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ARTICLE

Asymmetric synthesis of metallocenes with planar and central chirality by rhodium-catalyzed desymmetrization reactions

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Metallocenes with planar and central chirality has emerged as a privileged skeleton for chiral ligand design, and such ligands have exhibited tremendous success in various asymmetric catalysis protocols. Herein, we report a rhodium/chiral diene-catalyzed asymmetric desymmetrization of 1,2-diformylmetallocenes with aryl/alkenylboronic acids to give enantio-enriched formylmetallocenes, which are diastereoisomers of Ugi-type products. This catalytic system also enables kinetic resolution of 2-substituted 1-formylferrocene with a selectivity factor (s) of up to 4331. Compared with traditional synthesis methods, our method has the following advantages: 1) opposite diasterose-lectivity; 2) catalytic asymmetric synthesis; 3) single-step construction of planar and central chirality. The synthetic utility of the present method is demonstrated by the asymmetric synthesis of a series of chiral phosphine ligands, including Josiphos- and PPFA-type ligands

Introduction

Metallocenes possessing planar chirality are of great significance in organic synthesis, material science, and medicinal chemistry.[1] Compounds such as PPFA,[2] TRAP,[3] Josiphos,[4] BoPhoz,[5] Walphos,[6] Taniaphos,[7] Zhaophos,[8] and Wudaphos,[9] which possess both planar and central chirality, are extensively used in asymmetric catalysis. These ligands are typically prepared according to Ugi's procedure, which introduces additional planar chirality besides its inherent central chirality through diastereoselective *ortho*-lithiation (Scheme 1a).[10] One example of this is the synthesis of (*R*,*S*p)-ferrocenecarbaldehyde, which has proved successful as a catalyst for the asymmetric alkylation of aldehydes with dialkylzinc reagents, through the *ortho*-lithiation of (*R*)-(2-dimethylaminoethyl)ferrocene (Ugi's amine).[11b] Chiral Ugi's amine is typically prepared by a conventional method that relies heavily on the optical resolution of its racemate with the aid of resolving agents in specific proportions.[10a] As a result, the development of highly effective, simple, and reliable techniques for producing metallocenes with both central and planar chirality is seen as a significant pursuit in the realm of synthetic chemistry. Transition-metal-catalyzed enantioselective C–H functionalization of metallocenes has been the subject of

extensive research in relation to catalytic asymmetric synthesis (Scheme 1b).[12] There have been limited studies on the preparation of enantio-enriched planar chiral metallocenes through catalytic desymmetrization of prochiral compounds.[13] However, the simultaneous introduction of planar and central chirality in metallocenes in a single step with high diastereo- and enantioselectivity has seldom been reported.[14]

Scheme 1 Asymmetric synthesis of metallocenes with planar and central chirality.
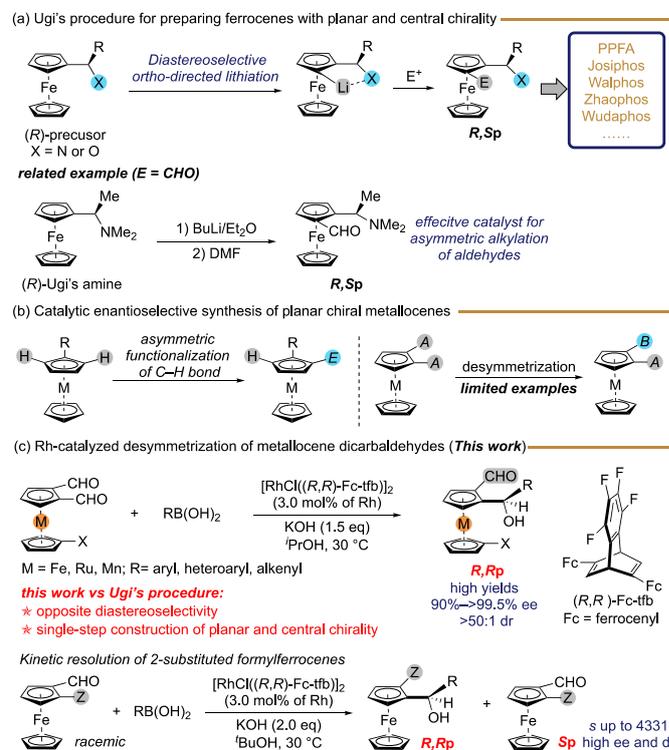
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ARTICLE

