Novel Chiral Biferrocene Ligands for Palladium-Catalyzed Allylic Substitution Reactions

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Eleven novel aminophosphine ligands have been synthesized, all of which contain a chiral 2,2′′-bridged biferroceno unit as part of a biferrocenoazepine substructure. The efficiency of these compounds as chiral auxiliaries in palladium-mediated allylic substitution reactions has been investigated. Depending on the degree of (steric) fit between proper ligands and cyclic or noncyclic substrates, reactions with 46−87% ee were achieved. The molecular structure of a palladium dichloride complex of one of the ligands was determined by X-ray diffraction and compared to its binaphthyl analogue. In the solid state, the azepine substructure of these two complexes adopts totally different conformations with either local C_2 (binaphthyl) or local C_1 (biferrocene derivative) symmetry. These structural changes are well-reproduced by empirical force field calculations and are also reflected in significantly different behavior in asymmetric catalysis.

Introduction

Enantiopure bidentate ligands of transition metal complexes with phosphorus and nitrogen donor sites have been the subject of considerable interest since their potential in asymmetric catalysis was discovered.[1] To date, bidentate PN ligands have been applied mainly in carbon−carbon and carbon−heteroatom bond-forming reactions. In general, for enantioselective catalysts, modular ligand structures have proved to be advantageous, since ligand fine-tuning by varying structural fragments or substituents is expected to allow their optimal adjustment to the requirements of a specific reaction mechanism, reagent, or substrate. Among carbon−carbon bond-forming processes, palladium-mediated allylic substitutions have found broad application as test reactions, mainly because many mechanistic details are relatively well-understood.[2,3] The catalytic cycle starts with an oxidative addition of a racemic allyl substrate to a palladium(0) precursor. In this step, several isomeric palladium(II) allyl complexes may be generated either directly or through a η^3−η^1−η^3 interconversion mechanism. A subsequent nucleophilic attack at one of the terminal allyl carbon atoms leads to η^2-coordinated palladium olefin complexes with a stereogenic carbon center adjacent to the coordinated double bond. Mechanistic investigations with different ligands and substrates have been reported and early and late transition states have been suggested for this step.[4] The enantioselectivity of the overall reaction has been attributed to the predominance of one of the allyl complexes in conjunction with a sterically or electronically substantiated regioselectivity of the nucleophilic attack. Irrespective of the origin of the asymmetric induction, the stereoelectronic substrate−ligand interactions are known to play an important role but still need to be optimized empirically. A wide variety of bidentate ligands have been investigated along with various types of nucleophiles, and some ligands show excellent enantioselectivities for differently substituted cyclic and noncyclic substrates.[5] Moreover, several applications in natural product syntheses have been reported.[6]

Aminophosphines 1−3 belong to a group of ligands that contain the 2,2′-bridged binaphthyl entity as part of a dihydrodinaphthazepine substructure[7] in which the

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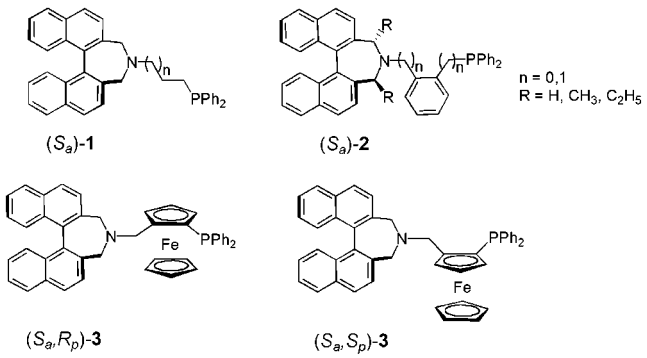

Figure 1. Binaphthyl ligands **1**−**3**.

tertiary nitrogen is situated in an environment of local C_2 symmetry (Figure 1). During investigations into the catalytic efficiency of these systems in allylic substitution reactions, we noticed that modification of the P−N tether[7b−d,8] and also the introduction of substituents in the benzyl positions of the binaphthyl core[9] showed a marked influence on the asymmetric induction. This effect was attributed to different steric interactions in the diastereomeric allyl intermediates, which results in either significantly different complex concentrations or changes of their individual reactivity and site selectivity. Unfortunately, structural changes that enhanced the ligand−substrate interaction were often accompanied by a loss of reactivity.[9]

One obvious shortcoming of the dinaphthoazepine substructure was the rather small biaryl angle of only 63°. With PN coordination in a square planar transition metal complex, a dicoordinated substrate will receive only a weak interaction with the dissymmetric unit. A ligand developing its steric dissymmetry closer to the substrate but without steric hindrance of the substrate coordination would therefore be desireable, more so if small substrates are of interest. Originally, we thought that replacing the binaphthyl unit of ligands such as **1**−**3** by biferrocene would allow the local C_2 symmetry of the azepine substructure to be maintained while, at the same time, changing its spatial requirements. We therefore aimed to synthesize a group of related biferrocene ligands with a modular architecture that would enable a stepwise adoption of the ligand structure with respect to electronic and steric demands of the substrates. Such an approach should allow a better fit into the chiral pocket.

Results and Discussion

On the basis of the ideas described above, a group of 11 structurally related biferrocene ligands, **4**−**14**, was prepared, all of which have a topology that is entirely different from previously investigated aminophosphines (Figure 2). A systematic investigation of electronic (**4**/**5**/**6**) or steric (**4**/**10**/**11**, **7**/**12**, **8**/**13**, **9**/**14**) factors as well as the influence of the chelate ring size (**4**/**7**/**8** or **9**, respectively, **10**/**12**) on reactivity and enantioselectivity was undertaken. In several cases, the existence of diastereomers with matched and mismatched stereogenic units was also considered (**8**/**9**, **10**/**11**, **13**/**14**).

Synthesis of Ligands. The synthesis of the ligands **4**−**14** was achieved by the same general route: (i) formation of an enantiopure biferrocene intermediate, (ii) reaction of this entity with a suitable bromo- or iodo-substituted amino derivative in order to build up the ligand skeleton, and (iii) replacement of the bromide or iodide by an appropriate phosphino group. All of the target ligands, **4**−**14**, were accessible from three enantiopure biferrocene intermediates: ligands **4**−**9** (without methyl substituents in the pseudo-benzyl position) from **23**[10] (Schemes 1−3), the methyl-substituted derivatives **10** and **12**−**14** from **28**[11] (Scheme 4), and **11** from **38** (Scheme 5).

