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Novel biferrocene-based phosphoramidite ligands: the combination of a rather unexplored chiral backbone and a privileged ligand scaffold

W. Kimpe[a], P. Janssens[a], K. Bert[a], S. Wackens[a], J. L. Goeman[a] and J. Van der Eycken[a*]

[a] Laboratory for Organic and Bioorganic Synthesis, Department of Organic and Macromolecular Chemistry, Ghent University, Krijgslaan 281 (S.4), B-9000 Ghent, Belgium, E-mail: Johan.VanderEycken@UGent.be, Fax: +32-9-264-49-98
*Corresponding author

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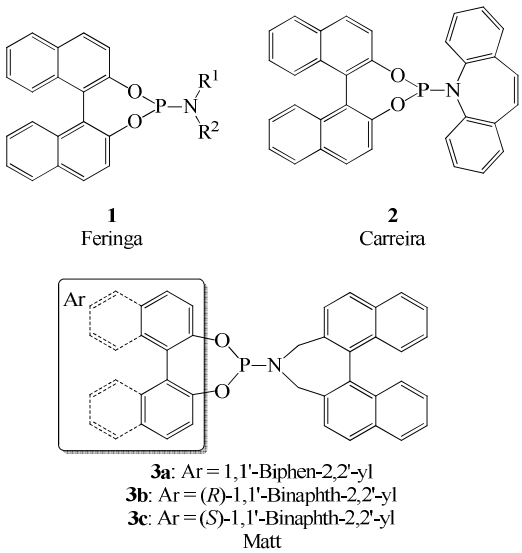
Abstract A small library of novel chiral monodentate phosphoramidite ligands, characterized by a dihydroazepine-biferrocene backbone was prepared. In order to obtain this biferrocene substructure, a mild and efficient homocoupling was developed. This allowed to synthesize the dihydroazepine ligand precursor and the phosphoramidite ligands with good overall yields and high enantiomeric excess. These ligands were successfully tested in a rhodium(I)-catalyzed hydrogenation of activated olefins.

1. Introduction

During last decades, there has been a tremendous interest in the production of optically active compounds for specialty materials, food and agrochemical industries, fragrancy industry and especially for the pharmaceutical industry.[1-3] Today, asymmetric transition metal catalysis has become one of the most efficient and interesting approaches for the synthesis of enantiopure compounds.[4-6] This growth of enantioselective catalysis calls for a permanent research for new and improved chiral ligands.[7] Given the complexity of most catalytic processes, the rigorous prediction of the required electronic and steric properties of a ligand in order to obtain high enantioselective inductions remains a difficult task.[8] The finetuning of reported ligands by modification of a ligand substructure, e.g. by introducing more bulky groups such as ferrocene, is one of the most straightforward promising strategies. A highly successful ligand family that allows for this type of modification is the family of phosphoramidites (represented as **1** in Figure 1). The first examples of these ligands were reported by Feringa in 1996 and since then, many phosphoramidites have been used in different types of transformations.[9-10] A general modification of these ligands involves the installation of different amines on the central phosphorus atom.[11] Phosphoramidite ligand **2** (Figure 1) is often used by the research group of Carreira in many enantioselective iridium-catalyzed reactions such as allylic substitutions[12] and vinylations[13] among others. In contrast to the monodentate phosphoramidites of Feringa, the olefin functional group coordinates to the iridium metal as well with the formation of a bidentate transition metal ligand complex. Other interesting monodentate phosphoramidite ligands have been reported by Matt *et. al.* (represented as **3** in Figure 1).[14] These ligands are characterized by the presence of an axially chiral binapthyl-based dihydroazepine substructure as the amine part of the phosphoramidite. This extra chiral moiety allows to replace the axially chiral binol ligand backbone, which is mostly used for the phosphoramidite ligand family, by an achiral biphenol. Consequently, the influence of the axial chirality of the dihydroazepine moiety as well as the 'matched' and 'mismatched' combinations of the axially chiral binol and axially chiral dihydroazepine ligand substructures were explored in the enantioselective rhodium(I)-catalyzed



1
Feringa

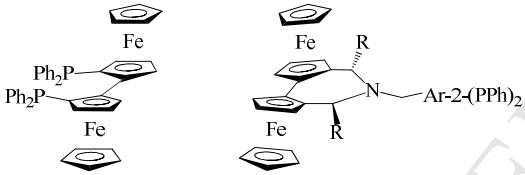
2
Carreira

3a: Ar = 1,1'-Biphen-2,2'-yl
3b: Ar = (*R*)-1,1'-Binaphth-2,2'-yl
3c: Ar = (*S*)-1,1'-Binaphth-2,2'-yl
Matt

Figure 1. Interesting examples of the phosphoramidite ligand family.

hydrogenation of activated olefins/esters of α-dehydroamino acids. Another interesting privileged ligand family is the well-known Josiphos family.[15] Among others, these are characterized by the presence of a planar chiral ferrocene

ligand scaffold.[16,17] The easy derivatization, the rigidity, the steric bulkiness and the possibility to introduce planar chirality are some interesting properties rendering the ferrocene backbone suitable as chiral scaffold for ligand design.[18] Consequently, it is often used for the development of novel chiral ligands.[15-18] In contrast, the biferrocene scaffold is significantly less explored as a ligand backbone in the field of asymmetric transition metal catalysis. Nevertheless, its extraordinary conformational behavior, due to the combination of planar as well as axial chirality elements, makes it an ideal structural ligand motive, very attractive for designing new chiral ligands.[17,19] Some interesting biferrocene-based ligands already known in literature are shown in Figure 2. The first one, **4**, is known as BIFEP (or 2,2''-bis(dipheny1phosphino)-1,1''-biferrocene) and represents the biferrocene analog of Noyori's highly successful BINAP ligand. Its enantioselective synthesis was described by the group of Weissensteiner in 2001.[20] This ligand has been tested in a range of transition metal catalyzed hydrogenation reactions of different substrates (olefins, ketones and imines).[20,21] Biferrocene-based bidentate *P*,*N*-type ligands **5**, characterized by the presence of a dihydroazepine heterocycle, were reported by Widhalm *et. al.*[22], discussing their multistep synthesis, their conformational behavior and their application in palladium-catalyzed asymmetric allylic substitution reactions. As shown in Figure 2, the aryl group is representing classical aromatic phenyl rings as well as both enantiomers of planar chiral diphenylphosphinoferrocene substructures.

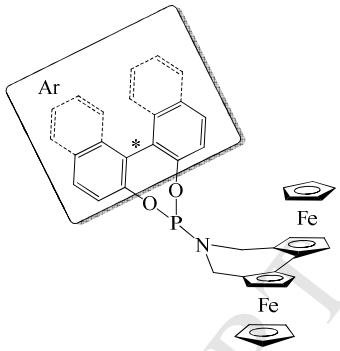


(R_p,R_p)-**4**

(R_p,R_p)-**5a**: R = H, Ar = Ph
(S,S,R_p,R_p)-**5b**: R = Me, Ar = Ph
(R_p,R_p)-**5c**: R = H, Ar = (S_p)-Fc
(R_p,R_p)-**5d**: R = H, Ar = (R_p)-Fc
(S,S,R_p,R_p)-**5e**: R = Me, Ar = (S_p)-Fc
(S,S,R_p,R_p)-**5f**: R = Me, Ar = (R_p)-Fc

Figure 2. Interesting biferrocene-based ligands.

In this paper we wish to report on the synthesis and screening of a small library of novel phosphoramidite ligands, characterized by the presence of a biferrocene-based dihydroazepine substructure (represented as **6** in Figure 3). The ligands we propose in this study are considered as the biferrocene analogs of the dihydroazepine phosphoramidite ligands published by Matt and co-workers.[14]



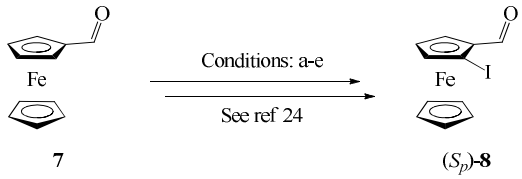
6a: Ar = 1,1'-Biphen-2,2'-yl
6b: Ar = (*R*)-1,1'-Binaphth-2,2'-yl
6c: Ar = (*S*)-1,1'-Binaphth-2,2'-yl

Figure 3. Novel biferrocene-based dihydroazepine phosphoramidite ligands **6a-6c**.