Planar chiral formylferrocenes are an important class of platform molecules, with the potential to be transformed and applied in the synthesis of chiral ligands and catalysts.[15] Herein, we describe a rhodium-catalyzed desymmetric addition[16] of organoboronic acids to 1,2-diformylmetallocenes, leading to the formation of chiral metalloceneformaldehydes with both planar and central chirality in high yields with high diastereo- and enantioselectivity (Scheme 1c). Furthermore, we successfully achieved kinetic resolution of planar chiral 2-substituted formylferrocenes using the same catalytic system. In previous work, the diastereomer of Ugi amine was prepared by multiple-step protection and deprotection, leading to low synthesis efficiency.[17] Our method offers several advantages over Ugi's procedure, including: 1) catalytic asymmetric synthesis; 2) simultaneous generation of planar and central chirality; 3) opposite planar diastereoselectivity; 4) simple and mild reaction conditions. We have demonstrated the practical application of our approach by synthesizing various chiral phosphine ligands, such as Josiphos- and PPFA-type ligands, in an asymmetric manner.

Results and discussion

As a model reaction, the addition of $PhB(OH)_2$ (**2a**, 1.0 equiv. with respect to **1a**) to 1,2-diformylferrocene (**1a**) was performed in the presence of 3.0 mol% of rhodium catalysts bearing several types of chiral diene[16e] and bisphosphine ligands and 1.5 equiv. of KOH in 2-propanol at 30 °C for 10 h (Table 1). The reaction with (R,R)-Fc-tfb[18] as a ligand gave a 93% yield of **3aa** with >99.5% ee, and its diastereoisomer **4aa** was not detected by ^{1}H NMR spectroscopy (entry 1). Another commonly used chiral diene ligand, (R,R)-Ph-bod, gave a moderate yield of a mixture of **3aa** and **4aa** with much lower enantioselectivity (entry 2). Other ligands, namely (R)-Segphos, (R)-Binap, and (R)-Ph-Phox, gave low yields of **3aa** with low stereoselectivity, and the formation of side product **5**, which was produced by hydrogenation of **1a**, was detected in these reactions (entries 3–5). Reactions in other protic solvents, namely dioxane/H_2O and MeOH, gave **3aa** with moderate enantioselectivity (entries 6 and 7). The reaction in ^tBuOH also gave **3aa** in high yield with high ee and dr (entry 8). The use of PhZnCl in place of $PhB(OH)_2$ gave a trace amount of **3aa** (entry 9).

Table 1 Optimization of catalytic conditions[a]
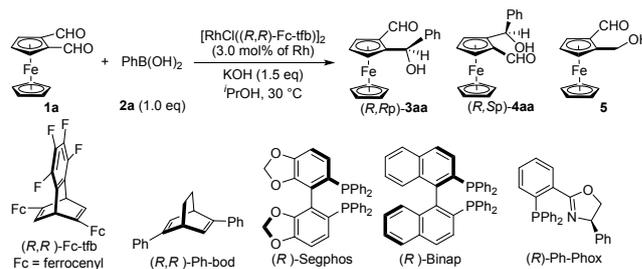
Entry	Variations from standard conditions (shown above)	Yield (%)[b] 3aa	dr[c] (3:4) 3aa	% ee[d] 3aa
1	None	93	>50:1	>99.5
2	$[RhCl((R,R)$-Ph-bod$)]_2$	44	67:33	51
3	$[RhCl(coe)_2]_2$ + (R)-Segphos	<5	–	–
4	$[RhCl(coe)_2]_2$ + (R)-Binap	11	63:37	24
5	$[RhCl(coe)_2]_2$ + (R)-Ph-Phox	10	80:20	0
6	dioxane/H_2O (10/1) instead of ^iPrOH	90	>50:1	79
7	MeOH instead of ^iPrOH	20	>50:1	79
8	^tBuOH instead of ^iPrOH	94	>50:1	96
9[e]	PhZnCl instead of $PhB(OH)_2$	<5	–	–

