Top Organomet Chem (2024) 74: 89–102
https://doi.org/10.1007/3418_2024_113

Published online: 31 January 2024

Planar Chiral Ferrocenes: A Concise Introduction

Petr Štěpnička

Abstract Due to its intrinsic beauty and unique properties, bis(η^5-cyclopentadienyl) iron or ferrocene continues to attract the attention of chemists even after seven decades from its discovery. One of the particularly attractive and active fields is the preparation of planar-chiral ferrocene derivatives, which found manifold use as auxiliary ligands in enantioselective transition metal catalysis and organocatalysis. This chapter briefly illustrates the historical context and recent trends in this area, paying particular attention to the development of synthetic routes leading to planar-chiral ferrocenes.

Keywords C-H activation · Directed metalation · Ferrocene · Planar chirality · Synthesis

Abbreviations

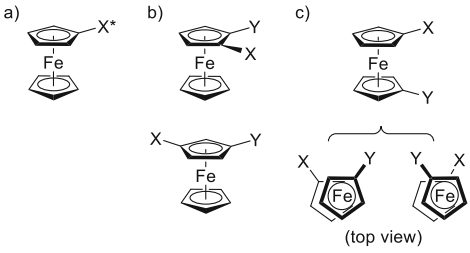
Ac	Acetyl
Ar	Aryl
Boc	*tert*-butyloxycarbonyl
BPPFA	2-[1-(Dimethylamino)ethyl]-1,1′-bis(diphenylphosphino)ferrocene
DMAP	4-(Dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
Fc	Ferrocenyl
H-L-Val-OH	L-valine

P. Štěpnička
Department of Inorganic Chemistry, Faculty of Science, Charles University, Prague, Czech Republic
e-mail: stepnic@natur.cuni.cz

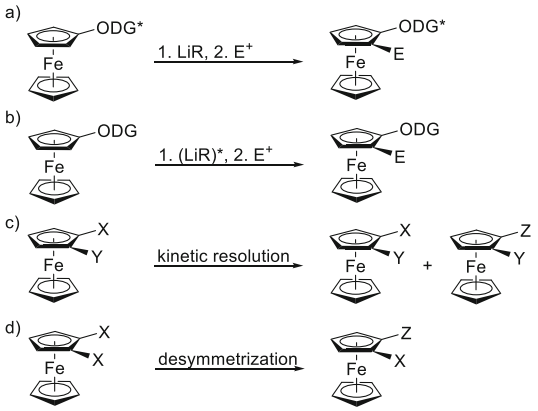
HPLC	High-performance liquid chromatography
n-BuLi	*n*-butyllithium
ODG	*Ortho*-directing group
Ph	Phenyl
PPFA	2-[1-(Dimethylamino)ethyl]-1-(diphenylphosphino)ferrocene
R	An unspecified hydrocarbyl substituent
t-Bu	*tert*-butyl
TMEDA	*N,N,N′,N′*-tetramethyl-1,2-diaminoethane

Cyclopentadienide anions have been widely applied as versatile auxiliary ligands for transition metals [1]. The first compound featuring π-coordinated $C_5H_5^-$ anion, bis(η^5-cyclopentadienyl)iron or ferrocene, [Fe(η^5-C_5H_2)$_2$] (**1**), was discovered and structurally characterized in the early 1950s [2]. Since then the chemistry of cyclopentadienyl complexes rapidly developed, resulting in a vast family of structurally diverse and widely practically utilized compounds [3–7]. When it comes to chiral metallocene derivatives, however, compounds derived from the exceptionally stable ferrocene, which is the archetypal representative of cyclopentadienyl metal complexes, still dominate due to their applications in catalysis. This chapter, which was partly adapted from Ref. [2] with permission from the Royal Society of Chemistry, attempts to briefly illustrate the chemistry of chiral ferrocenes, mainly focusing on the synthetic routes leading to these compounds. Given the enormous number of chiral ferrocene derivatives synthesized to date and their manifold applications, this chapter cannot adequately cover all aspects. Therefore, the reader is referred to review articles and books cited here that summarize the chemistry of chiral ferrocene compounds in more detail [3–21].