Biferrocene **23**, the key intermediate in the preparation of ligands **4**−**9**, was easily accessible in two steps from enantiopure **15** (Scheme 1). In a homocoupling reaction, 2-iodo-1-dimethylaminomethylferrocene, **15**, was transformed either under Ullmann conditions (Cu, 110 °C, 37%) or oxidatively [BuLi, $Fe(acac)_3$, 35%] into 2,2″-bis-

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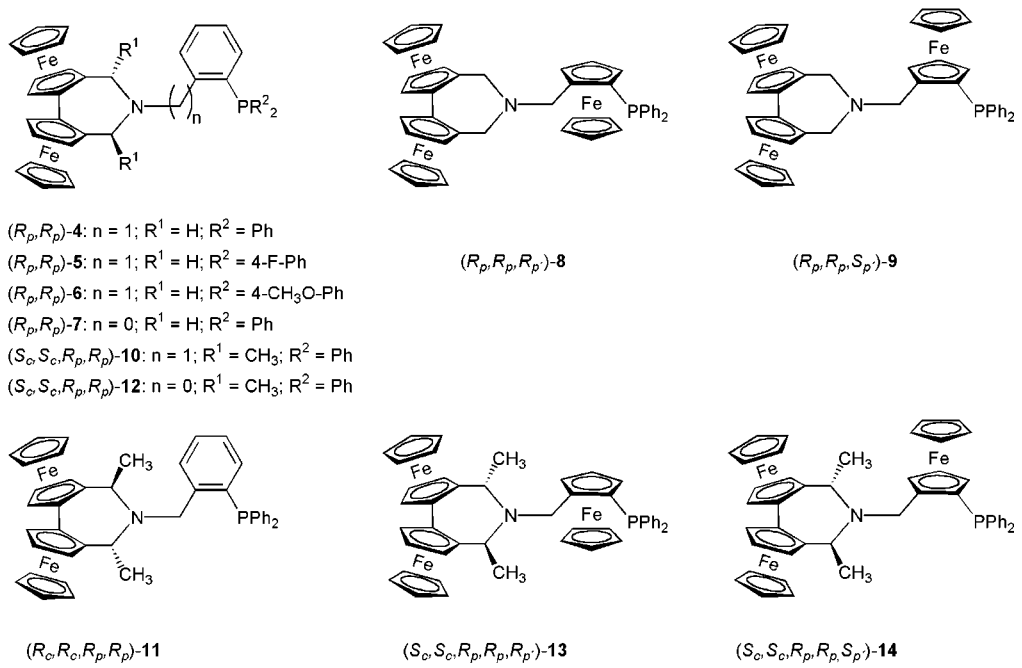
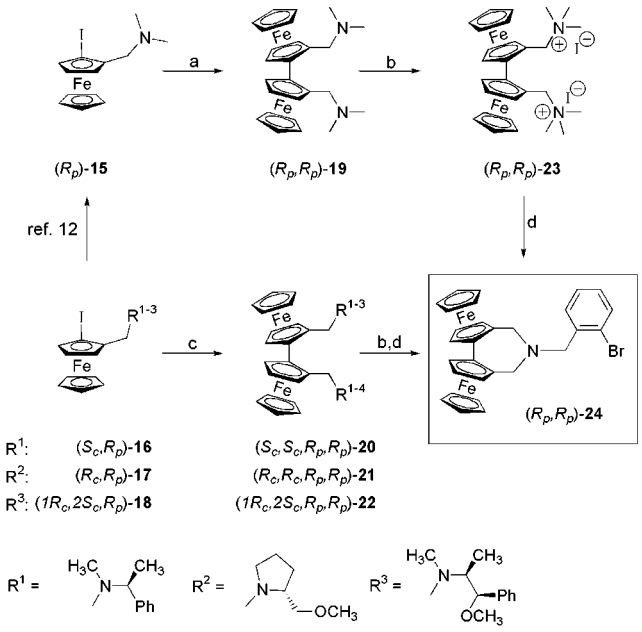


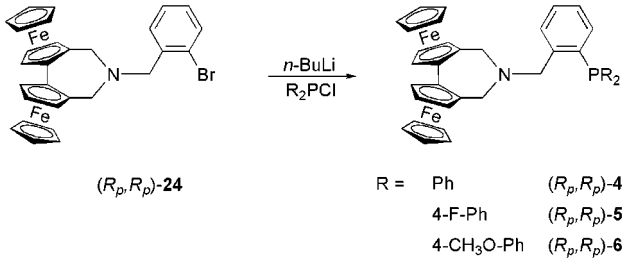
Figure 2. Novel biferrocene ligands **4**−**14**.

Scheme 1[a]



[a] Reagents: (a) *n*-BuLi, $Fe(acac)_3$ or Cu, 110 °C; (b) CH_3I, acetonitrile; (c) Cu, 130−136 °C; (d) 2-bromobenzylamine hydrochloride, triethylamine, acetonitrile, reflux.

Scheme 2



(dimethylaminomethyl)-1,1′′-biferrocene, **19**, which, on treatment with methyl iodide, gave **23** in 92% yield. Reaction of **23** with bromo-substituted amines (2-bromobenzylamine, 2-bromoaniline, and 2-bromoferrocenylmethylamine) or, more conveniently, with their hydrochlorides afforded the azepine precursors **24**−**27** (Schemes 1 and 3) in 52% (**27**) to 90% (**24**) yield. In a final step, ligands **4**−**9** were obtained in 55−71% yield by reacting each bromo derivative **24**−**27** with *n*-BuLi, followed by addition of an excess of the appropriate diarylchlorophosphine (Schemes 2 and 3).

The synthesis of **23** required the enantiomerically pure starting material **15**, and this was easily accessible from enantiopure iodo derivatives **16**−**18**, as we described previously.[12] The diastereomers (S_c,S_p)-**16** and (S_c,R_p)-**16** were actually obtained as intermediates in a resolution procedure of racemic **15** with the use of phenylethylamine,[12] and these compounds could be readily separated by column chromatography. Enantiopure **17** and **18**, on the other hand, were obtained through highly diastereoselective *o*-lithiation/iodations of *N*-ferrocenylmethyl-*O*-methylprolinol[13] (**17**) or *N*-ferrocenylmethyl-*O*-methylephedrine (**18**), an auxiliary recently developed in our group.[14]

In an attempt to shorten the synthesis, we tried to use these precursors of **15** as alternative starting materials for the synthesis of intermediate **24**. Indeed, iodides **16**−**18** could be transformed into biferrocenes **20**−**22** [**20**, Cu, 136 °C, 72%; *n*-BuLi, $Fe(acac)_3$, 44%; **21**, Cu, 130 °C, 64%; **22**, Cu, 130 °C, 58%], and these were subsequently reacted with methyl iodide and 2-bromobenzylamine hydrochloride to give the azepine intermediate **24** (yields from **20**, 41%; **21**, 40%; **22**, 63%).