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), KOH (0.15 mmol), $[RhCl((R,R)$-Fc-tfb$)]_2$ (3.0 mol% Rh), and 2-propanol (1.0 mL) at 30 °C for 10 h. [b] Isolated yield. [c] dr (diastereomeric ratio) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Considering the accuracy of ^{1}H NMR spectroscopy, the dr is >50:1. [d] % ee was determined by HPLC on a chiral stationary phase column. [e] Reaction conditions: **1a** (0.10 mmol), PhZnCl (0.20 mmol), $[RhCl((R,R)$-Fc-tfb$)]_2$ (3.0 mol% Rh), and THF (1.0 mL) at 30 °C for 10 h.

Having established the optimal reaction conditions (Table 1, entry 1), the substrate scope of this desymmetrization reaction of various 1,2-diformylmetallocenes with $PhB(OH)_2$ (**2a**) was examined, and the results are summarized in Scheme 2a. Desymmetrization of **1b**, with a Me_3Si- group at the 1'-position of the ferrocene cyclopentadiene moiety, proceeded well to give the corresponding product **3ba** with high diastereo- and enantioselectivity (entry 2). Using the present method, chiral ruthenocene derivative **3ca** and tricarbonylcyclopentadienyl manganese derivative **3da** were successfully obtained in high yields with excellent dr and high ee values under the standard conditions (entries 3 and 4).

Scheme 2b provides an overview of the results obtained for reactions of 1,2-diformylferrocene (**1a**) with diversely functionalized organoboronic acids **2**, including aryl-, heteroaryl-, and alkenylboronic acids, under the standard conditions. The desymmetric addition proceeded smoothly for $ArB(OH)_2$ **2b**–**2j**, which are aromatic groups consisting of aryl moieties with methoxy, trifluoromethoxy, methyl, trimethylsilyl, halo, trifluoromethyl, and ester substituents at the *para* position (entries 5–13). The corresponding products **3ab**–**3aj** were obtained in high yields with high diastereo- and enantioselectivity (>50:1 dr, 84–>99.5% ee). However, the presence of electron-withdrawing groups generally decreased the enantioselectivity. Arylboronic acids **2k**–**2m**, with electron-donating and -withdrawing substituents at their *meta* position,