Generally, there are three types of chirality encountered in ferrocene derivatives: central, planar, and helical (Scheme 1). While central chirality is usually associated with the substituent(s) appended to the ferrocene core, the other two chirality types reflect the specific steric properties of the ferrocene unit. Generally, planar chirality in cyclopentadienyl complexes is enabled by the coordination of a metal center, formally [$(C_5H_5)Fe^+$–$C_5H_5^-$] for ferrocene, which differentiates the two enantiotopic faces of the planar and aromatic cyclopentadienide anion. In contrast, helical chirality results from blocking the rotation of the parallel cyclopentadienyl rings along the molecular axis in heteroannularly substituted ferrocene derivatives,



Scheme 1 Representative types of ferrocenes with (**a**) central, (**b**) planar, and (**c**) axial chirality (X, Y = various substituents; additional substituents can be present at the unsubstituted cyclopentadienyl ring)

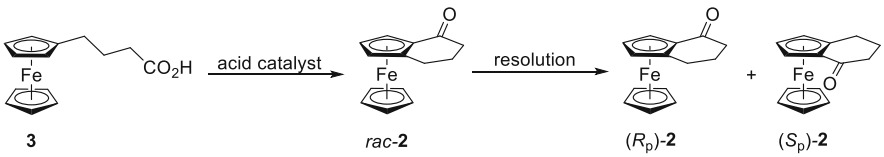


Scheme 2 Synthesis of planar-chiral ferrocenes: (**a**) diastereoselective lithiation/functionalization of ferrocenes with chiral ortho-directing groups (ODG*), (**b**) diastereoselective lithiation/functionalization of ferrocenes with ortho-directing groups (ODG) and chiral bases, (**c**) kinetic resolution of racemic ferrocenes, and (**d**) desymmetrization of achiral ferrocenes (X, Y, Z = various substituents, E^+ = electrophile). Routes (**a**) and (**b**) were equally well applied for the synthesis of planar-chiral ferrocenes through the C−H bond activation/functionalization sequence

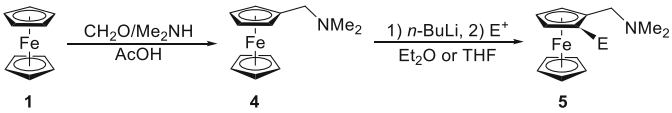
either in the solid state or by bridging the cyclopentadienyl rings (such as in ferrocenophanes).

There are several main routes toward chiral ferrocenes that differ depending on the type of chirality introduced (Scheme 2). Ferrocene derivatives with central chirality are synthesized in conventional manner by attaching or generating a chiral center in a molecule containing the ferrocene moiety. In contrast, planar chiral derivatives are typically obtained by diastereoselective methods when a suitable functional group at the ferrocene unit is used to direct further functionalization to the adjacent position at the ferrocene core (usually position 2 and rarely position 3). Without any chiral "influence," this functionalization expectedly gives rise to a racemic mixture of planar chiral products. In contrast, reactions performed with a chiral directing group or a chiral reagent can produce mixtures enriched with one of the two stereoisomers. These reactions often employ the lithiation/electrophilic quenching approach, using either a chiral ferrocene derivative and common organolithium compound or, alternatively, a simple ferrocene derivative and a chiral metalating agent during the metalation step. More recently, this approach was extended toward C−H bond activation reactions at the ferrocene moiety. Methods relying on kinetic resolution and desymmetrization of suitable ferrocene derivatives remain less widely explored and practically utilized [22, 23].

Initial attempts at preparing planar-chiral ferrocenes were based on the conventional synthetic approaches developed for organic compounds [24, 25]. These methods typically afforded racemic mixtures of enantiomers, which were resolved either via diastereoisomeric derivatives or, less commonly, by chromatography over chiral stationary phases [26]. The first planar chiral ferrocene derivative resolved into (R_p)- and (S_p)-enantiomers was 1,2-(α-ketotetramethylene)ferrocene (**2**), which is