Although compound **24** was obtained in all four synthetic pathways from starting materials **15**−**18** in comparable overall yields (28, 30, 26, and 37%, respectively),

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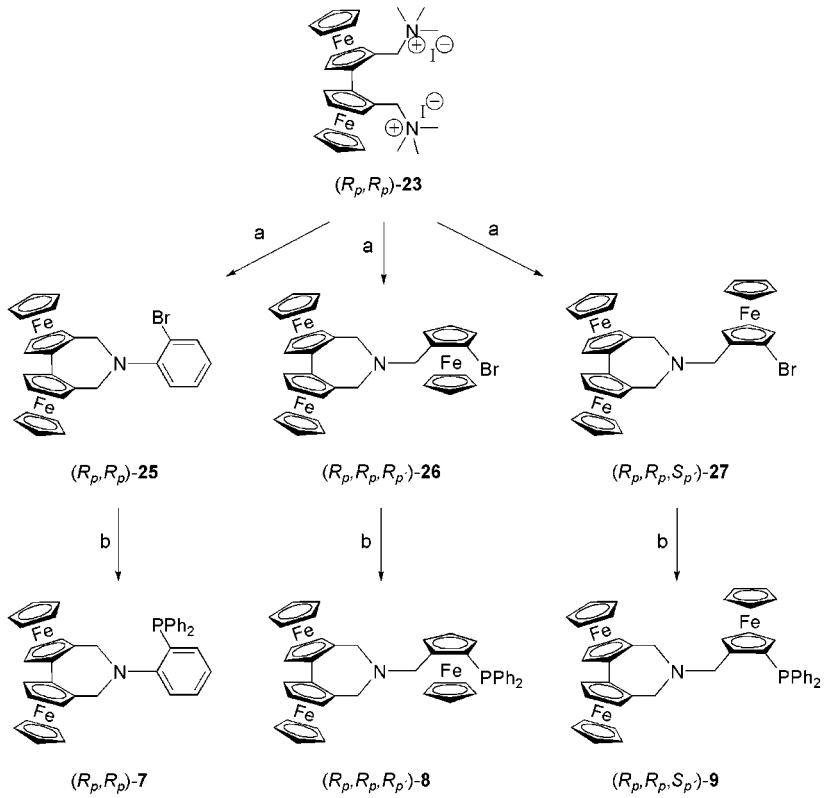
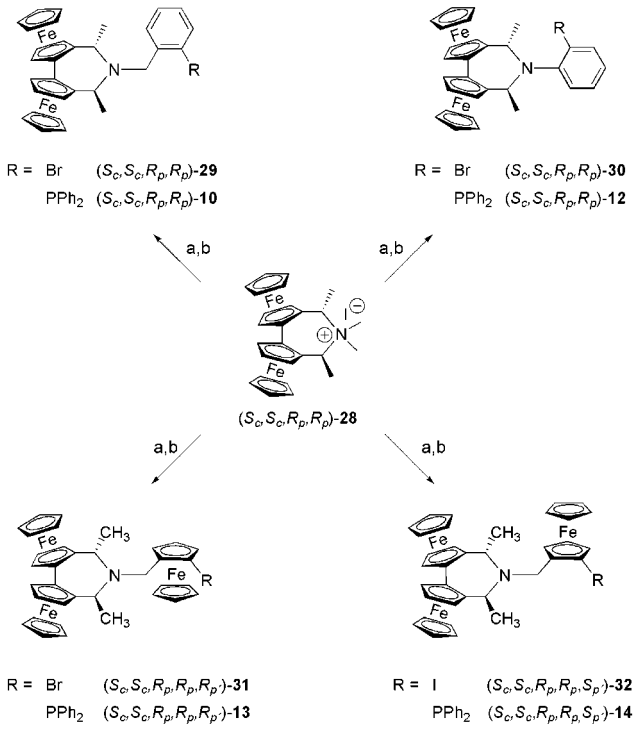
Scheme 3[a]



[a] Reagents: (a) 2-bromoaniline hydrochloride or (*R*)- or (*S*)-2-bromoaminomethylferrocene, triethylamine, acetonitrile, reflux; (b) *n*-BuLi (−40 °C), Ph_2PCl (−78 °C).

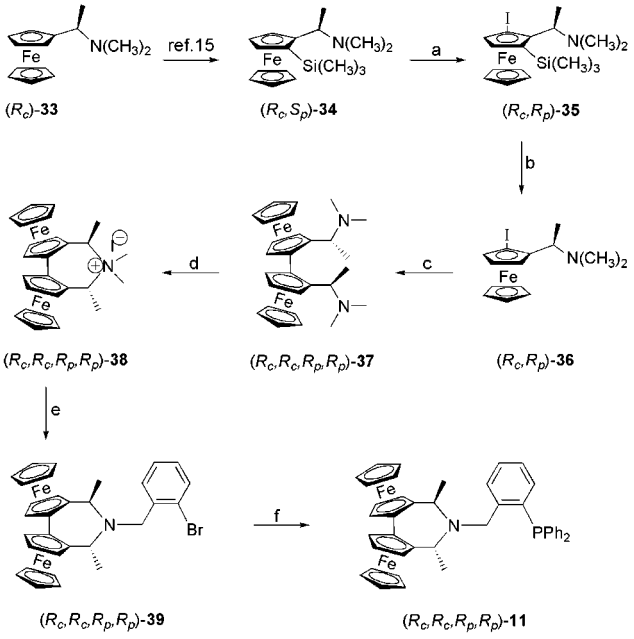
Scheme 4[a]



[a] Reagents: (a) 2-bromobenzylamine hydrochloride or 2-bromoaniline hydrochloride or (*R*)-2-bromoaminomethylferrocene or (*S*)-2-iodoaminomethylferrocene, triethylamine, acetonitrile, reflux; (b) *n*-BuLi (−40 °C), Ph_2PCl (−78 °C).

the route **18** → **22** → **24** proved to be most economical and, moreover, appeared to be the least time-consuming.

Scheme 5[a]



[a] Reagents: (a) *n*-BuLi, I_2 (−78 °C); (b) KO^{t}Bu, DMSO, rt; (c) *n*-BuLi, $Fe(acac)_3$; (d) CH_3I, acetonitrile; (e) 2-bromobenzylamine hydrochloride, triethyamine, acetonitrile, reflux; (f) *n*-BuLi (−40 °C), Ph_2PCl (−78 °C).

The azepinium salt **28**[11] (for **10**, **12**−**14**) and its diastereomer **38** (for **11**) served as the central precursors for the synthesis of the 3,5-dimethyl-substituted dihydroazepine ligands **10**−**14** (Schemes 4 and 5). Both diastereomers were prepared from enantiopure (*R*)-**33**.

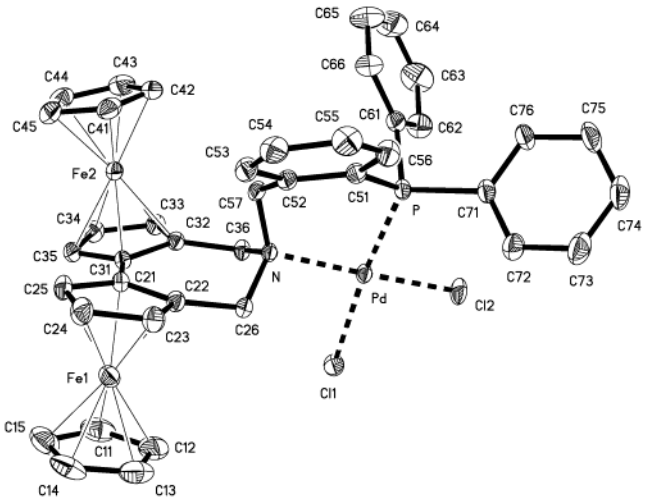


Figure 3. Molecular structure of **4**·$PdCl_2$·$3CHCl_3$ [(R_p,R_p)-**40**·$3CHCl_3$]. The solvate molecules and hydrogen atoms have been removed for clarity.