2. Results and Discussion

2.1. Ligand Synthesis

The synthesis of an optically pure biferrocene backbone theoretically requires the synthesis of an enantiomerically pure planar chiral ferrocene compound. A variety of methods to prepare this type of structures have already been reported by different research groups.[17,23] One of these is the Kagan's general approach, based on a chiral acetal, obtained from malic acid.[24] This approach allowed to prepare planar chiral α-iodoferrocenecarboxaldehyde (S_p)-**8** in high enantiomeric excess (Scheme 1).



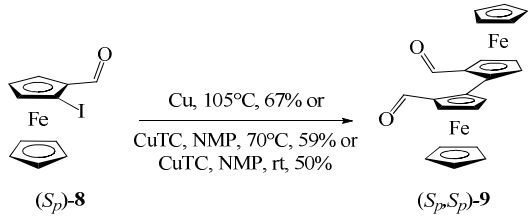
7 (S_p)-**8**

Conditions: (a) $H(COMe)_3$, $PTSA.H_2O$, MeOH, 80°C; (b) (*S*)-1,2,4-butanetriol, CSA, 4 Å Mol. Sieves, $CHCl_3$, rt; (c) 1. NaH, THF, 0°C; 2. MeI, 0°C to rt; (d) 1. *t*-BuLi, Et_2O, -78°C to rt; 2. $(CH_2I)_2$, THF, -78°C to rt; (e) $PTSA.H_2O$, CH_2Cl_2, H_2O, rt.

Scheme 1. Synthesis of (S_p)-**8** via Kagan's general approach.

For our study, planar chiral aldehyde (S_p)-**8** was chosen as an important intermediate for the synthesis of the biferrocene ligand backbone. Indeed, the Ullmann homocoupling reaction, with metallic copper at 105°C allowed to synthesize dialdehyde (S_p,S_p)-**9** (Scheme 2) in a yield of 67%. The latter turned out to be a very light sensitive compound requiring some practical precautions (see experimental part for more details). However, a novel method, based on a procedure reported by Liebeskind *et.al.* for the coupling of aryl halides at lower temperatures, using copper(I) thiophene-2-carboxylate (CuTC) in NMP, was developed during our study, as shown in Scheme 2.[25] Yields of 59% and 50% were obtained when the temperature was set at respectively 70°C and room

temperature. For both methods using metallic copper and CuTC, it was possible to prepare enantiopure dialdehyde (S_p,S_p)-**9**, starting from highly enantiopure α-iodoaldehyde (S_p)-**8** (96% ee). More interestingly, it was possible to obtain enantiopure (S_p,S_p)-**9** starting from a scalemic mixture of (S_p)- and (R_p)-α-iodoaldehyde of only 68% ee. When this scalemic mixture was homocoupled, *meso*-compound (R_p,S_p)-**9** was formed and could be observed on TLC as a separate spot. This *meso*-compound could be separated by flash chromatography from its diastereomer (S_p,S_p)-**9**.

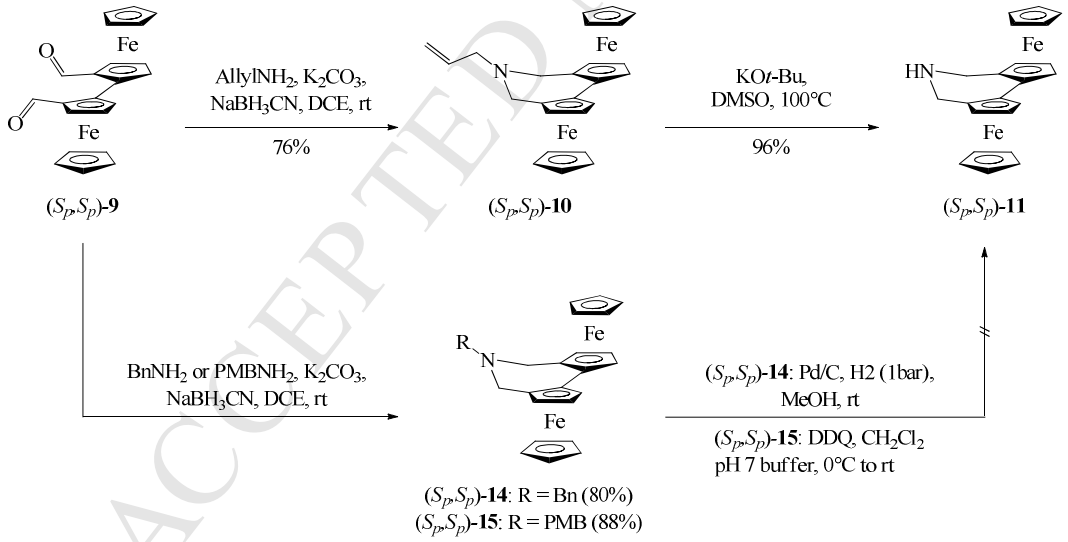


(S_p)-**8** (S_p,S_p)-**9**

Scheme 2. Ullmann homo coupling of planar-chiral ferrocenecarboxaldehyde (S_p,S_p)-**9**.

Dialdehyde (S_p,S_p)-**9** allowed to install the dihydroazepine very efficiently via reductive amination. Reactions with liquid ammonia and $NaBH_3CN$ or $NaBH(OAc)_3$ did not lead to any successful results. Therefore, three primary amines, benzylamine, *para*-methoxybenzylamine and allylamine, each containing a removable protecting alkyl group, were introduced using $NaBH_3CN$ as reducing agent. Good yields of 76-88% were obtained for these transformations (Scheme 3). Removal of the benzyl group ((S_p,S_p)-**14**) via a Pd/C reduction with hydrogen gas and removal of the *para*-methoxybenzyl group ((S_p,S_p)-**15**) using DDQ did not lead to the formation of the target ligand precursor (S_p,S_p)-**11**. However, as shown in Scheme 3, the allyl protected dihydroazepine biferrocene (S_p,S_p)-**10** allowed to efficiently synthesize (S_p,S_p)-**11**. The latter was prepared with a yield of 96% after removal of the allyl protecting group with KO-*t*Bu in DMSO at 100°C and subsequent mild acidic work-up with a saturated NH_4Cl solution.

Several protocols have been developed for the preparation of phosphoramidite ligands.[26] In initial experiments, the procedure applied by Matt *et. al* was tested.[14] This consists of a two-step reaction in which the diol is first reacted with phosphorus trichloride (PCl_3), followed by reaction with the secondary amine, both steps in the presence of a tertiary amine as a base. Unfortunately, this protocol gave no conversion. However, the most frequently used procedure for the synthesis of bulky phosphoramidite ligands consists of a two-step reaction in which the secondary amine is first reacted with PCl_3, followed by reaction with a diol, both steps in the presence of a base.[26c,27] Because the chiral biferrocene is generally considered to be (very) bulky, this protocol was subsequently applied for the preparation of the target biferrocene-based phosphoramidite ligands (Scheme 4). This procedure afforded the proposed ligands only in rather low yields varying between 29-44%.



Scheme 3. Preparation of biferrocene dihydroazepine ligand precursor **11**.