Scheme 3 Synthesis of **2**



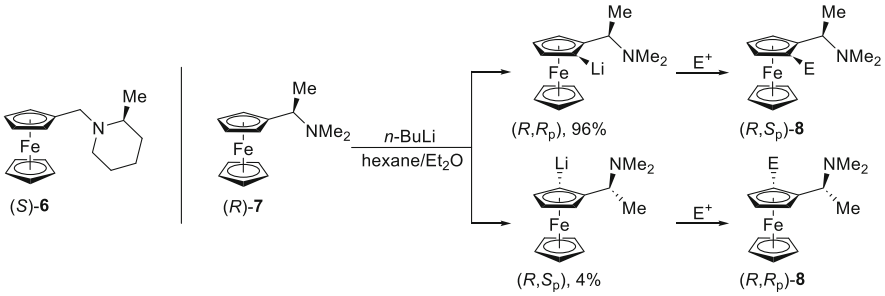
Scheme 4 Synthesis and lithiation of [(dimethylamino)methyl]ferrocene (**4**)

accessible (in racemic form) by acid-catalyzed intramolecular acylation from 4-ferrocenylbutanoic acid (**3**) [27]. This compound was resolved via diastereomeric hydrazones obtained from (−)-menthylhydrazine [28], and the absolute configuration of the (+)-isomer was established using chemical methods (Scheme 3) [29].

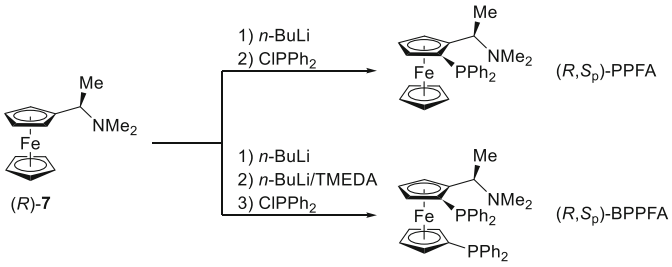
Later on, the development of synthetic routes toward planar chiral ferrocenes became intimately associated with the design, synthesis, and applications of chiral ferrocene ligands, mostly phosphines, in homogeneous transition metal catalysis. These compounds are usually obtained by diastereoselective functionalization of chiral starting materials and, hence, combine central chirality with chirality at the cyclopentadienyl plane. Compounds featuring only planar chirality remain less common.

Access to such planar chiral ferrocenes was opened in 1965 through the research of Hauser and coworkers [30], showing that initial lithiation of [(dimethylamino)-methyl]ferrocene (**4**) [31, 32] with *n*-butyllithium *n*-BuLi occurs preferentially in position 2 of the ferrocene unit and that an excess of *n*-BuLi is needed to achieve lithiation at the unsubstituted cyclopentadienyl ring (Scheme 4). Soon afterwards, the concept of directed *ortho*-lithiation was extended into diastereoselective variants using chiral aminoferrocenes **6** [33, 34] and **7** [35] (Scheme 5). Of these compounds, *N*,*N*-dimethyl-1-ferrocenylethylamine, Ugi's amine (**7**), proved particularly useful for further synthesis because of its synthetic accessibility in optically pure form, high stereoselectivity of the lithiation reaction (*dr* = 96:4), and ability to undergo nucleophilic replacement of the NMe_2 group (S_N1-type substitution) that proceeds with the retention of configuration at the stereogenic carbon [36]. The latter property, a result of the exceptional stabilization of ferrocenylmethylium cations as plausible and even isolable intermediates [37], is preserved for 2-substituted derivatives and was observed for analogous compounds containing other easily leaving groups (e.g., NMe_3^+ and OAc instead of NMe_2 in the side chain), thus widening the scope of accessible compounds.

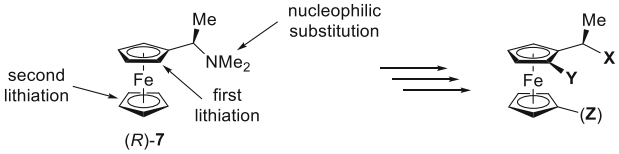
Already in the 1970s, Kumada and coworkers utilized lithiation of Ugi's amine to prepare chiral ferrocene P,N-donors, (R,S_p)-PPFA and (R,S_p)-BPPFA (Scheme 6)