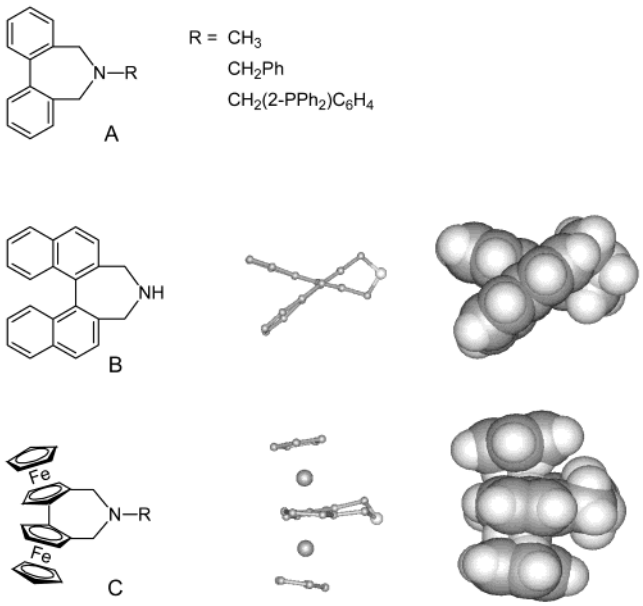


Figure 4. Biaryl- and biferrocenoazepines used as models in empirical force field calculations (A, C). Different spatial requirements of binaphthyl (B) or bisferroceno (C) azepine subunits.

According to a published procedure,[11] *o*-lithiation of **33** with *n*-BuLi followed by homocoupling with $Fe(acac)_3$ and subsequent treatment of the biferrocene intermediate with methyl iodide gave **28**. The diastereomer **38** was made in a similar two-step sequence from **36**, which in the first step was reacted with *n*-BuLi followed by treatment with $Fe(acac)_3$ to give biferrocene **37** in 67% yield. In the second step, treatment with methyl iodide led to the azepinium salt **38** (99%). Enantiopure iodide **36** was obtained in three steps from **33** by adapting a published procedure for analogous derivatives.[15]

It is interesting to note that the applicability of the two homocoupling methods, either with $Fe(acac)_3$ or under Ullmann conditions, appeared to be complementary. While the oxidative coupling worked in a satisfactory manner with α-methylated ferrocenylamines **33** or **36**, the unsubstituted diastereomers **16** and **17** afforded almost no coupling product at all. Only **19** was formed from **15** (albeit in low yield, 35%), but this was accompanied by a considerable amount of 2-aminomethyl-2″-formyl-1,1″-biferrocene and starting material. In contrast, the Ullmann coupling of **16** and **17** afforded the biferrocenes **20** and **21** in 72 and 64% yield, respectively.

Starting from the azepinium salts **28** or **38**, the benzylmethylated aminophosphine ligands **10**−**14** were obtained in enantiomerically pure form in 23−64% overall yield by applying the same two-step sequence as described above for the synthesis of **4**−**9** from **23**.

X-ray Structure Analysis. Complex (R_p,R_p)-**40**, obtained by treating a solution of (R_p,R_p)-**4** in benzene with $Pd(CH_3CN)_2Cl_2$, crystallizes in the form of a chloroform solvate, **4**·$PdCl_2$·$3CHCl_3$, in the triclinic space group *P*1 (no. 1) with one formula unit per cell. An ORTEP plot of the molecular structure is shown in Figure 3. Crystallographic data are given in the Experimental Section, and further details such as bond lengths and angles are given in the Supporting Information. The general structural features of **40** are as expected for this type of complex. However, in contrast to the molecular structure of the palladium allyl complex of binaphthyl ligand **2**[16] (Figure 1, $n = 1$, $m = 0$, R = H), in which the azepine subunit is in a rather strainless twist conformation of local C_2 symmetry with a biaryl angle of 63°, the connected Cp rings of **40** are found in a nearly coplanar arrangement (dihedral angle between planes C21−C25 and C31−C35 = 14.4°) that forces the seven-membered ring system into an envelope-like conformation of local C_1 symmetry.

Empirical Force Field Calculations. To rationalize these strong structural differences, we carried out empirical force field calculations.[17] Minimum energy structures of a number of differently substituted biferrocenoazepines and their related biaryl derivatives, including the palladium dichloride complex **40** and its biphenyl analogue, were searched for [Figure 4, R = CH_3, CH_2Ph, $CH_2(2\text{-}Ph_2P)Ph$]. To make a better comparison, calculations on biphenyl rather than binaphthyl derivatives were carried out. The reason for this is that 6,6′-substituents are expected to prevent a biaryl system from adopting a coplanar arrangement of the aryl groups, an arrangement that is necessary in an envelope-like azepine structure. Details on the calculations are given in the Supporting Information.

Qualitatively, the following results were obtained: (i) in the case of all biphenyl derivatives, only minimum energy structures with an azepine subunit of local C_2 (or very close to local C_2) symmetry and with a rather strainless twist conformation were located, while (ii) all biferrocene ligands can adopt conformers with both the twist and the envelope-like azepine subunit. Furthermore, in the envelope-like structure, the substituents at the nitrogen atom can be located either in an axial or an equatorial position.

The order of minimum energy structures for all biferrocene ligands was as follows: independent of the substituents at nitrogen, the envelope-like conformer with an axial substituent was always of lowest energy, fol-

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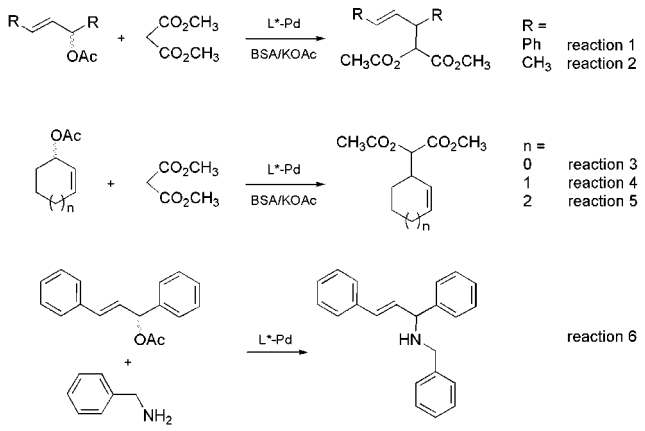
(16) Widhalm, M.; Nettekoven, U.; Kalchhauser, H.; Mereiter, K.; Calhorda, M.-J.; Félix, V. *Organometallics* **2002**, *21*, 315.

(17) PCMODEL V 7.0; Serena Software, Box 3076, Bloomington, IN 47402-3076.

Scheme 6



lowed by the structure with an equatorial substituent [2.7, 6.6, and 4.3 kcal/mol for R = CH_3, CH_2Ph, and CH_2-(2-PPh_2)C_6H_4, respectively]. The conformers with an azepine subunit of local C_2 symmetry were always found to be of highest energy. The same result was obtained for the palladium dichloride complex of **4** (**40**) and its biphenyl analog: for **40** a molecular structure similar to that found in the solid state was calculated to be of lowest energy (~5.8 kcal/mol more stable than the C_2-type structure), while the azepine unit of the biphenyl analogue was calculated to adopt a twist conformation comparable to that of **2** in the solid state.[16]

On the basis of the results of the calculations, we conclude that in the case of the biferrocene derivatives an envelope-like azepine conformation is more stable than a twisted arrangement. There are two reasons for this conclusion: (i) as compared to the six-membered aryl rings, bond angles within the Cp ring are smaller, while the bond angles within the azepine moiety necessarily increase. This enables a nearly coplanar arrangement of the ferrocene units, a situation that is even more favored by the fact that the steric interactions of ortho-substituents are less pronounced in the five-membered Cp rings as compared to six-membered aryl rings. (ii) Steric interactions between substituents at the nitrogen atom and one of the ferrocenyl units are reduced in an envelope-like conformation.