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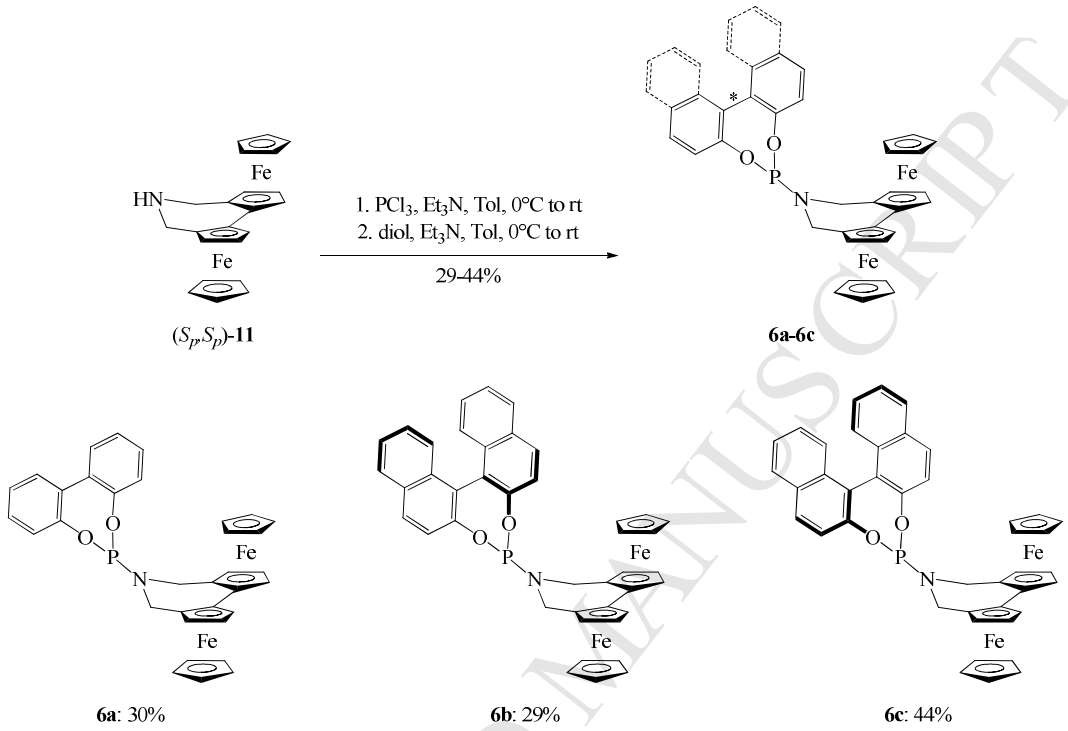
2.2. Catalytic Asymmetric Hydrogenation Reaction

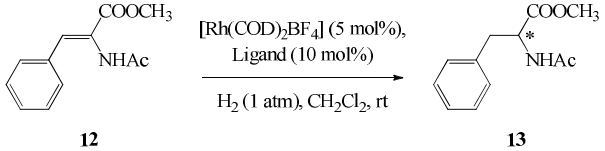
Catalytic asymmetric hydrogenation reactions of prochiral substrates such as olefins, ketones and imines are one of the most powerful and most studied transformations in the field of asymmetric catalysis.[28] A variety of transition metals such as rhodium, ruthenium, iridium and palladium are frequently used in combination with different types of chiral ligands. Moreover, for many years now, the rhodium(I)-catalyzed asymmetric hydrogenation of activated olefins, such as itaconic acids,



Scheme 4. Synthesis of a small library of biferrocene-based dihydroazepine phosphoramidite ligands **6a**-**6c**.

dehydroamino acids and derivatives of both, is a benchmark test reaction for novel monodentate ligands.[10,11,14,29] Therefore, substrate **12** was chosen for our preliminary experiments, in order to demonstrate the potential of the novel biferrocene-based monodentate phosphoramidite ligands. The results of these test reactions are shown in Table 1. Standard reaction conditions were chosen for the test reactions. These involve a hydrogen pressure of 1 atmosphere using a balloon, room temperature, dichloromethane as solvent, 24 h reaction time and a catalyst loading of 5 mol% rhodium as $[Rh(COD)_2BF_4]$ in combination with 10 mol% of the monodentate ligands. Full conversion in combination with a rather low ee-value of 26.2% in favor of the (*S*)-enantiomer was obtained for ligand **6a**, characterized by the presence of a chiral biferrocene backbone and an achiral biphenol ligand substructure. Therefore, this experiment indicates the potential of the chiral biferrocene ligand backbone as such for asymmetric induction in this hydrogenation reaction. Ligands **6b** and **6c**, characterized by a chiral biferrocene backbone in combination with axially chiral (*R*)-binol or (*S*)-binol respectively, were synthesized in order to explore the effect of a 'matched' and 'mismatched' combination. Indeed, an excellent conversion of 95% in combination with a significantly higher enantiomeric excess of 67.6% was obtained for ligand **6b**, which was therefore identified as the 'matched' combination. On the other hand, a lower conversion of 84% and a significantly lower enantiomeric excess of only 4.0% in favor of the (*R*)-enantiomer was observed for ligand **6c**. Therefore, the latter was assigned to have the mismatched combination. Based on these experiments it can be concluded that the asymmetric induction of the chiral biferrocene backbone is overruled by the axial chirality of the binapthyl group of the diol. However, the biferrocene ligand backbone definitely has a potential as a ligand scaffold.

Table 1. Results for the Rh(I)-catalyzed asymmetric hydrogenation of enamide **12** using novel biferrocene-based phosphoramidite ligands **6a**-**6c**.



12 **13**

Substrate	Ligand	Time (h)	Conv (%)	ee (%)
12	**6a**	24	100	26.2 (*S*)

12	**6b**	24	95	67.6 (*S*)
12	**6c**	24	84	4.0 (*R*)

3. Conclusion

In conclusion, we have disclosed the synthesis of three novel chiral monodentate biferrocene-based phosphoramidite ligands. Therefore we started from enantioenriched planar chiral α-iodoferrocenecarboxaldhyde (S_p)-**8**, obtained via the Kagan approach.[24] Afterwards, we developed a novel very mild Ullmann homocoupling reaction with CuTC at room temperature. This allowed to efficiently synthesize the biferrocene dihydroazepine ligand precursor in a few steps and a high yield. The final step towards the desired ligands, however was rather cumbersome and yields between 29-44% were obtained. Nevertheless, this allowed to test these ligands in a benchmark testreaction, the rhodium(I)-catalyzed hydrogenation of enamide **12**. To explore the influence of the biferrocene backone as well as 'matched' and 'mismatched' effects, biphenol as wel as both enantiomers of axial chiral binol were applied as the diol substructure of the phosphoramidite ligands. Very good conversions and an ee-value up to 67.6% were observed, indicating the potential of the novel chiral phosphoramidite ligands and the corresponding biferrocene ligand backbone.
Despite different attempts, we were unfortunately not able to grow crystals from the ligands nor from a rhodium complex, suitable for X-ray analysis. These attempts involve dissolving minimal amounts of the ligands in CH_2Cl_2 or toluene and slow evaporation of the solvents. For the attempts towards the rhodium complexes, $[Rh(COD)_2BF_4]$ was added to the mixture which was stirred properly before slow evaporation of the solvents.

4. Experimental

4.1. General Experimental Methods

Unless otherwise stated, all reagents were obtained commercially and used without further purification. All reactions were carried out under an argon atmosphere in dry solvents under anhydrous conditions, unless otherwise noted. Dichloroethane, Et_3N and DIPEA were dried via distillation over CaH_2. Toluene was dried via distillation over sodium with benzophenone as indicator. Other anhydrous solvents were purchased as such. Analytical TLC was performed by using Machery-Nagel SIL G-25 UV_{254} plates. Flash chromatography was carried out with Rocc silica gel (0.040-0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker avance 300 or a Bruker Avance 400 or a Bruker AM 500 spectrometer as indicated, with chemical shifts reported in ppm relative to TMS, by using the residual solvent signal as a standard, and relative to 85% aqueous phosphoric acid for ^{31}P NMR spectra. IR spectra were recorded with a Perkin-Elmer SPECTRUM-1000 FTIR spectrometer with a Pike Miracle Horizontal Attenuated Total Reflectance (HATR) module. ESI-MS was performed on an Agilent 1100 series with a single quadrupole MS detector G1946C (type VL) equipped with an API-ESI source. High Resolution Mass Spectrometry (HRMS) was performed on an Agilent 1100 series connected to a 6220A TOF-MS detector equipped with an APCI-ESI multimode source or a Kratos MS50TC mass spectrometer (EI). For all MS-analysis the standard solvent was a 50:50 mixture of MeOH:5mM aqueous NH_4OAc and a sample volume of 5µL was injected. LC-MS analyses were performed on an Agilent 1100 series HPLC connected to a UV-DAD detector and a single quadrupole MS detector G1946C (type VL) equipped with an API-ESI source by using a Phenomenex Kinetex C18 column (150 x 4.6 mm, 5 µm particle size). All measurements were performed at 35°C, a flow rate of 1 mL/min and sample volume of 15 µL was injected. Mili-Q water and HPLC quality grade CH_3CN were used. Analytical chiral separations were performed on an Agilent 1100 series HPLC system using a Chiralcel OD-H column (250 x 4.6 mm, 5 µm particle size) or a Chiralpak AS-H column (250 x 4.6 mm, 5 µm particle size), connected to a UV-DAD detector. All measurements were performed at 35°C, a flow rate of 1 mL/min and a sample volume of 20 µL. HPLC quality grade solvents were used for all measurements. Optical rotations were measured using a Perkin-Elmer 214 polarimeter at 589 nm.