Scheme 5 The structure of (*S*)-**6** and diastereoselective lithiation of Ugi's amine (*R*)-**7** producing planar chiral substitution products **8**. The change in the stereochemical descriptors reflects the changed priority of the substituents according to the Cahn-Ingold-Prelog rules (E > Li)



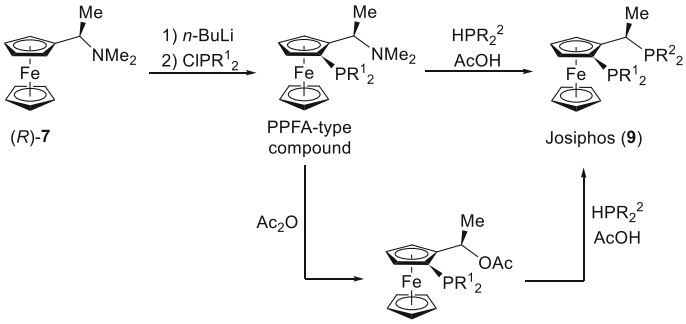
Scheme 6 Synthesis of PPFA and BPPFA from Ugi's amine. The synthesis of BPPFA can be performed in a stepwise manner, which allows the introduction of two different phosphine groups



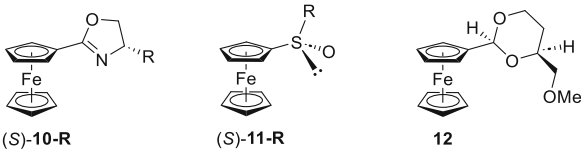
Scheme 7 Schematic depictions of the synthetic transformations of Ugi's amine that affords chiral ferrocene derivatives (X, Y, and Z are various functional groups)

[38], which were evaluated as efficient chiral supporting ligands in asymmetric alkene hydrogenation [39, 40] and ketone hydrosilylation [38] over chiral rhodium catalysts and in alkene hydrosilylation [41] and Kumada cross-coupling using palladium catalysts [42, 43]. The family of chiral phosphinoferrocene ligands (Scheme 7) was further widened via stereoconservative nucleophilic replacement of the NMe_2 group that resulted in a range of multi-donor (usually hybrid [44]) derivatives combining phosphine and other ligating groups (N-, P-, S-, O-donors, etc.) [45], which were also applied in transition metal-mediated asymmetric organic transformations [46].

In particular, replacing the NMe_2 group in PPFA-type compounds with another phosphine moiety produced chiral diphosphines from the Josiphos family



Scheme 8 Synthesis of Josiphos ligands

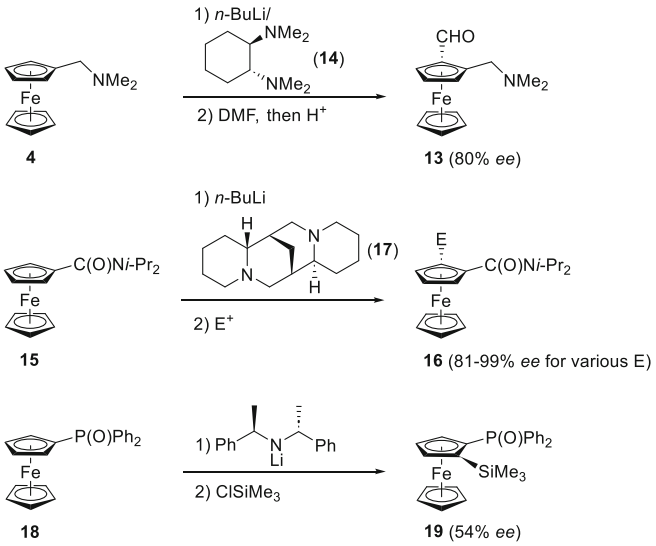


Scheme 9 Examples of chiral ferrocenes used in diastereoselective *ortho*-lithiation reactions (Note: the synthesis of **10-R** and **12** makes use of common chiral pool: while compounds **10-R** are prepared from β-amino alcohols accessible from α-amino acids, (*S*)-1,2,4-butanetriol required for the synthesis of **12** is obtained by reduction of L-malic acid)

(compounds **9** in Scheme 8) [47]. The possibility of independently altering the chirality at the cyclopentadienyl plane and in the side chain as well as the phosphine substituents (R^1 and R^2) in these ligands enabled their tuning according to the particular use, which consequently opened ways to their massive applications in transition-metal catalysis in laboratory and even industry scale [48, 49] and also stimulated the synthesis of numerous, structurally related P,N- and P,P-ligands with varied spacer and donor groups [3–21].