Allylic Substitution. Asymmetric allylic substitution reactions with typical cyclic and noncyclic substrates were performed (Scheme 6). Experimental details and tables of all results are given in the Supporting Information. Table 1 lists the best results obtained in allylic substitution reactions 1−6 with ligands **4**−**14**. Reaction 1 was used to optimize the reaction conditions with dimethylmalonate and *N*,*O*-bis(trimethylsilyl)acetamide (BSA)/KOAc as the base. In a comparative study, all reactions were conducted on a 1 mmol scale with 1 mol % of catalyst prepared in situ from the appropriate ligands and $[Pd(allyl)Cl]_2$ (1:0.5) in CH_2Cl_2 at room temperature. A reaction time of 1−2 h for complete conversion was sufficient, apart from ligands **9**, **12**, and **14**, where longer periods were required. Longer reaction times were also required for reaction 2 with an aliphatic substrate. The reaction was generally faster with cyclic substrates, and isolated yields were excellent (92−99%). In contrast, the amination of 1,3-diphenyl-2-propenyl acetate with benzylamine proceeded slowly, and isolated yields after a reaction time of 48 h varied considerably.

A clear dependence of the sense of asymmetric induction on the configuration of the biferrocene unit was observed for noncyclic substrates. Products with the (*R*)-configuration were formed in reaction 1 with a moderate to good level of enantioselectivity. An exception to this trend concerns ligand **14**, which gave the product with the (*S*)-configuration and with only 5% ee. Reaction 2 generally proceeded with a low level of enantioselectivity in the range 3−46%. In most cases the product configuration changed to (*R*), probably due to the lack of π stacking interactions between substrate and ligand phenyl groups. The best result (46% ee) was obtained with ligand **9**, which contains a further chiral ferrocene moiety of matching configuration. When the mismatched ligand **8** was used, the enantioselectivity dropped to 16%. A similar effect of matching/mismatching carbon and ferrocene configuration can be seen from the results for ligands **4**, **10**, and **11**. For example, ligand **4**—without a methyl-substituted azepine ring and with a low degree of steric interaction in close proximity to the nitrogen coordination site—gave 15% ee, while the mismatched ligand **10** led to a drop in the ee to 4%. The matched ligand **11**, however, led to a product with 26% ee but with the opposite configuration (*R*).

In the case of cyclic substrates (reactions 3−5), the metallocene configuration of the PN-bridging ferrocene unit proved to have a predominant effect on the enantioselectivity and product configuration. On using ligand **8** instead of ligand **9**, there is a change from 53%, 57%, and 74% ee and (*S*)-configuration to 59%, 65%, and 77% ee and (*R*)-configuration. A similarly pronounced relationship was found between ligands **13** and **14**. The substrate cycloheptenyl acetate (reaction 5) proved to be most sensitive to structural changes of the ligands. Comparison of **4**, **7**, and **8** or **4**, **7**, and **9** shows that the effect of the size of the chelate ring is less pronounced and is dominated by configurational differences in **8** and **9**.

In contrast to steric effects, the influence of electronic effects on the enantioselectivity was found to be small and without a clear trend. In only one case, when cyclopentenyl acetate was used as the substrate (reaction 3), was the asymmetric induction improved. In this case a value of 27% ee was improved to 58% ee by changing the electron-withdrawing phosphino group of **5** to an electron-donating phosphine in **6**.

Conclusions

The use of a modular and stereoselective approach has enabled a new class of aminophosphine ligands, all of which contain a biferroceno azepine subunit, to be synthesized. Eleven ligands were prepared for use as auxiliaries in asymmetric allylic substitution reactions. On the basis of the results of empirical force field calculations and on an X-ray diffraction study, we conclude that the biferrocenoazepine subunit, both in the free ligands and as part of a palladium dichloride complex, prefers an envelope-like conformation of the seven-membered ring rather than a twisted arrangement of local C_2 symmetry. The latter situation has been found experimentally for binaphthyl analogues.

In allylic substitution reactions, two noncyclic and three cyclic substrates (reactions 1−5) were alkylated enantioselectively with dimethyl malonate to give products with 46−87% ee. In addition, the amination of 1,3-diphenylprop-2-ene-1-yl acetate with benzylamine pro-

Table 1. Results of Allylic Alkylation and Amination Reactions 1−6 (ee) with Ligands 4−14

ligand	enantiomeric excess (configuration)[a]					
	rxn 1	rxn 2	rxn 3	rxn 4	rxn 5	rxn 6
(R_p,R_p)-4	**87** (*R*)	15 (*S*)	33 (*S*)	50 (*S*)	77 (*S*)	**86** (*S*)
(R_p,R_p)-**5**	86 (*R*)	16 (*S*)	27 (*S*)	49 (*S*)	77 (*S*)	75 (*S*)
(R_p,R_p)-**6**	79 (*R*)	11 (*S*)	58 (*S*)	49 (*S*)	69 (*S*)	82 (*S*)
(R_p,R_p)-**7**	70 (*R*)	39 (*S*)	41 (*S*)	61 (*S*)	**81** (*S*)	24 (*S*)
(R_p,R_p,R_p)-**8**	42 (*R*)	16 (*S*)	53 (*S*)	57 (*S*)	74 (*S*)	2 (*R*)
(R_p,R_p,S_p)-**9**	69 (*R*)	**46** (*S*)	**59** (*R*)	**65** (*R*)	77 (*R*)	74 (*S*)
(S_c,S_c,R_p,R_p)-**10**	64 (*R*)	4 (*S*)	11 (*S*)	22 (*S*)	23 (*S*)	80 (*S*)
(R_c,R_c,R_p,R_p)-**11**	79 (*R*)	26 (*R*)	12 (*S*)	1 (*S*)	1 (*S*)	65 (*S*)
(S_c,S_c,R_p,R_p)-**12**	60 (*R*)	6 (*R*)	55 (*S*)	43 (*S*)	70 (*S*)	77 (*S*)
(S_c,S_c,R_p,R_p,R_p)**13**	59 (*R*)	3 (*S*)	42 (*S*)	46 (*S*)	65 (*S*)	41 (*S*)
(S_c,S_c,R_p,R_p,S_p)-**14**	5 (*S*)	24 (*S*)	11 (*R*)	36 (*R*)	1 (*R*)	20 (*S*)

[a] Boldfaced figures indicate maxium e.e. for this reaction.

ceeded with 86% ee (reaction 6). The enantioselectivity with noncyclic substrates was found to be mainly controlled by the configuration of the biferrocene moiety but modulated by methyl substituents on the azepine ring as well as by the configuration of the P−N linking ferroceno group. In contrast, for cyclic substrates the product configuration depends primarily on the configuration of the ferroceno group located in the central region between the P and N coordination sites. From both the structural and the catalytic point of view, the investigated biferrocenoazepines constitute a new class of ligands that are not directly comparable to their biaryl (binaphthyl) analogues.