*4.2. Metallic copper based synthesis of (S_p,S_p)-[1,1'-biferrocenyl]-2,2'-dicarboxaldehyde (S_p,S_p-**9**):* An oven-dried, 50 mL round-bottom flask was charged with (S_p)-**8** (2.610 g, 7.68 mmol). Metallic copper (1.950 g, 30.71 mmol, 4 eq) was carefully added in such way that all of the starting material was covered with copper. A heavy, egg-shaped stirring bar was carefully added and the reaction flask was wrapped in aluminum foil. The reaction was stirred overnight at 105°C. The crude reaction mixture was taken up in CH_2Cl_2 and filtered over Celite, while the filtrate was collected in a round-bottom flask which was wrapped in aluminum foil. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography [1] (gradient *n*-hexane/EtOAC: 8/2 to 6/4) affording (S_p,S_p)-**9**, with a yield of 66.8%, as a red solid. R_f (*n*-hexane/EtOAc: 7/3): 0.25. ^{1}H-NMR: (500 MHz, $CDCl_3$): δ = 4.31 (s, 10H), 4.74 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 2H), 4.94 (dd, *J* = 2.4 Hz, *J* = 1.6, 2H), 4.95 (dd, *J* = 2.8 Hz, *J* = 1.6, 2H), 9.94 (s, 2H) ppm. ^{13}C-NMR: (125 MHz, $CDCl_3$): δ = 68.8 (CH x2), 71.0 (CH x10), 71.9 (CH x2), 76.6 (CH x2), 78.6 (C x2), 85.3 (C x2), 192.2 (CH x2) ppm. IR (HATR): υ_{max} = 3921, 3561, 3315, 3101, 3009, 2941, 2840, 2778, 2764, 1661, 1652, 1426, 1409, 1395, 1289, 1208, 1106, 998, 990, 825, 774, 733, 679 cm^{-1}. HRMS (ESI): calculated for $C_{22}H_{19}Fe_2O_2$ $[M+H]^+$: 427.0078; found: 427.0079. Optical rotation: $[\alpha]_D^{20} = -257$ (c 0.1, CH_2Cl_2).

*4.3. CuTC based synthesis of (S_p,S_p)-[1,1'-biferrocenyl]-2,2'-dicarboxaldehyde (S_p,S_p-**9**):* An oven-dried 5 mL round-bottom flask was charged with a magnetic stirring bar, (S_p)-**8** (68 mg, 0.20 mmol) and CuTC (114 mg, 0.60 mmol,

[1]Because **9** is light sensitive, the column was wrapped in aluminum foil as well. First a mixed fraction of ferrocenecarboxaldehyde **7** and α-iodoferrocenecarboxaldehyde (S_p)-**8** was collected. The polarity of the eluent system was raised to *n*-hexane/EtOAC: 7/3 and the *meso* form (R_p,S_p)-**9** was collected. The polarity of the eluent system was raised to *n*-hexane/EtOAC: 6/4 and (S_p,S_p)-[1,1'-bifferrocenyl]-2,2'-dicarboxaldehyde (S_p,S_p)-**9** was collected in a round bottom flask which was wrapped in aluminum foil.

3 eq). Anhydrous NMP (1.0 mL) was added and the reaction flask was wrapped in aluminum foil. The reaction mixture was heated to 70°C and stirred overnight. Then, the reaction mixture was allowed to cool to room temperature, diluted with Et_2O and filtered over Celite. Et_2O was removed under reduced pressure. The residu was taken up in Et_2O (10 mL) and washed 3 times with water (10 mL). The organic phase was dried over anhydrous $MgSO_4$ and filtered. Et_2O was removed under reduced pressure and the resulting residue was purified by flash chromatography [1] (gradient: *n*-hexane/EtOAC: 8/2 to 6/4) affording (S_p,S_p)-**9**, with a yield of 59.0%, as a red solid.

*4.4. Synthesis of (S_p,S_p)-N-benzyl-3,5-dihydro-4H-diferrocenyl-[c,e]-azepine (S_p,S_p-**14**):* An oven-dried, 25 mL two-neck round-bottom flask was charged with a magnetic stirring bar, (S_p,S_p)-**9** (118 mg, 0.28 mmol). Freshly distilled dichloroethane (8.0 mL) was added followed by a solution of benzylamine in dichloroethane (1.3 M, 850 µL, 1.1 mmol, 4 eq). The reaction mixture was stirred for 5 min at room temperature and $NaBH_3CN$ (609 mg, 9.69 mmol, 35 eq) and anhydrous K_2CO_3 (153 mg, 1.11 mmol, 4 eq) were added. The reaction was stirred overnight at room temperature and quenched with a saturated solution of $NaHCO_3$ (30 mL). The aqueous phase was extracted 3 times with CH_2Cl_2 (30 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered. The solvents were removed under reduced pressure and the resulting residue was purified by flash chromatography (*n*-hexane/EtOAc/Et_3N: 8/2/0.2) affording (S_p,S_p)-**14**, with a yield of 79.9%. R_f (*n*-hexane/EtOAc 7/3): 0.14. ^{1}H-NMR: (500 MHz, $CDCl_3$): δ = 3.72 (d, *J* = 15.0 Hz, 2H), 3.88-3.89 (m, 2H), 3.89 (d, *J* = 15.0 Hz, 2H), 3.95 (s, 10H), 3.99-4.00 (m, 2H), 4.11 (dd, *J* = 2.4 Hz, *J* = 2.2 Hz, 2H), 4.39 (dd, *J* = 2.4 Hz, *J* = 1.4 Hz, 2H), 7.36 (m, 5H) ppm. ^{13}C-NMR: (125 MHz, $CDCl_3$): δ = 56.4 (CH_2 x2), 60.4 (CH_2), 65.8 (CH x2), 66.3 (CH x2), 67.7 (CH x2), 69.9 (CH x10), 82.6 (C x2), 84.5 (C x2), 127.0 (CH), 128.3 (CH), 128.9 (CH), 139.3 (C) ppm. IR (HATR): υ_{max} = 3920, 3087, 2923, 2852, 1731, 1493, 1453, 1357, 1265, 1130, 1104, 1028, 999, 815, 804, 734, 698 cm^{-1}. HRMS (ESI): calculated for $C_{29}H_{28}Fe_2N$ $[M+H]^+$: 502.0915; found: 502.0917. Optical rotation: $[\alpha]_D^{20}$ = -508 (c 1.2, $CHCl_3$).