gave high yields of the corresponding products **3ak–3am** with enantioselectivity of 89–90% ee (entries 14–16). The reaction of *ortho*-substituted arylboronic acid **2n** also took place, gave the corresponding product **3an** in high yield with excellent diastereo- and enantioselectivity (entry 17). The desymmetric addition of **1a** also proceeded smoothly for polysubstituted arylboronic acids **2o–2q** to give the corresponding products **3ao–3aq** in high yields with both high diastereo- and enantioselectivity (entries 18–20). The desymmetric addition of heteroarylboronic acids **2r** and **2s** gave moderate yields of the corresponding products **3ar** and **3as** with both high dr and ee (entries 21 and 22). Desymmetric alkenylation of **1a** with 1-cyclopentenylboronic acid (**2t**) also gave a high yield of the corresponding product **3at** with high dr and ee (>50:1 dr, 94% ee, entry 23).
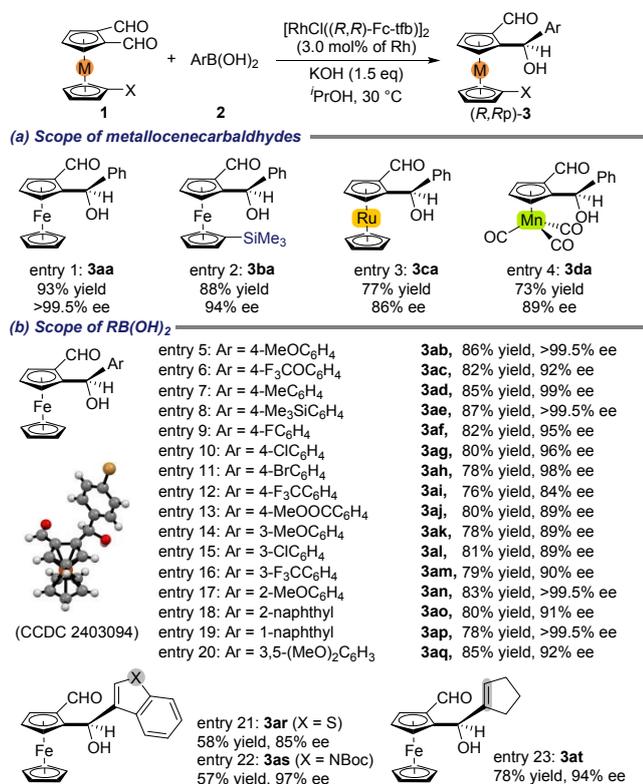
Scheme 2 Rh-catalyzed desymmetric addition of organoboronic acids to metallocene dicarbaldehydes: substrate scope. Reaction conditions: **1** (0.10 mmol), **2** (0.10 mmol), KOH (0.15 mmol), [RhCl((*R,R*)-Fc-tfb)]₂ (3.0 mol% Rh), and 2-propanol (1.0 mL) at 30 °C for 10 h. Isolated yield. dr (diastereomeric ratio) was determined by ¹H NMR spectroscopy of the crude reaction mixture. Considering the accuracy of ¹H NMR spectroscopy, the dr is >50:1. % ee was determined by HPLC on a chiral stationary phase column. The absolute configuration of **3ah** was determined to be *R*,*R*_P by X-ray crystallographic analysis (CCDC 2403094).

The (*R,R*p)-configuration for compound **3ah** can be rationalized by the stereochemical pathway shown in Scheme 3. The steric match among the ferrocenyl and aldehyde moieties of **1a**, Rh-Ph fragment, and the chiral (*R,R*)-Fc-tfb ligand might be very important for achieving the high level of stereo-control. For chiral recognition of the two enantiotopic aldehyde groups of **1a**, the coordination of **1a** with Rh/(*R,R*)-Fc-tfb is more favorable in the configuration **IMA** than in **IMB**, leading to the

formation of planar chirality in the (*R*p)-configuration. This can be originate from the favorable non-covalent interactions, i.e. π-stacking interaction between the ferrocenyl moiety of **1a** and the ferrocenyl group on the olefin of (*R,R*)-Fc-tfb and hydrogen-bonding interaction between the aldehyde fragment of **1a** and the Rh-Ph moiety. To avoid the unfavorable steric hindrance between the carbonyl and ferrocenyl moieties of **1a** and the ferrocenyl group on the olefin of (*R,R*)-Fc-tfb, **IMA** is preferred to **IMC** or **IMD**, offering the (*R*)-configuration product. Thus, the Rh/(*R,R*)-Fc-tfb catalyst effectively constructs the stereochemical model of (*R,R*p)-configuration.
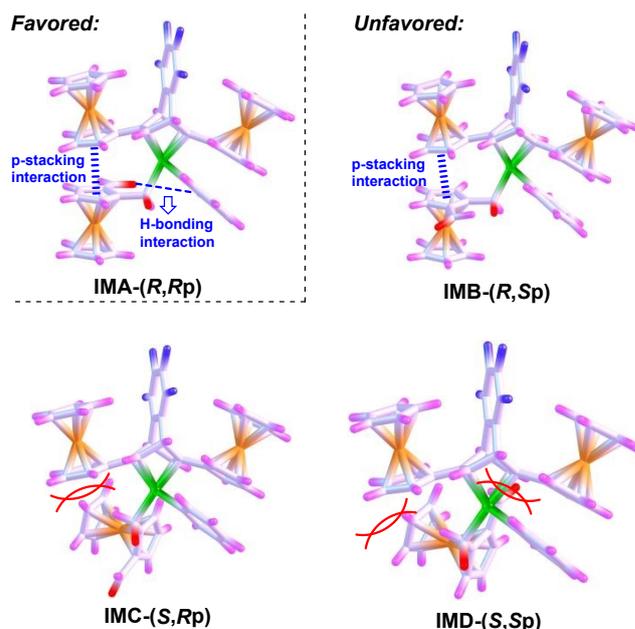
Scheme 3 Proposed stereochemical pathway.