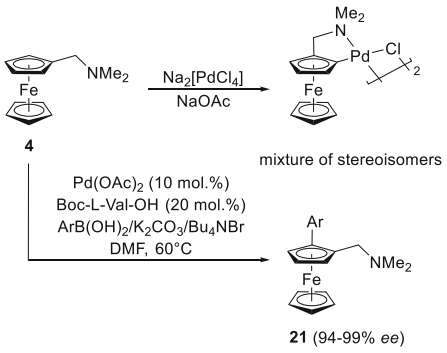
The high efficiency and robustness of the synthetic methods based on diastereoselective *ortho*-lithiation/functionalization of chiral ferrocene amines obviously initiated a search for other applicable chiral directing groups [50]. Among the approaches developed to date, C-chiral ferrocene oxazolines **10-R** [51–53], S-chiral sulfoxides **11-R** [54, 55], and acetal **12** [56, 57] (Scheme 9) proved particularly attractive because they are practical in terms of accessibility and subsequent transformation, produce valuable synthetic intermediates, or even provide a direct access to new ligands (viz., chiral ferrocene oxazolines [51–53, 58, 59]).

As mentioned above, complementary synthetic approaches (Scheme 10) toward planar chiral ferrocenes were developed based on the metalation of prochiral substrates bearing suitable directing groups such as amine **4** [60], tertiary amide **15** [61–64], and phosphine oxide **18** [65, 66] using adducts generated from organolithium compounds and chiral amines (e.g., (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine (**14**) and (−)-sparteine (**17**)) and chiral amides such as (*R*,*R*)-lithium bis(1-phenylethyl)amide (see the last entry in Scheme 10; 95% yield, *ee* 54%).



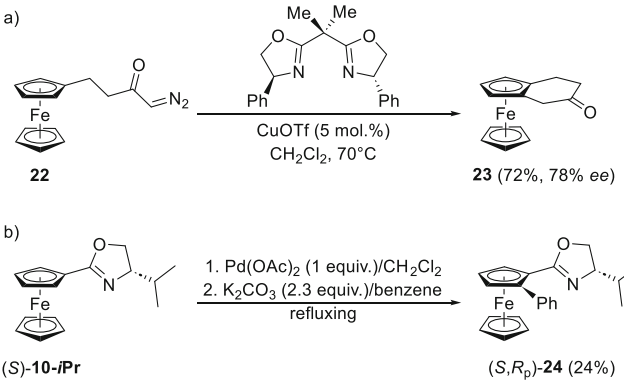
Scheme 10 Directed *ortho*-lithiation of ferrocenes with chiral bases

Scheme 11 Conventional ortho-palladation of amine **4** and the asymmetric variant of this reaction proceeding with concomitant C−C bond formation

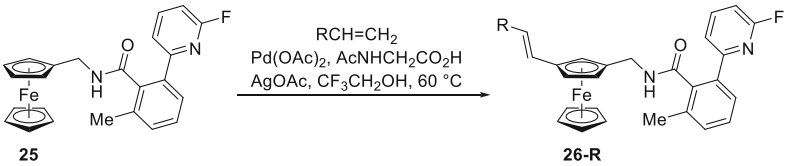


Recently, mixed Li-Zn and Li-Cd amides resulting from bis(1-phenylethyl)amine and analogs, where one 1-phenylethyl substituent was replaced for a terpene residue, were successfully applied in directed lithiation of alkyl ferrocene carboxylates $FcCO_2R$ (Fc = ferrocenyl). The best results (*ee*'s up to 71%) were obtained when $LiNR_2$ and ZnR_2 were combined (E = CH(Me)Ph) [67].