*4.5. Synthesis of (S_p,S_p)-N-4-methoxybenzyl-3,5-dihydro-4H-diferrocenyl-[c,e]-azepine (S_p,S_p-**15**):* An oven-dried, 25 mL two-neck round-bottom flask was charged with a magnetic stirring bar, (S_p,S_p)-**9** (118 mg, 0.28 mmol). Freshly distilled dichloroethane (8.0 mL) was added followed by a solution of *para*-methoxybenzylamine in dichloroethane (1.3 M, 850 µL, 1.1 mmol, 4 eq). The reaction mixture was stirred for 5 min at room temperature and $NaBH_3CN$ (609 mg, 9.69 mmol, 35 eq) and anhydrous K_2CO_3 (153 mg, 1.11 mmol, 4 eq) were added. The reaction was stirred overnight at room temperature and quenched with a saturated solution of $NaHCO_3$ (30 mL). The aqueous phase was extracted 3 times with CH_2Cl_2 (30 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered. The solvents were removed under reduced pressure and the resulting residue was purified by flash chromatography (*n*-hexane/EtOAc/Et_3N: 8/2/0.2) affording (S_p,S_p)-**15**, with a yield of 88.2%. R_f (*n*-hexane/EtOAc: 7/3): 0.14. ^{1}H-NMR: (500 MHz, $CDCl_3$): δ = 3.70 (d, *J* = 14.9 Hz, 2H), 3.80-3.82 (m, 2H), 3.83 (s, 3H), 3.86 (d, *J* = 14.9 Hz, 2H), 3.95 (s, 10H), 3.98-4.01 (m, 2H), 4.10 (dd, *J* = 2.4 Hz, *J* = 2.2 Hz, 2H), 4.38 (dd, *J* = 2.2 Hz, *J* = 1.4 Hz, 2H), 6.89 (br d, *J* = 8.5 Hz, 2H), 7.3 (br d, *J* = 8.5 Hz, 2H) ppm. ^{13}C-NMR: (125 MHz, $CDCl_3$): δ = 55.3 (CH_3), 56.2 (CH_2 x2), 59.8 (CH_2), 65.8 (CH x2), 66.2 (CH x2), 67.7 (CH x2), 70.0 (CH x10), 82.6 (C x2), 84.5 (C x2), 113.7 (CH), 130.1 (CH), 158.7 (C) ppm. *1 C not observed.* IR (HATR): υ_{max} = 3916, 3090, 2925, 2833, 1610, 1584, 1455, 1440, 1357, 1300, 1170, 1130, 1104, 1031, 999, 814, 733, 703 cm^{-1}. HRMS (ESI): calculated for $C_{30}H_{30}Fe_2NO$ $[M+H]^+$: 532.1021; found: 532.1032. Optical rotation: $[\alpha]_D^{20}$ = -454 (c 1.0, $CHCl_3$)

*4.6. Synthesis of (S_p,S_p)-N-allyl-3,5-dihydro-4H-diferrocenyl-[c,e]-azepine (S_p,S_p-**10**):* An oven-dried, 25 mL two-neck round-bottom flask was charged with a magnetic stirring bar, (S_p,S_p)-**9** (118 mg, 0.28 mmol). Freshly distilled dichloroethane (8.0 mL) was added followed by a solution of allylamine in dichloroethane (1.3 M, 850 µL, 1.1 mmol, 4 eq). The reaction mixture was stirred for 5 min at room temperature and $NaBH_3CN$ (609 mg, 9.69 mmol, 35 eq) and anhydrous K_2CO_3 (153 mg, 1.11 mmol, 4 eq) were added. The reaction was stirred overnight at room temperature and quenched with a saturated solution of $NaHCO_3$ (30 mL). The aqueous phase was extracted 3 times with CH_2Cl_2 (30 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered. The solvents were removed under reduced pressure and the resulting residue was purified by flash chromatography (*n*-hexane/EtOAc/Et_3N: 8.5/1.5/0.2) affording (S_p,S_p)-**10**, with a yield of 75.6%. R_f (*n*-hexane/EtOAc: 7/3): 0.19. ^{1}H-NMR: (400 MHz, $CDCl_3$): δ = 3.31 (dd, *J* = 13.7 Hz, *J* = 6.8 Hz, 1H), 3.37 (dd, *J* = 13.7 Hz, *J* = 5.8 Hz, 1H), 3.72 (d, *J* = 14.9 Hz, 2H), 3.96 (d, *J* = 14.9 Hz, 2H), 4.06 (br dd, *J* = 2.3 Hz, *J* = 1.3 Hz, 2H), 4.1 (br dd, *J* = 2.3 Hz, *J* = 2.1 Hz, 2H), 4.36 (br dd, *J* = 2.1 Hz, *J* = 1.3 Hz, 2H), 5.20 (dd, *J* = 10.3 Hz, *J* = 1.4 Hz, 1H), 5.21 (dd, *J* = 17.1 Hz, 1.4 Hz, 1H), 5.96 (dddd, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 6.8 Hz, *J* = 5.8 Hz, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$): δ = 56.3 (CH_2 x2), 59.4 (CH_2), 65.7 (CH x2), 66.2 (CH x2), 67.6 (CH x2), 69.9 (CH x10), 82.2 (C x2), 84.6 (C x2), 117.5 (CH_2), 136.3 (CH) ppm. IR (HATR): υ_{max} = 3081, 2928, 2797, 2362, 2336, 1636, 1452, 1432, 1406, 1316, 1219, 1130, 1102, 1076, 1026, 997, 975, 922, 846, 810, 804, 757 cm^{-1}. HRMS (ESI): calculated for $C_{25}H_{26}Fe_2N$ $[M+H]^+$: 452.0759; found: 452.0751. Optical rotation: $[\alpha]_D^{20}$ = -659 (c 1.7, $CHCl_3$).

*4.7. Synthesis of (S_p,S_p)-N-H-3,5-dihydro-4H-diferrocenyl-[c,e]-azepine (S_p,S_p-**11**):* An oven-dried pressure tube was charged with a magnetic stirring bar, (S_p,S_p)-**10** (90 mg, 0.20 mmol) and KO*t*-Bu (112 mg, 1.00 mmol, 5 eq). Anhydrous DMSO (7.0 mL) was added and the pressure tube was closed with a stopper. The reaction mixture was heated up to 100°C for 2 h. The reaction was allowed to cool to room temperature. The dark suspension was diluted with Et_2O (30 mL) and carefully quenched with a saturated solution of NH_4Cl (30 mL). The organic phase was separated and washed 3 times with water (30 mL) and once with brine (30

mL). The organic phase was dried over anhydrous $MgSO_4$ and filtered. Et_2O was removed under reduced pressure and pure (S_p,S_p)-**11** was obtained as a yellow solid with a yield of 96.2%. R_f (*n*-hexane/EtOAc/Et_3N: 2/7/1): 0.33. ^{1}H-NMR: (500 MHz, $CDCl_3$): δ = 3.92 (d, *J* = 16.0 Hz, 2H), 3.96 (s, 10H), 4.05 (d, *J* = 16.0 Hz, 2H), 4.11-4.13 (m, 4H), 4.30 (app t, *J* = 1.9 Hz, 2H) ppm. ^{13}C-NMR: (125 MHz, $CDCl_3$): δ = 51.6 (CH_2 x2), 65.4 (CH x2), 66.4 (CH x2), 67.6 (CH x2), 69.6 (CH x10), 82.0 (C x2), 88.0 (C x2) ppm. IR (HATR): υ_{max} = 3075, 2909, 2851, 2359, 2331, 1616, 1442, 1406, 1354, 1307, 1212, 1115, 1102, 1030, 998, 809, 780, 737, 674 cm^{-1}. HRMS (ESI): calculated for $C_{22}H_{22}Fe_2N$ $[M+H]^+$: 412.0446; found: 412.0448. Optical rotation: $[\alpha]_D^{20}$ = -399 (c 0.09, $CHCl_3$).