The catalytic cycle for the rhodium/chiral diene-catalyzed asymmetric desymmetrization of 1,2-diformylmetallocenes is proposed in Scheme 4. 1,2-Addition of 1,2-diformylferrocene (**1a**) with phenyl-rhodium species **II**, which is generated by transmetalation of PhB(OH)₂ with [Rh]–OR species **I**, affords an rhodium alkoxide species **III**. Further protonation of intermediate **III** gives product **3aa** and regenerate [Rh]–OR species **I**.
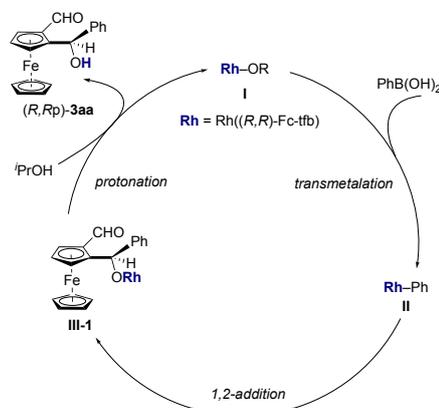
Scheme 4 Proposed catalytic cycle.

Next, the Rh/(R,R)-Fc-tfb catalytic system was successfully applied to the kinetic resolution (KR) of racemic 2-substituted formylferrocenes (Scheme 5). The KR of 2-silyl formylferrocene **1e** with 2-methylphenylboronic acid in the presence of the Rh/(R,R)-Fc-tfb catalyst in *tert*-butanol proceeded smoothly with 51% conversion, giving the arylation product **3e** (>50:1 dr) with 96% ee and recovered **1e** with >99.5% ee, and the corresponding selectivity factor (*s*) for *rac*-**1e** was 280. This KR methodology also proved to be highly efficient towards **1f** bearing a phosphine oxide group, giving a high *s*-factor value, with a high yield of the corresponding product **3f**, and both **3f** and recovered **1f** having high ee. The KR of **1g**, with a Me$_3$Si-group at the 1'-position of the ferrocene moiety, proceeded well and gave the corresponding product **3g** with an excellent *s*-factor (*s* = 4331).
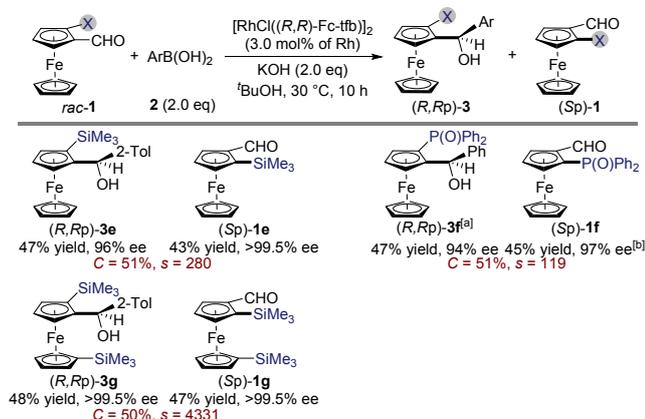
Scheme 5 Kinetic resolution of planar chiral 2-substituted formylferrocenes. Reaction conditions: **1** (0.10 mmol), **2** (0.20 mmol), KOH (0.20 mmol), [RhCl((R,R)-Fc-tfb)]$_2$ (3.0 mol% Rh), and ^{t}BuOH (1.0 mL) at 30 °C for 10 h. Calculated conversion, *C*. = ee$_1$/(ee$_1$+ee$_3$). The % ee was determined by HPLC on a chiral stationary phase column. Selectivity factor, *s* = ln[(1–*C*)(1–ee$_1$)]/ln[(1–*C*)(1+ee$_1$)]. Diastereomeric ratio (dr) = >50:1 (determined by ^{1}H NMR) spectroscopy. ^{a} At 80 °C. ^{b} Compound **1f** was transformed to compound **12a** (Scheme 6) for HPLC analysis.