Chiral directing groups or chiral transition metal catalysts were also used to accomplish enantioselective C−H bond activation at the ferrocene moiety [68]. In the 1970s, Sokolov et al. demonstrated that orthopalladation of Ugi's amine produced two diastereoisomeric palladium complexes, analogous to **20** (Scheme 11, top), in an 85:15 ratio [69] and that palladation of achiral amine **4** [70] can be achieved in an asymmetric manner when using *N*-acetyl-L-valine/NaOH as a stoichiometric additive [71, 72]. Several decades later, asymmetric C−H activation of **4** with concomitant C−C bond formation was achieved with the composite



Scheme 12 Asymmetric C−H functionalization of ferrocene derivatives



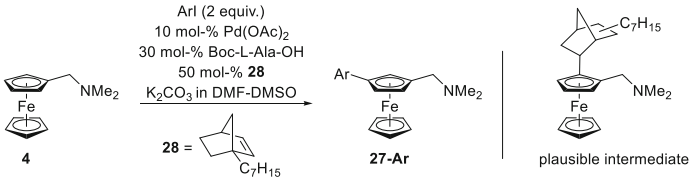
Scheme 13 Catalytic alkenylation of amide **25**

Pd-catalyst and boronic acid to give aryl-substituted compounds **21** (Scheme 11) [73].

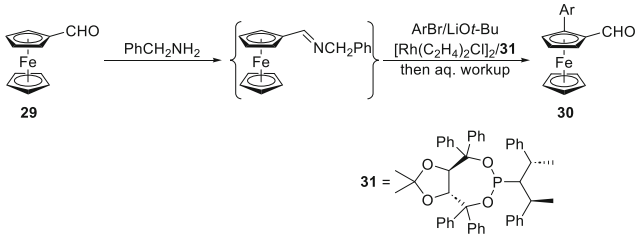
In 1997, Siegel and Schmalz reported that insertion of a carbene in situ-generated from diazo compound **22** in the presence of a chiral copper catalyst produces planar-chiral ketone **23** with a good yield and *ee* (72% and 78%, respectively; see Scheme 12a) [74]. An intermolecular arylation based on C−H activation/C−C bond formation was observed when reacting chiral oxazoline (*S*)-**10-*i*Pr** with benzene in the presence of a palladium catalyst and a base. This reaction produced compound **24** as single diastereoisomer in 24% yield (Scheme 12b). Minor amounts of the doubly arylated product (2,5-isomer) were also detected [75].

During the subsequent research, the array of the directing groups suitable for efficient catalytic C−H bond functionalization reactions of ferrocenes proceeding under the formation of new C−C bonds in enantioselective manner was markedly expanded, e.g., towards ferrocene N-heterocycles, amides, thioamides, azines, and acyl derivatives and even the palette of the tandem reactions was considerably widened [68, 76–84]. As an illustrative example can serve the recently disclosed C−H activation/alkenylation of ferrocene amide **25** containing an extended, pyridine-based directing group. This reaction occurs in position 3 of the ferrocene core and thus offers an alternative access to the difficult-to-prepare 1,3-disubstituted ferrocenes in racemic form [85, 86] (Scheme 13).

An alternative approach to 1,3-disubstituted ferrocenes **27-Ar** has been developed based on remote arylation of amine **4** utilizing a $Pd(OAc)_2$/Boc-L-Val-OH



Scheme 14 Remote, palladium-catalyzed arylation of amine **4**

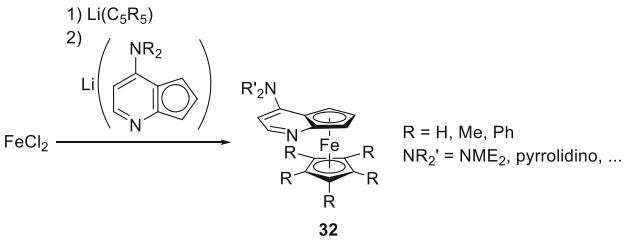


Scheme 15 Asymmetric Rh-catalyzed C−H bond arylation of ferrocene aldehydes

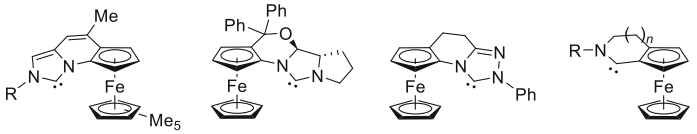
catalyst and a norbornene derivative (racemic), which serves as a temporary blocking group (in position adjacent to the amine substituent) and a mediator in the subsequent functionalization at position 3 of the ferrocene core (Scheme 14). The scope of compounds accessible by this method is very wide because many substituents are tolerated at the aryl halide and the products retain the reactivity of the parent amine (including ortho-functionalization).