*4.8. Synthesis of biphenol-based phosphoramidite ligand (**6a**):* An oven-dried Schlenk tube charged with a magnetic stirring bar and (S_p,S_p)-**11** (73 mg, 0.18 mmol) was cooled to 0°C using an ice-water bath. A solution of Et_3N in toluene (0.36 M, 5.0 mL, 1.80 mmol, 10 eq) was added, followed by dropwise addition of a solution of freshly distilled PCl_3 in toluene (0.57 M, 316 µL, 0.18 mmol, 1 eq). The reaction mixture was stirred for 10 min at 0°C, allowed to warm up to room temperature and stirred for an additional 2 h. The reaction was cooled again to 0°C and a suspension of 2,2'-biphenol (33 mg, 0.18 mmol, 1.0 eq) in toluene (3.0 mL) was added, followed by addition of a solution of Et_3N in toluene (0.36 M, 1.2 mL, 0.44 mmol, 2.5 eq). The reaction mixture was stirred for 10 min at 0°C, allowed to warm up to room temperature and stirred overnight. The reaction was quenched with water (70 mL) and extracted 3 times with CH_2Cl_2 (70 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous $MgSO_4$ and filtered. The organic solvents were removed under reduced pressure and the resulting residue was purified by flash chromatography (*n*-hexane/EtOAc: 98/2) affording **6a**, with a yield of 30.2%, as a yellow solid. R_f (*n*-hexane/EtOAc: 7/3): 0.78. ^{1}H-NMR: (400 MHz, $CDCl_3$): δ = 3.90 (dd, *J* = 2.3 Hz, *J* = 1.5 Hz, 2H), 4.01 (s, 10H), 4.09 (app t, *J* = 2.3 Hz, 2H), 4.22 (dd, $^2J_{HH}$ = 15.8 Hz, $^3J_{PH}$ = 7.4 Hz, 2H), 4.36 (dd, *J* = 2.3 Hz, *J* = 1.5 Hz, 2H), 4.37 (dd, $^2J_{HH}$ = 15.8 Hz, $^3J_{PH}$ = 8.4 Hz, 2H), 6.87-6.92 (m, 1H), 7.24-7.33 (m, 4H), 7.41 (td, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 7.48-7.53 (m, 2H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$): δ = 49.6 (CH_2 x2, d, J_{CP} = 22.7 Hz), 65.6 (CH x2), 66.2 (CH x2), 67.8 (CH x2), 69.8 (CH x10), 81.9 (C x2), 86.3 (C x2, d, J_{CP} = 4.4 Hz), 122.0 (CH), 122.6 (CH), 124.3 (CH), 124.7 (CH), 129.2 (CH), 129.3 (CH), 129.5 (CH), 129.7 (CH), 130.5 (C, d, J_{CP} = 2.9 Hz), 131.2 (C, d, J_{CP} = 3.7 Hz), 151.0 (C, d, J_{CP} = 6.6 Hz), 151.2 (C, d, J_{CP} = 3.7 Hz) ppm. ^{31}P-NMR: (162 MHz, $CDCl_3$): 144.57 ppm. IR (HATR): υ_{max} = 3083, 2953, 2922, 2854, 1474, 1433, 1365, 1245, 1225, 1189, 1123, 1097, 1042, 1031, 1005, 882, 846, 818, 793, 762, 732, 702, 676 cm^{-1}. HRMS (ESI): calculated for $C_{34}H_{29}Fe_2NO_2P$ $[M+H]^+$: 626.0629, found: 626.0617; calculated for $C_{34}H_{28}Fe_2NO_2P$ $[M]^{\cdot+}$: 625.0551, found: 625.0527. Optical rotation: $[\alpha]_D^{20}$ = -396 (c 0.10, $CHCl_3$).

*4.9. Synthesis of (R)-binol-based phosphoramidite ligand (**6b**):* An oven-dried Schlenk tube charged with a magnetic stirring bar and (S_p,S_p)-**11** (30 mg, 0.073 mmol) was cooled to 0°C using an ice-water bath. A solution of Et_3N in toluene (0.36 M, 2.0 mL, 0.73 mmol, 10 eq) was added, followed by dropwise addition of a solution of freshly distilled PCl_3 in toluene (0.57 M, 128 µL, 0.073 mmol, 1 eq). The reaction mixture was stirred for 10 min at 0°C, allowed to warm up to room temperature and stirred for an additional 2 h. The reaction was cooled again to 0°C and a suspension of (*R*)-binol (21 mg, 0.073 mmol, 1.0 eq) in toluene (1.0 mL) was added, followed by addition of a solution of Et_3N in toluene (0.36 M, 0.5 mL, 0.18 mmol, 2.5 eq). The reaction mixture was stirred for 10 min at 0°C, allowed to warm up to room temperature and stirred overnight. The reaction was quenched with water (25 mL) and extracted 3 times with CH_2Cl_2 (25 mL). The combined organic phases were washed with brine (40 mL), dried over anhydrous $MgSO_4$ and filtered. The organic solvents were removed under reduced pressure and the resulting residue was purified by flash chromatography (*n*-hexane/EtOAc: 98/2) affording **6b**, with a yield of 28.7%, as a yellow solid. R_f (*n*-hexane/EtOAc: 7/3): 0.75. ^{1}H-NMR: (500 MHz, $CDCl_3$): δ = 3.79 (dd, *J* = 2.3 Hz, *J* = 1.5 Hz, 2H), 3.97-4.01 (m, 2H), 3.98 (s, 10H), 4.00-4.02 (m, 2H), 4.26 (dd, $^2J_{HH}$ = 15.7 Hz, $^3J_{PH}$ = 8.7 Hz, 2H), 4.29 (dd, *J* = 2.4 Hz, *J* = 1.5 Hz, 2H), 7.24-7.28 (m, 1H), 7.32-7.37 (m, 2H), 7.39-7.52 (m, 5H), 7.89-7.91 (m, 2H), 7.99-8.03 (m, 2H) ppm. ^{13}C-NMR: (125 MHz, $CDCl_3$): δ = 49.6 (CH_2 x2, d, J_{CP} = 21.8 Hz), 65.5 (CH x2), 66.3 (CH x2), 67.4 (CH x2), 69.8 (CH x10), 81.9 (C x2), 86.4 (C x2, d, J_{CP} = 3.6Hz), 121.9 (CH), 122.1 (CH), 123.9 (C, d, J_{CP} = 5.5 Hz), 124.6 (CH), 124.8 (CH), 126.1 (CH), 126.1 (CH), 127.0 (CH x2), 128.3 (CH), 128.3 (CH), 130.1 (CH), 130.2 (CH), 130.7 (C), 131.4 (C), 132.7 (C), 132.8 (C), 132.8 (C), 149.6 (C), 150.1 (C, d, J_{CP} = 4.5 Hz) ppm. ^{31}P-NMR: (162 MHz, $CDCl_3$): 145.23 ppm. IR (HATR): υ_{max} = 3088, 2954, 2921, 2852, 1589, 1506, 1463, 1431, 1326, 1227, 1202, 1124, 1103, 1061, 1039, 1004, 951, 932, 913, 820, 799, 747, 697, 683, 626 cm^{-1}. HRMS (ESI): calculated for $C_{42}H_{33}Fe_2NO_2P$ $[M+H]^+$: 726.0942, found: 726.0922; calculated for $C_{42}H_{32}Fe_2NO_2P$ $[M]^{\cdot+}$: 725.0864, found: 725.0862. Optical rotation: $[\alpha]_D^{20}$ = -549 (c 0.10, $CHCl_3$).