To demonstrate the synthetic potential of our method, the products were expeditiously transformed into potentially useful phosphine ligands (Scheme 6). A ferrocenyl-based chiral diol ligand (FERRODIOL), prepared from optically pure aminoformylferrocene, has been developed as a chiral ligand for scandium-catalyzed asymmetric Diels–Alder reactions.[19] As shown in Scheme 6a, FERRODIOL **6** was easily prepared by the diastereoselective addition of a Grignard reagent to compound **3aa**, which was obtained as indicated in Table 1, entry 1. Moreover, a new Josiphos-type ligand **9** was prepared through a sequence that comprised reduction, acylation, and diastereoselective S$_N$1-type reaction with HPPh$_2$ as a nucleophilic reagent. There are very few examples of bisphosphanes that possess only planar chirality. Here, we successfully prepared several enantiopure Josiphos-type ligands **12a–12c** with planar chirality as the sole source of chirality. Their rhodium complexes proved to be efficient catalysts for the asymmetric hydrogenation of various alkenes (Scheme 6b).[20] Thus, starting from **1f**, ligands **12a–12c** were efficiently synthesized through a sequence that involved reduction with NaBH$_4$, S$_N$1-type reaction, and reduction with HSi(OEt)$_3$. Subsequently, addition of Grignard reagent MeMgBr to **1e** yielded alcohol **13**, which was then converted into acetate **14** by treating it with acetic anhydride (Scheme 6c). The crude compound **14** served as starting material for the synthesis of a ferrocene-derived chiral monophosphine ligand **15** by a simple S$_N$1-type reaction with HPPh$_2$.[21] Moreover, compound **14** was also transformed into **16**, the diastereoselectivity of which is opposite to that of the product obtained from Ugi's amine through nucleophilic substitution with HNMe$_2$. Furthermore, the chiral PPFA ligand derivative **17** was obtained in 85% isolated yield by diphenylphosphination of the lithiated ferrocene, produced through the reaction of **16** with butyllithium. The efficiency of ligand **17** was demonstrated by a Pd-catalyzed asymmetric allylic alkylation reaction (87% yield, 90% ee) (Scheme 6d).[22] Similarly, the new PPFA ligand also underwent S$_N$1 reactions with HPPh$_2$ and HPCy$_2$, and subsequent desilication afforded Josiphos ligands **18** and **19**, respectively, in high yields. Desilication of compound **17** also gave the normal PPFA ligand **20** in high yield. In summary, various chiral ligands, including FERRODIOL **6**, new Josiphos-type ligand **9**, Josiphos-type ligands **12a–12c** without central chirality, a ferrocene-derived chiral monophosphine ligand **15**, PPFA-type ligand **17**, known Josiphos ligands **18** and **19**, and known PPFA ligand **20**, were successfully produced.