Experimental Section

General Methods. Melting points were determined on a Kofler melting point apparatus and are uncorrected. NMR spectra were recorded at 400.132 MHz (^{1}H) and 100.624 MHz (^{13}C) in $CDCl_3$ if not stated otherwise. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C), CH_2Cl_2 (5.31 and 53.7 ppm for ^{1}H and ^{13}C), DMSO (2.50 and 39.5 ppm for ^{1}H and ^{13}C), and 85% H_3PO_4 (^{31}P). Italic ^{13}C data indicate that the signals could not be assigned unambiguously. Mass spectra were EI at 70 eV, if not stated otherwise. Optical rotations were measured in $CHCl_3$ at 20 °C. CD spectra were recorded on a dichrograph in CH_2Cl_2 at 20 °C. Elemental analyses were performed at the Mikroanalytisches Laboratorium der Universität Wien (Mag. J. Theiner). All reactions requiring inert conditions were conducted under Ar using standard Schlenk techniques. Ether was distilled from $LiAlH_4$, acetonitrile and benzene were distilled from calcium hydride, and THF was dried over potassium prior to use. Chromatographic separations were performed under gravity either on silica gel (40−63 μm) or alumina (activity II−III, 0.063−0.200 mm).

Iron(III) acetylacetonate was dried overnight at 100 °C under high vacuum. Copper was activated according to ref 18. (R_p)- And (S_p)-1-iodo-2-dimethylaminomethylferrocene (**15**),[12] (S_c,R_p)- or (S_c,S_p)-1-iodo-2-(1-phenylethylaminomethyl)ferrocene (**16**),[12] (R_c,R_p)-1-iodo-2-[(2-methoxymethylpyrrolidin-1-yl)]-methylferrocene (**17**),[12] (1R_c,2S_c)-1-iodo-2-[*N*-(1-methoxy-1-phenylprop-2-yl)-*N*-methylaminomethyl]ferrocene (**18**),[14] (R_c,R_c,S_p,S_p)-*N*,*N*-dimethyl-3,5-dimethyl-3,5-dihydro-4*H*-diferroceno[*c*,*e*]azepinium iodide (**28**),[11] and (R_c,S_p)-2-(1-*N*,*N*-dimethylamino)-ethyl-1-trimethylsilylferrocene (**34**)[15] were synthesized as described in the literature.

(R_p,R_p)-*N*-(2-Diphenylphosphinobenzyl)-3,5-dihydro-4*H*-diferroceno[c,e]azepine (4). To a solution of azepine (R_p,R_p)-**24** (660 mg, 1.14 mmol) in THF (20 mL) was added *n*-BuLi (0.88 mL, 1.6 M, 1.41 mmol) at −40 °C. The reaction mixture was stirred for 2 h, and Ph_2PCl (385 mg, 1.71 mmol) was added at −78 °C. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution, and the organic phase was separated, washed with brine, and dried with Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on silica gel. Elution with PE/Et_2O/Et_3N (40:5:1) afforded **4** (611 mg, 62%) as a yellow solid:

mp 73−75 °C; ^{1}H NMR δ 3.35 (d, 2H, J = 15.6 Hz, CH_2), 3.57 (d, 2H, J = 15.6 Hz, CH_2), 3.88 (m, 2H, Cp-H), 3.90 (s, 10H, Cp-H), 3.98 (d, 1H, J = 13.6 Hz, CH_2), 4.07 (t, 2H, J = 2.5 Hz, Cp-H), 4.17 (dd, 1H, J = 13.6, 2.5 Hz, CH_2), 4.34 (m, 2H, Cp-H), 6.96−7.00 (m, 1H, Ph), 7.17−7.37 (m, 13 H, Ph); ^{13}C NMR δ 54.38 (CH_2), 57.38 (d, J = 16.7 Hz, CH_2), 65.96 (Cp-CH), 66.24 (Cp-CH), 67.35 (Cp-CH), 69.82 (Cp), 82.46 (Cp-C), 85.23 (Cp-C), 127.12 (Ph-CH), *128.13*, *128.17*, *128.30* (Ph-CH), 128.30 (d, J = 11.4 Hz, Ph-CH), 129.27 (d, J = 5.3 Hz, Ph-CH), 133.47 (d, J = 19.0 Hz, Ph-CH), 133.66 (d, J = 19.0 Hz, Ph-CH), 134.41 (Ph-CH), *137.96*, *137.12*, *137.21*, *137.29* (Ph-C), 138.65 (d, J = 11.4 Hz, Ph-C), 144.57 (d, J = 22.8 Hz, Ph-C); ^{31}P NMR δ −14.01; MS (210 °C) *m*/*z* (rel %) = 685 (66, M^+), 500 (7), 410 (100); $[\alpha]_\lambda^{20}$ = +553 (589 nm), +603 (578 nm), +838 (546 nm), (c = 0.50); CD λ_{max} ($\Delta\epsilon$) = 280 nm (21.5), 298 nm (−3.80), 306 nm (−3.65), 343 (5.01), 455 nm (2.84) (c = 9.83 × 10^{-4} mol/L). Anal. Calcd for $C_{41}H_{36}Fe_2NP$: C, 71.85; H, 5.29; N, 2.04. Found: C, 71.57; H, 5.53; N, 2.01.

(R_p,R_p)- and (S_p,S_p)-2,2″-Bis(*N*,*N*-dimethylaminomethyl)-1,1″-biferrocene (19). Method A. To a solution of (R_p)- or (S_p)-1-iodo-2-dimethylaminomethylferrocene (**15**) (1.68 g, 4.55 mmol) in dry ether (8 mL) was added *n*-butyllithium in hexane (3.4 mL, 1.6 M, 5.46 mmol). The mixture was stirred at room temperature for 2 h and then cooled to 0 °C. A solution of iron-(III) acetylacetonate (2.47 g, 7.00 mmol) in degassed benzene (10 mL) was added rapidly to the reaction mixture. The rust-colored thick sludge was stirred at 0 °C for 10 min and then for an additional 22 h at room temperature. The reaction was hydrolyzed with 10% NaOH and filtered over a plug of Celite, and the cake was washed with CH_2Cl_2 and water. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried with $MgSO_4$. The solvent was removed and the residue was chromatographed on silica gel. Elution with PE/Et_2O/Et_3N (1:3:1) gave biferrocene **19** in the last band as a yellow oil (380 mg, 35%).

Method B. To a solution of (R_p)- or (S_p)-1-iodo-2-dimethylaminomethylferrocene (**15**) (3.30 g, 8.9 mmol) in CH_2Cl_2 (5 mL) was added activated copper bronze (15 g) and the solvent was evaporated. The resulting solid was heated under an argon atmosphere to 110 °C for 12 h. Then the mixture was cooled to room temperature and was washed repeatedly with CH_2Cl_2. The solvent was removed and the residue was purified by column chromatography on silica gel. Elution with PE/Et_2O/Et_3N (10:10:1) gave 960 mg of starting material **15** in the first band, followed by biferrocene **19** as a red oil (562 mg, 37%).