*4.10.Synthesis of (S)-binol-based phosphoramidite ligand (**6c**):* An oven-dried Schlenk tube charged with a magnetic stirring bar and (S_p,S_p)-**11** (60 mg, 0.15 mmol) was cooled to 0°C using an ice-water bath. A solution of Et_3N in toluene (0.36 M, 4.1 mL, 1.46 mmol, 10 eq) was added, followed by dropwise addition of a solution of freshly distilled PCl_3 in toluene (0.57 M, 256 µL, 0.15 mmol, 1 eq). The reaction mixture was stirred for 10 min at 0°C, allowed to warm up to room temperature and stirred for an additional 2 h. The reaction was cooled again to 0°C and a suspension of (*S*)-binol (42 mg, 0.15 mmol, 1.0 eq) in toluene (2.0 mL) was added, followed by addition of a solution of Et_3N in toluene (0.36 M, 1.0 mL, 0.36 mmol, 2.5 eq). The reaction mixture was stirred for 10 min at 0°C, allowed to warm up to room temperature and stirred overnight. The reaction was quenched with water (50 mL) and extracted 3 times with CH_2Cl_2 (50 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous $MgSO_4$ and filtered. The organic solvents were removed under reduced pressure and the resulting residue was purified by flash chromatography (*n*-hexane/EtOAc: 98/2) affording **6c**, with

a yield of 43.6%, as a yellow solid. R_f (*n*-hexane/EtOAc: 7/3): 0.71. ^{1}H-NMR: (400 MHz, $CDCl_3$): δ = 3.83 (m, 2H), 4.00 (s, 10H), 4.12 (app t, *J* = 2.4 Hz, 2H), 4.14 (dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{PH}$ = 7.5 Hz, 2H), 4.35 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{PH}$ = 8.3 Hz, 2H), 4.39 (dd, *J* = 2.4 Hz, *J* = 1.5 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 1H), 7.22-7.26 (m, 1H), 7.28-7.36 (m, 2H), 7.40-7.50 (m, 3H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.90-7.97 (m, 2H), 7.99 (d, *J* = 8.8 Hz, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$): δ = 49.7 (CH_2 x2, d, J_{CP} = 23.5 Hz), 65.5 (CH x2), 66.1 (CH x2), 68.2 (CH x2), 69.9 (CH x10), 82.0 (C x2), 85.9 (C x2, J_{CP} = 4.4 Hz), 121.9 (CH), 122.9 (CH), 124.0 (C, J_{CP} = 5.1 Hz), 124.5 (CH), 124.9 (CH), 125.9 (CH), 126.1 (CH), 127.1 (CH x2), 128.3 (CH), 128.3 (CH), 130.2 (CH), 130.4 (CH), 130.6 (C), 131.4 (C), 132.5 (C), 132.8 (C), 132.8 (C), 149.1 (C), 149.3 (C), 149.3 (C) ppm. ^{31}P-NMR: (162 MHz, $CDCl_3$): 143.47 ppm. IR (HATR): υ_{max} = 3089, 3054, 2958, 2923, 2853, 2359, 2341, 1619, 1590, 1506, 1462, 1431, 1366, 1328, 1261, 1229, 1204, 1124, 1104, 1043, 1066, 1031, 1007, 982, 951, 927, 820, 800, 750, 737, 696 cm^{-1}. HRMS (ESI): calculated for $C_{42}H_{33}Fe_2NO_2P$ $[M+H]^+$: 726.0942, found: 726.0899; calculated for $C_{42}H_{32}Fe_2NO_2P$ $[M]^{\cdot+}$: 725.0864, found: 725.0867. Optical rotation: $[\alpha]_D^{20} = -60.7$ (c 0.14, $CHCl_3$).

*4.11. Synthesis of methyl Z-2-acetamido-3-phenylacrylate (**12**):* An oven-dried 50 mL round-bottom flask was charged with a magnetic stirring bar and α-acetamidocinnamic acid (2.21 g, 10.7 mmol). Anhydrous DMF (20 mL), anhydrous DIPEA (3.7 mL, 21.5 mol, 2 eq) and iodomethane (2.7 mL, 43.1 mmol, 4 eq) were added. The reaction mixture was stirred overnight at room temperature, quenched with a saturated solution of NH_4Cl (100 mL) and extracted three times with EtOAc (100 mL). The combined organic phases were washed with a 10 mol% solution of $KHCO_3$ (100 mL) and a 10 mol% solution of citric acid (100 mL) and dried over Na_2SO_4. After filtration and removal of the organic solvents under reduced pressure, the obtained solid was washed with Et_2O and *n*-hexane. Methyl *Z*-2-acetamido-3-phenylacrylate **12** was obtained as a white solid with a yield of 82.3%. R_f (CH_2Cl_2/EtOAc: 85/15): 0.19. ^{1}H-NMR: (400 MHz, $CDCl_3$): δ = 2.15 (s, 3H), 3.86 (s, 3H), 6.98 (br s, 1H), 7.10-7.85 (m, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$): δ = 23.5 (CH_3), 52.7 (CH_3), 124.2 (C), 128.6 (CH x2), 129.5 (CH), 129.6 (CH x2), 132.2 (CH), 133.7 (C), 165.7 (C), 168.7 (C) ppm. ESI-MS *m/z* (rel. intensity %): 242.1 (100) $[M+Na]^+$, 220.1 (25) $[M+H]^+$.

*4.12. General procedure for the Rhodium(I)-catalyzed asymmetric hydrogenation of **12**:* An oven-dried Schlenk tube was connected to an argon Schlenk line, charged with a magnetic stirring bar, $Rh(COD)_2BF_4$ (2.8 mg, 6.89 µmol, 1 mol%) and a ligand (**6a**, **6b** or **6c**) (13.8 µmol, 2 mol%). Degassed[2] CH_2Cl_2 (3 mL) was added to the catalyst mixture, which was stirred for 30 min at room temperature. Methyl *Z*-2-acetamido-3-phenylacrylate **12** (151 mg, 689 µmol) was added, and hydrogen gas was bubbled through the reaction mixture for 10 min. The reaction was stirred overnight at room temperature under a hydrogen atmosphere using a balloon. The reaction mixture was filtered over a short plug of silica gel and eluted with EtOAc. The solvents were removed under reduced pressure and **13** was obtained as a white solid. Conversion and enantiomeric excess were determined by chiral LC analysis on a Chiralcel OD-H column (250 x 4.6 mm, particle size 5 µm), solvent: *n*-hexane/EtOH (95:5), flow rate = 1 mL/min, t = 30 min, T = 35°C, retention times: 11.20 min for (*R*)-**13**, 12.80 min for (*S*)-**13** and 20.81 min for starting material **12**. The absolute configuration of **13** was assigned via correlation of its specific rotation with literature values.[30] R_f (CH_2Cl_2/EtOAc: 90/10): 0.18. ^{1}H-NMR: (500 MHz, $CDCl_3$): δ = 1.98 (s, 3H), 3.09 (dd, *J* = 13.9 Hz, *J* = 5.8 Hz, 1H), 3.14 (dd, *J* = 13.9 Hz, *J* = 5.8 Hz, 1H), 3.73 (s, 3H), 4.83 (app dt, *J* = 7.8 Hz, *J* = 5.8 Hz, 1H), 5.95 (br s, 1H), 7.07-7.11 (m, 2H), 7.22-7.32 (m, 3H) ppm. ^{13}C-NMR: (125 MHz, $CDCl_3$): δ = 23.3 (CH_3), 38.0 (CH_2), 52.5 (CH), 53.2 (CH_3), 127.3 (CH), 128.4 (CH), 128.8 (CH), 135.9 (C), 169.8 (C), 172.2 (C) ppm. ESI-MS *m/z* (rel. intensity %): 222.1 (74) $[M+H]^+$, 180.1 (92), 162.1 (100), 120.1 (50).

[2] Degassing was accomplished by bubbling of H_2-gas through the solvent for 10 min. using a balloon.

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References and notes

[1] Lorenz, H.; Seidel-Morgenstern, A., *Angew. Chem. Int. Ed.*, **2014**, *53*, 1218-1251.

[2] (a) Rouhi, A. M., *Chem. Eng. News*, **2003**, *81*, 56-61. (b) Jeschke, P., *Pest. Manag. Sci.*, **2018**, *74*, 2389-2404. (c) Blaser, H.-U., Hoge, G., Lotz, M., Nettekoven U., Schnyder, A. Spindler, F., *Chimia*, **2008**, *62*, 476-481.

[3] (a) Sheldon, R. A., *Chirotechnology: Industrial Synthesis of Optically Active Compounds*, Marcel Dekker, New York, **1993**. (b) *Chiral Drugs: Chemistry and Biological Action*, Eds: G.-Q. Lin, Q.-D. You, J.-F. Cheng, Wiley, Hoboken, **2011.**

[4] Vervecken, E.; Van Overschelde, M.; Noël, T.; Gök, T.; Rodríguez, S. A.; Cogen, S.; Van der Eycken, J.; *Tetrahedron: Asymmetry*, **2010**, *21*, 2321-2328.