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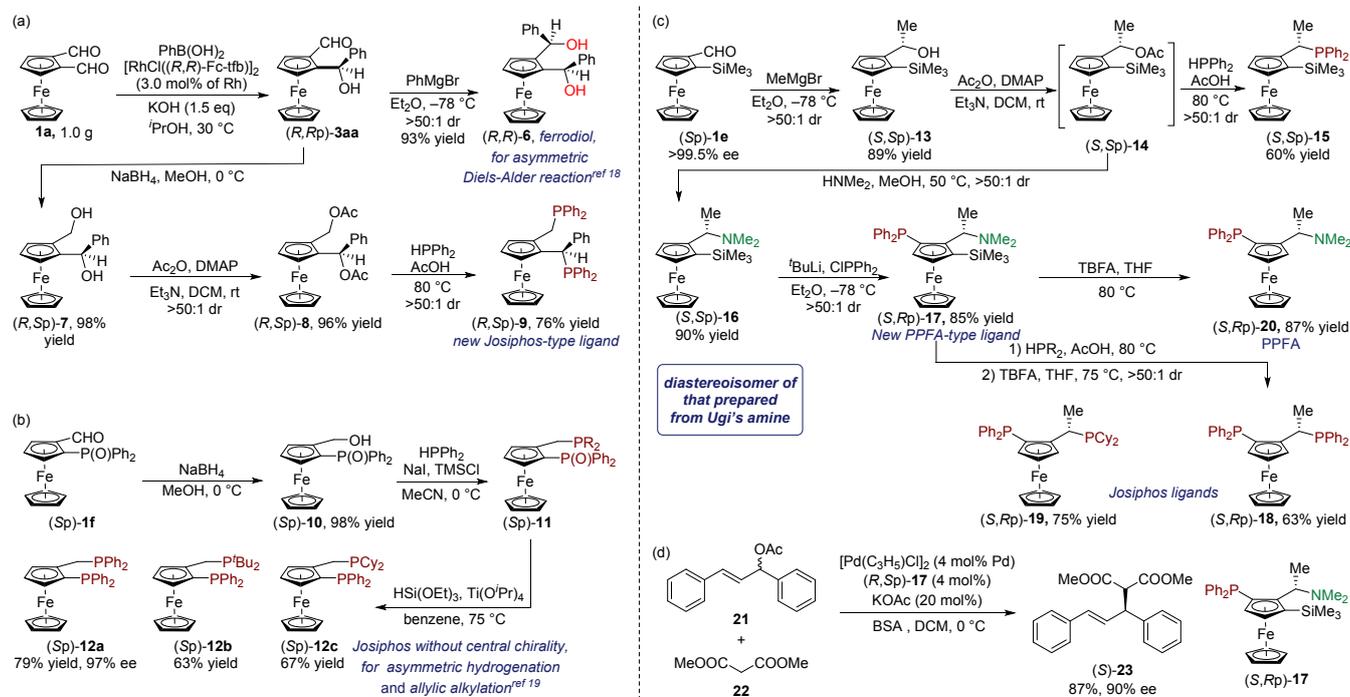
Scheme 6 Synthetic transformations.

Conclusions

In summary, we have developed a highly efficient synthesis of enantiopure planar and central chiral metallocenes based on rhodium-catalyzed asymmetric addition under mild conditions. These chiral metallocenes, created through the simultaneous construction of planar and central chirality from achiral 1,2-diformylmetallocene, were obtained in high yields with excellent diastereo- and enantioselectivity. Furthermore, the KR reaction proceeded smoothly, achieving a selectivity factor of up to 4331. The synthetic utility of the present method has been demonstrated by the asymmetric synthesis of a series of chiral phosphine ligands, including Josiphos- and PPFA-type ligands.

Author contributions

The manuscript was written through contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data and X-ray crystallographic data of compound **3ah** (CCDC-2403094). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x