(R_p,R_p)-**19**: ^{1}H NMR δ 1.95 (s, 12H, 4 CH_3), 3.15 (d, 2H, J = 13.0 Hz, CH_2), 3.23 (d, 2H, J = 13.0 Hz, CH_2), 4.23 (m, 2H, Cp-H), 4.25 (s, 10H, Cp-H), 4.29 (m, 2H, Cp-H), 4.40 (m, 2H, Cp-H); ^{13}C NMR δ 45.10 (CH_3), 57.14 (CH_2), 66.41 (Cp-CH), 69.61 (Cp), 70.03 (Cp-CH), 71.02 (Cp-CH), 85.03 (Cp-C), 85.10

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(Cp-C); MS (90 °C) *m*/*z* (rel %) = 484 (44, M^+), 439 (32), 395 (24), 242 (4); $[\alpha]_\lambda^{20}$ = +1855 (589 nm), +2063 (578 nm), +2463 (546 nm), (*c* = 1.00); CD λ_{max} ($\Delta\epsilon$) = 285 nm (10.1), 342 nm (−1.92), 470 nm (5.07) (*c* = 1.05 × 10^{-3} mol/L). Anal. Calcd for $C_{26}H_{32}Fe_2N_2$: C, 64.49; H, 6.66; N, 5.78. Found: C, 64.43; H, 6.81; N, 5.61.

(*S*$_p$,*S*$_p$)-**19**: $[\alpha]_\lambda^{20}$= −1813 (589 nm), −2056 (578 nm), −2426 (546 nm), (*c* = 1.00); CD λ_{max} ($\Delta\epsilon$) = 285 nm (−10.1), 340 nm (1.90), 471 nm (−5.05) (*c* = 1.03 × 10^{-3} mol/L).

(1*R*$_c$,2*S*$_c$,1*R*′$_c$,2*S*′$_c$,*R*$_p$,*R*$_p$)-2,2″-Bis[*N*-(1-methoxy-1-phenylprop-2-yl)-*N*-methylaminomethyl]-1,1″-biferrocene (22). Biferrocene **22** was synthesized from (1*R*$_c$,2*S*$_c$)-1-iodo-2-[*N*-(1-methoxy-1-phenylprop-2-yl)-*N*-methylaminomethyl]ferrocene (**18**) using method B at 130 °C, as described for the synthesis of **19**. Crystallization of the residue afforded compound **22** as an orange solid in 58% yield:

mp 213 °C; ^{1}H NMR δ 0.99 (d, 6H, *J* = 6.6 Hz, CH_3), 1.96 (s, 6H, CH_3), 2.76 (m, 2H, CH), 3.22 (s, 6H, OCH_3), 3.27 (d, 2H, *J* = 13.6 Hz, CH_2), 3.44 (d, 2H, *J* = 13.6 Hz, CH_2), 4.10 (m, 2H, Cp-H), 4.14 (m, 4H, 2 CH and 2 Cp-H), 4.20 (s, 10H, Cp-H), 4.34 (m, 2H, Cp-H), 7.22−7.37 (m, 10H, Ph); ^{13}C NMR δ 9.42 (CH_3), 36.80 (CH_3), 52.10 (CH_2), 56.57 (CH_3), 64.68 (CH), 66.02 (Cp-CH), 69.38 (Cp-CH), 69.43 (Cp-CH), 70.89 (CH), 84.68 (Cp-H), 86.52 (br s, Cp-C), 126.87 (Ph-H), 126.94 (Ph-CH), 127.99 (Ph-CH), 141.75 (Ph-C); MS (220 °C) *m*/*z* (rel %) = 752 (15, M^+), 631 (41), 574 (100); $[\alpha]_\lambda^{20}$ = +463 (589 nm), +516 (578 nm), +822 (546 nm) (*c* = 0.37). Anal. Calcd for $C_{44}H_{52}Fe_2N_2O_2$: C, 70.22; H, 6.96; N, 3.72. Found: C, 70.04; H, 6.91; N, 3.73.

Bismethyl Iodide of (*R*$_p$,R$_p$)- and (*S*$_p$,S$_p$)-2,2″-Bis(*N*,*N*-dimethylaminomethyl)-1,1″-biferrocene (23). Biferrocene **19** (900 mg, 1.86 mmol) was dissolved in acetonitrile (5 mL), and iodomethane (2.64 g, 18.6 mmol) was added dropwise. A yellow precipitate formed during the addition of iodomethane. The mixture was stirred for a further 1 h at room temperature and then ether (30 mL) was added slowly. The reaction mixture was stirred for 30 min and the precipitate was filtered off and washed with ether. The product was dried under vacuum to give a yellow powder (1.31 g, 92%):

mp 193 °C (dec); ^{1}H NMR (DMSO-d_6) δ 2.70 (s, 18H, 6 CH_3), 4.45 (s, 10H, Cp-H), 4.50 (d, 2H, *J* = 15.2 Hz, CH_2), 4.63 (m, 2H, Cp-H), 4.65 (d, 2H, *J* = 15.2 Hz, CH_2), 4.77 (m, 2H, Cp-H), 4.93 (m, 2H, Cp-H); ^{13}C NMR (DMSO-d_6) δ 51.81 (CH_3), 63.77 (CH_2), 69.50 (Cp-CH), 70.63 (Cp), 71.46 (Cp-CH), 73.41 (Cp-C), 73.83 (Cp-CH), 85.92 (Cp-C).

(*R*$_p$,*R*$_p$)- and (*S*$_p$,*S*$_p$)-*N*-(2-Bromobenzyl)-3,5-dihydro-4*H*-diferroceno[c,e]azepine (24). Route *A*. Compound **23** (1.26 g, 1.64 mmol), 2-bromobenzylamine hydrochloride (402 mg, 1.8 mmol), triethylamine (222 mg, 2.2 mmol), and anhydrous acetonitrile (20 mL) were mixed in a Schlenk tube. The degassed mixture was refluxed under an argon atmosphere for 9 h. The reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel. Elution with PE/Et_2O/Et_3N (60:1:3) afforded azepine **24** (837 mg, 90%).

Route B. Biferrocene **22** was first methylated in acetonitrile with excess iodomethane using the method described for compound **23**. The resulting yellow solid was used without further purification and was reacted with 2-bromobenzylamine hydrochloride and triethylamine in anhydrous acetonitrile as described for route A. Azepine **24** was isolated in an overall yield of 63%.

(*R*$_p$,*R*$_p$)-**24**: yellow solid; mp 127−129 °C; ^{1}H NMR δ 3.78 (d, 2H, *J* = 15.6 Hz, CH_2), 3.93−3.99 (m, 14H, CH_2 and 10 Cp-H), 3.99 (bm, 2H, Cp-H), 4.11 (t, 2H, *J* = 2.0 Hz, Cp-H), 4.38 (bm, 2H, Cp-H), 7.10−7.14 (m, 1H, Ph), 7.29−7.33 (m, 1H, Ph), 7.53−7.57 (m, 2H, Ph); ^{13}C NMR δ 56.71 (CH_2), 59.30 (CH_2), 65.86 (Cp-CH), 66.35 (Cp-CH), 67.54 (Cp-CH), 69.90 (Cp), 82.46 (Cp-C), 84.88 (Cp-C), 124.47 (Ph-C), 127.17 (Ph-CH), 128.28 (Ph-CH), 130.44 (Ph-CH), 132.75 (Ph-CH), 138.75 (Ph-C); MS (150 °C) *m*/*z* (rel %) = 581/579 (100/90, M^+), 500 (4), 410 (16); $[\alpha]_\lambda^{20}$ = +664 (589 nm), +705 (578 nm), +964 (546 nm), (*c* = 0.55); CD λ_{max} ($\Delta\epsilon$) = 279 nm (16.7), 286 nm (−1.04), 295 nm (−3.92), 341 (4.26), 454 nm (2.50) (*c* = 9.43 × 10^{-4} mol/L). Anal. Calcd for $C_{29}H_{26}Fe_2NBr$: C, 60.04; H, 4.52; N, 2.41. Found: C, 59.45; H, 4.70; N, 2.36.