[5] (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**; (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley-VCH: New York, **2000**; (c) *New Frontiers in Asymmetric Catalysis*; Mikami, K.; Lautens, M., Eds.; Wiley-Interscience, **2007**.

[6] (a) Federsel, H.-J., *Nat. Rev. Drug. Disc.*, **2005**, *4*, 685-697; (b) Taylor, M.S.; Jacobsen, E.N., *Proc. Natl. Acad. Sci. U.S.A.*, **2004**, *101*, 5368-5373.

[7] (a) Noël, T.; Bert, K.; Van der Eycken, E.; Van der Eycken, J., *Eur. J. Org. Chem.*, **2010**, 4056-4061. (b) Mahatthananchai, J., Dumas, A. M., Bode, J. W., *Angew. Chem. Int. Ed.*, **2012**, *51*, 10954-10990.

[8] Inoguchi, K.; Sakuraba, S.; Achiwa, K., *Synlett*, **1992**, 169-178.

[9] de Vries, A. H. M.; Meetsma, A.; Feringa, B. L., *Angew. Chem. Int. Ed.*, **1996**, *35*, 2374-2375.

[10] Teichert, J. F.; Feringa, B. L., *Angew. Chem. Int. Ed.*, **2010**, *49*, 2486-2528.

[11] Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G., *Acc. Chem. Res.*, **2007**, *40*, 1267-1277.

[12] C. Defieber, M. A. Ariger, P. Moriel, E. M. Carreira, *Angew. Chem. Int. Ed.*, **2007**, *46*, 3139-3143.

[13] Hamilton, J. Y.; Sarlah, D.; Carreira, E. M., *J. Am. Chem. Soc.*, **2013**, *135*, 994-997.

[14] Eberhardt, L.; Armspach, D.; Matt, D.; Toupet, L.; Oswald, B., *Eur. J. Org. Chem.*, **2007**, 5395-5403.

[15] (a) Blaser, H. U.; Brieden, W.; Pugin B.; Spindler, F.; Studer, M.; Togni, A., *Top. Catal.*, **2002**, *19*, 3-16; (b) Blaser, H. U. ; Spindler F.; Studer, M.; *Appl. Catal., A.*, **2001**, *221*, 119-143; (c) Blaser H. U., *Adv. Synth. Catal.*, **2002**, *344*, 17-31.

[16] (a) Arrayás, R. G.; Adrio, J.; Carretero, J. C., *Angew. Chem. Int. Ed.*, **2006**, *45*, 7674-7715; (b) Colacot, T. J., *Chem. Rev.*, **2003**, *103*, 3101-3118; (c) Barbaro, P.; Bianchini, C.; Giambastiani, G.; Parisel, S. L., *Coord. Chem. Rev.*, **2004**, *248*, 2131-2150; (d) Atkinson, R. C. J.; Gibson, V. C.; Long, N. J., *Chem. Soc. Rev.*, **2004**, *33*, 313-328. (e) Noël, T.; Van der Eycken J., *Green Process. Synth*, **2013**, *2*, 297-309

[17] *Chiral Ferrocenes in Asymmetric Catalysis*, Dai, L.-X.; Hou X.-L., Eds, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2010**

[18] Dai, L.-X.; Tu, T.; You, S.-L.; Deng W.-P.; Hou, X.-L., *Acc. Chem. Res.*, **2003**, *36*, 659-667.

[19] Krajnik, P.; Kratky, C.; Schlögl, K. Widhalm, M., *Monatsch. Chem.*, **1990**, *121*, 945-953.

[20] Xiao, L.; Mereiter, K.; Spindler F.; Weissensteiner, W., *Tetrahedron: Asymmetry*, **2001**, *12*, 1105-1108.

[21] Espino, G.; Xiao, L.; Puchberger, M.; Mereiter, K.; Spindler F.; Manzanno, B. R.; Jalón, F. A.; Weissensteiner, W., *Dalton Trans.*, **2009**, 2751-2763.

[22] Xia, L.; Weissensteiner, W.; Mereiter, K.; Widhalm, M., *J. Org. Chem.*, **2002**, *67*, 2206-2214.

[23] Schaarsmidt, D.; Lang H., *Organometallics*, **2013**, *32*, 5668-5704.

[24] (a) Riant, O.; Samuel, O.; Kagan, H. B.; *J. Am. Chem. Soc.*, **1993**, *115*, 5835-5836; (b) Riant, O.; Samuel, O.; Flessner, T.; Taudine, S.; Kagan, H. B., *J. Org. Chem.*, **1997**, *62*, 6733-6745.

[25] Zhang, S.; Zhang, D.; Liebeskind L. S., *J. Org. Chem.*, **1997**, *62*, 2312-2313.

[26] (a) Weyl, H., *Methoden der Organischen Chemie*, Müler, E., Ed, Thieme, Stuttgart, **1964**, Vol XII/2; (b) Edmundson, R. S., in *Comprehensive Organic Chemistry*, Barton, D. H. R., Ollis, W. D., Pergamon Press., Oxford, **1979**, Vol. 2, part 10.3; (c) Van Rooy, A.; Burgers, D.; Kamer, P. C. J.; van Leeuwen, P. W. N. M., *Recl. Trav. Chim. Pays-Bas*, **1996**, *115*, 492-498.

[27] Choi, Y. H.; Choi, J. Y.; Yang, H. Y.; Kim, Y. H., *Tetrahedron: Asymmetry*, **2002**, *13*, 801-804.

[28] Tang, W.; Zhang, X., *Chem. Rev.*, **2003**, *103*, 3029-3063.

[29] (a) Jerphagnon, T.; Renaud, J.-L.; Bruneau, C., *Tetrahedron: Asymmetry*, **2004**, *15*, 2101-2111; (b) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L., *J. Am. Chem. Soc.*, **2002**, *124*, 14552-14553; (c) Reetz, M. T.; Sell, T., *Tetrahedron Lett.*, **2000**, *41*, 6333-6336. (d) Claver C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G., *Chem. Commun.*, **2000**, 961-962; (e) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L., *J. Am. Chem. Soc.*, **2000**, *122*, 11539-11540; (f) van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L., *Adv. Synth. Catal.*, **2002**, *344*, 1003-1007; (g) van den Berg, M.; Minnaard, A. J.; Haak. R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries. A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G., *Adv. Synt. Catal.*, **2003**, *345*, 308-325.

[30] (a) Vineyard, B. D.; Knowles, W.S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J., *J. Am. Chem. Soc.*, **1977**, *99*, 5946-5952; (b) Togni, A.; Breutel, B.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A., *J. Am. Chem. Soc.*, **1994**, *116*, 4062-4066 (c) Pye, J. P.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J., *J. Am. Chem. Soc.*, **1997**, *119*, 6207-6208.

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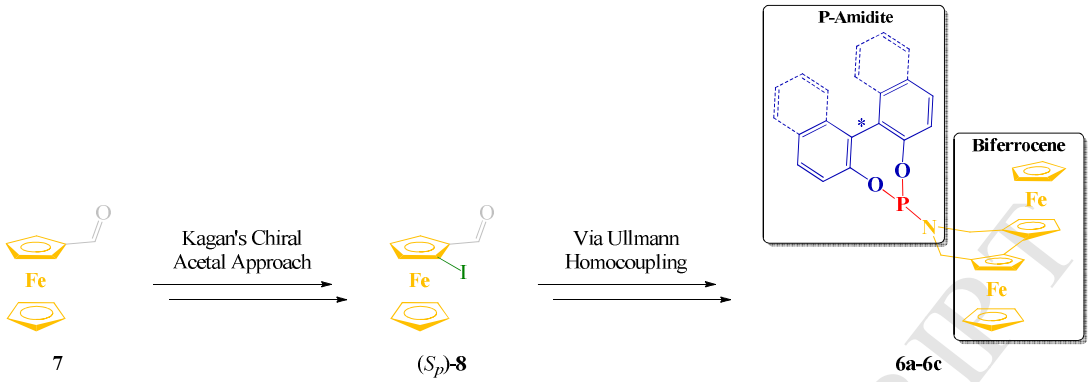

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