In a recent paper, You and coworkers reported on asymmetric, Rh-catalyzed arylation of imine generated in situ from ferrocene carboxaldehyde (**29**) and benzylamine (Scheme 15), which produces (after hydrolysis) 2-arylated ferrocene carboxaldehydes **30-Ar** with up to 83% yield and >99% *ee* under optimized conditions (10 mol-% Rh and 20 mol-% of chiral phosphoramidite ligand **31** at 80°C). This method tolerates various substituents at the aryl bromide (alkyl, OMe, NMe_2, SMe, halide, ester, or heterocycle) and on the unsubstituted C_5H_5 ring of the starting aldehyde (e.g., alkyl, vinyl, aryl) and thus offers an efficient complementary alternative to synthetic routes employing chiral acetal **12**.

Planar chirality is also encountered in suitably annellated ferrocenes [87] (see compound **2** mentioned above). Further examples of such compounds include planar chiral analogs of 3-(dimethylamino)pyridine (DMAP), compounds **32**, which were extensively studied as organocatalysts [87–90]. Initially, these compounds were obtained by sequential addition of cyclopentadienide reagents to $FeCl_2$ (Scheme 16), and the product mixture was separated using chemical methods (via diastereoisomers) or chiral HPLC. Later on, convergent asymmetric routes to these compounds were devised, employing chiral acetal **12** and the analogous compound permethylated at the other cyclopentadienyl ring as the starting materials [91, 92]. Further attractive examples of chiral annellated ferrocenes include chiral ferrocene-based carbene ligands [93–95] represented by compounds **33**–**37** (Scheme



Scheme 16 Synthesis of ferrocene-fused DMAP analogs **32**



Scheme 17 Examples of planar-chiral ferrocene carbene ligands (only the carbene structure is shown even when the free carbene was not isolated but trapped as a ligand; R is usually a sterically demanding and/or aromatic substituent such as isopropyl, phenyl, or mesityl)

17). The synthesis of **33** involved the preparation of a racemic annellated precursor and its resolution into enantiomers. The free carbene was isolated and utilized as both an organocatalyst and an auxiliary ligand in transition metal-mediated reactions [96, 97]. Conversely, carbene **34** was prepared by diastereoselective functionalization of a chiral ferrocene precursor and was isolated in the form of an Ir(I) complex, subsequently tested in Ir-catalyzed quinoline hydrogenation (free carbene was not isolated) [98]. In a similar vein, the planar chiral carbene **35** was obtained in several steps from acetal **12** and isolated in the form of a CuCl complex [99]. The same starting material was used to prepare the homologous compounds **36** and **37**, which were evaluated as ligands in Ir-catalyzed asymmetric transfer hydrogenation and in Cu-catalyzed borylation of *tert*-butyl cinnamate [100–103].

Although far from exhaustive, this overview of the routes leading to planar chiral ferrocene derivatives illustrates the rapid and extensive developments in the area of planar chiral ferrocenes during the approximately seven decades, which passed since the discovery of the parent compound. These developments, which changed chiral ferrocenes from mere laboratory curiosities to useful molecules are driven by wide and rapidly emerging applications of these compounds in fields as diverse as molecular synthesis, catalysis, material science, and bioorganometallic chemistry [104–106]. Even though the currently available synthetic methods offer reliable access to a wide array of ferrocene derivatives, despite revolving around relatively few synthetic principles, further research is still highly desirable as it may result in alternative and possibly more efficient (in terms of both the yield and stereoselectivity) and atom economical processes. These should further widen the scope of accessible compounds and also mitigate problems with subsequent

manipulation of the auxiliary substituents. In this view, approaches based on the functionalization of ferrocene C−H bonds appear particularly attractive. In turn, this research can open further application fields and enable wider applications of chiral ferrocenes in transition metal catalysis as well as in organocatalysis.

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