V. Shklyaev, V. Y. Sosnovskikh, *Tetrahedron Lett.* **2019**, *60*, 150916.
[55] S. González-Pelayo, O. Bernardo, J. Borge, Luis A. López, *Adv. Synth. Catal.* **2021**, *363*, 819–825.
[56] B. S. Bhakuni, A. Yadav, S. Kumar, S. Patel, S. Sharma, S. Kumar, *J. Org. Chem.* **2014**, *79*, 2944–2954.
[57] M. Ito, M. Okamura, K. S. Kanyiva, T. Shibata, *Organometallics* **2019**, *38*, 4029–4035.

Manuscript received: October 22, 2021
Revised manuscript received: December 3, 2021
Accepted manuscript online: December 7, 2021