(*S*$_p$,*S*$_p$)-**24**: yellow solid; mp 127−129 °C; $[\alpha]_\lambda^{20}$ = −660 (589 nm), −699 (578 nm), −949 (546 nm), (*c* = 0.52).

(*R*$_p$,*R*$_p$)-[*N*-(2-Diphenylphosphinobenzyl)-3,5-dihydro-4*H*-diferroceno[c,e]azepine-*N*,*P*] Dichloropalladium(II) (40). A solution of azepine **4** (68.5 mg, 0.1 mmol) in dry benzene (2 mL) was degassed and transferred into a solution of $(CH_3CN)_2PdCl_2$ (24.6 mg, 0.095 mmol) in benzene (2 mL). The mixture was stirred overnight at room temperature under argon. The resulting precipitate was filtered off and dried under vacuum to give complex **40** as a red solid (66 mg, 77%):

mp 165 °C (dec); ^{1}H NMR (250 MHz, CD_2Cl_2, 240 K) δ 3.35 (d, 1H, *J* = 13.0 Hz, CH_2), 3.73 (s, 1H, Cp-H), 3.76 (bs, 5H, Cp-H), 3.85 (d, 1H, *J* = 15.5 Hz, CH_2), 3.97 (s, 5H, Cp-H), 4.07−4.19 (m, 3H, Cp-H and CH_2), 4.28 (s, 1H, Cp-H), 4.56 (bs, 1H, Cp-H), 4.61 (s, 1H, Cp-H), 5.07 (pt, 1H, *J* = 11.5 Hz, CH_2), 5.45 (d, 1H, *J* = 15.3 Hz, CH_2), 6.02 (d, 1H, *J* = 15.3 Hz, CH_2), 6.67 (bs, 1H, Ph), 6.86 (m, 1H, Ph), 7.42−7.90 (m, 12H, Ph); ^{13}C NMR (250 MHz, CD_2Cl_2, 240 K) δ 56.83 (d, *J* = 10.6 Hz, CH_2), 57.85 (CH_2), 63.58 (CH_2), 65.95 (Cp-H), 66.03 (Cp-CH), 66.45 (Cp-CH), 66.60 (Cp-H), 67.36 (Cp-CH), 69.86 (Cp), 70.15 (Cp), 70.38 (Cp-H), 78.27 (Cp-C), 79.66 (Cp-C), 82.15 (Cp-C), 83.26 (Cp-C), 123.94 (d, *J* = 52.6 Hz, Ph-C), 124.51 (d, *J* = 49.8 Hz, Ph-C), 126.84 (d, *J* = 70.4 Hz, Ph-C), 128.09 (d, *J* = 12.6 Hz, Ph-CH), 129.52 (d, *J* = 10.9 Hz, Ph-CH), 129.98 (d, *J* = 9.2 Hz, Ph-CH), 131.23−134.50 (several m, Ph-CH), 138.66 (d, *J* = 15.7 Hz, Ph-C); ^{31}P NMR δ 25.97; MS (FD) *m*/*z* (rel %) = 827.9 (50, M − Cl); $[\alpha]_\lambda^{20}$ = +218 (589 nm), +242 (578 nm), +369 (546 nm), (*c* = 0.12); CD λ_{max} ($\Delta\epsilon$) = 293 nm (8.15), 298 nm (−10.5), 304 nm (74.8), 309 (−25.4), 355 nm (7.58), 456 nm (1.68). (*c* = 9.97 × 10^{-4} mol/L).

X-ray Crystallographic Study of (*R*$_p$,*R*$_p$)-40·3CHCl$_3$. Crystals of **40** suitable for X-ray structure analysis were obtained by evaporation crystallization from $CHCl_3$ in the form of the air-stable solvate (*R*$_p$,*R*$_p$)-**40**·3$CHCl_3$. The compound ($C_{44}H_{39}Cl_{11}Fe_2NPPd$, M_{calcd} = 1219.77) forms orange-red inclined prisms and crystallizes in the acentric and chiral triclinic space group *P*1 (no. 1), *a* = 10.906(6) Å, *b* = 11.205(6) Å, *c* = 11.719(6) Å, α = 103.44(2)°, β = 116.36(2)°, γ = 90.02-(2)°, *V* = 1239.2(11) Å^3, *Z* = 1, D_{calcd} = 1.636 g/m^3, *T* = 295(2) K. A Bruker Smart platform diffractometer with CCD area detector, Mo-Kα radiation, graphite monochromator, and λ = 0.71073 Å was used. A total of 27 190 reflections covering an entire sphere of the reciprocal space with Θ_{max} = 30° were collected, giving 14 014 independent reflections, with correction for absorption with SADABS[19] and R_{int} = 0.021. The structure was solved with direct methods and was refined on F^2 with the program SHELXL97[20] using anisotropic temperature factors for non-hydrogen atoms. Hydrogen atoms were inserted in idealized positions and were refined riding with the atoms to which they were bonded. An orientation disorder of the $CHCl_3$ molecules was taken into account. Final R1 = 0.047 and wR2 = 0.093 with 578 parameters and all 14 014 data, and a residual electron density between −0.34 and 0.44 e Å^{-3}, Flack absolute structure parameter 0.01(2), and chirality of the structure in agreement with the chemistry were found. Selected bond lengths (Å) and angles (deg): Pd−N, 2.145(3); Pd−P, 2.245(2); Pd−Cl2, 2.275(2); Pd−Cl1, 2.397(2); N−Pd−P, 93.2(1); N−Pd−Cl2, 173.1(1); N−Pd−Cl1, 91.0(1); P−Pd−Cl2, 88.8(1); P−Pd−Cl1, 173.2(1); Cl2−Pd−Cl1, 87.7-(1); C22−C21−C31−C32, 14.1(6). Two of the $CHCl_3$ molecules are anchored via clear-cut C−H···Cl hydrogen bonds to Cl1 (Figure 3).

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Supporting Information Available: Experimental details for the synthesis of compounds **5**−**14**, **20**, **21**, **25**−**32**, and **35**−**39**, including spectral and analytical data; experimental details and full lists of catalytic results from the use of ligands **4**−**14**; details on empirical force field calculations and output files for **4** and **40** and their related biaryl derivatives; and listings of full crystallographic data, atomic coordinates, anisotropic temperature factors, bond lengths, bond angles, and least-squares planes for (R_p,R_p)-**40**·3$CHCl_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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