JOC Article

Modular Approach to Novel Chiral Aryl-Ferrocenyl Phosphines by Suzuki Cross-Coupling†

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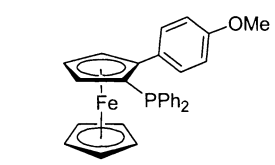
Two novel planar chiral and atropisomeric P,N and P,O aryl-ferrocenyl ligand systems have been developed. The strategy is short and involves a new synthetic approach to aryl-ferrocenyl compounds via a Suzuki cross-coupling procedure. The modular design can easily give access to variety of chiral mono- and bidentate ligands. Two simple derivatives of a novel chiral bidenate P,N ligand belonging to the MOPF family have been synthesized and tested in the enantioselective copper-catalyzed addition of diethyl zinc to an enone and a "difficult" diester. Moderate to excellent yields and enantioselectivities up to 58% were obtained using 1 mol % $Cu(OTf)_2$ and 1.5 mol % chiral ligand.

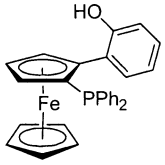
Introduction

The synthesis of custom chiral ligands is a pivotal task for modern asymmetric synthesis. In the course of our study to develop new ligands, we recently envisioned a new chiral pseudobiarylic ligand backbone consisting of a functionalized aryl group attached to a planar chiral ferrocene. The first class of complexes derived from this universal ligand architecture, the aryl-monophosphino ferrocenes (aryl-MOPF ligands), was recently disclosed.[1]

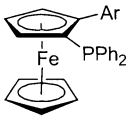
Due to hindered rotation around the biarylic linkage, some of these complexes, in addition to being planar chiral, also exist as atropisomeric entities. Therefore, these novel ligand structures mimic the chirality found in well-known chiral biarylic ligands, e.g., Noyori's BINAP **2**, MOP **3**, and aza-analogue MAP **4** introduced by Hayashi and Kočovský, respectively, and Nozaki's phosphinophosphite ligand Binaphos **5**.[2] However, at the same time, they have the decisive advantage of being modular, e.g., the biarylic backbone can easily be varied by changing the aryl halides in the cross-coupling step in the preparation (see below). This is not possible in the binaphthyl family of ligands.



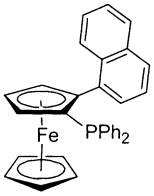
(*S*)-**1a**
p-MeO-phenyl-MOPF



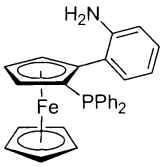
(*S*)-**1c**
o-OH-phenyl-MOPF



1
(*S*)-aryl-MOnoPhosphino-Ferrocene
[(*S*)-aryl-MOPF]



(*S*)-**1b**
1-Naphthyl-MOPF



(*S*)-**1d**
o-NH_2-phenyl-MOPF

In our earlier studies, we have focused on the synthesis of simple nonfunctionalized aryl-MOPF ligands and applied them in ultrafast asymmetric hydrosilylation reactions.[1] In this paper, we present an approach to functionalized aryl-MOPF ligands containing a free

† Part 3 of the series "Synthesis and Application of Aryl-Ferrocenyl (Pseudo-Biarylic) Complexes". For parts 1 and 2, see ref 1.

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|| University of Copenhagen.

(1) (a) Pedersen, H. L.; Johannsen, M. *Chem. Commun.* **1999**, 2517. (b) Pedersen, H. L.; Johannsen, M. *J. Org. Chem.* **2002**, *67*, 7982. See also: (c) Bothe, U.; Rudbeck, H. C.; Tanner, D.; Johannsen, M. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 3305.

(2) BINAP: For the first contribution, see: (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. For reviews and accounts, see, e.g.: (b) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. MOP Ligands: For the first contribution, see: (c) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. For a review and accounts on the use of MOP ligands, see: (d) Hayashi, T. *Acta Chem. Scand.* **1996**, *50*, 259. (e) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354. MAP: For the first contribution, see: (f) Vyskočil, Š.; Smrčina, M.; Hanuš, V.; Polášek, M.; Kočovský, P. *J. Org. Chem.* **1998**, *63*, 7738. BINAPHOS: For the first contribution, see: (g) Sakai, N.; Mano, S.; Nozaki, K. Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033. For an overview, see, e.g.: (h) Breit, B.; Seiche, W. *Synthesis* **2001**, 1.

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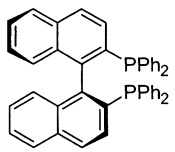
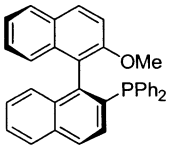
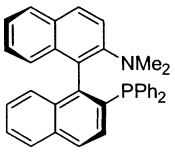


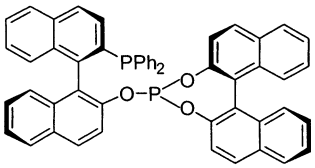
(*S*)-BINAP **2**



(*S*)-MeO-MOP **3**



(*S*)-MAP **4**



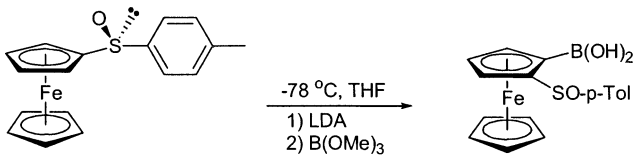
(*R,S*)-BINAPHOS **5**

amino (*S*)-**1c** and hydroxyl groups (*S*)-**1d** available for further manipulations. To accomplish this task, we have discovered that the Suzuki cross- coupling reaction is a highly efficient procedure for synthesizing the aryl-ferrocenyl backbone, giving the desired compounds in good to excellent yields. Furthermore, the first preliminary results using simple derivatives of the parent *o*-NH_2-phenyl-MOPF ligand (*S*)-**1d** in the copper-catalyzed addition of diethylzinc to an unsaturated ketone and a diester substrate are also shown.[3]

Results and Discussion

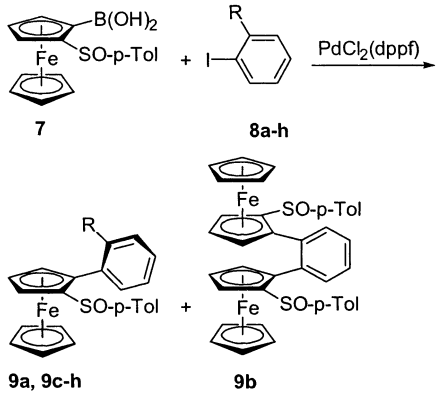
Several efficient methods for the synthesis of chiral 1,2-disubstituted ferrocenes based on diastereoselective ortho lithiation of ferrocenyl derivatives containing chiral ortho directing groups have already been reported.[4] To create a more diverse ligand system, it is necessary to have an interchangeable chiral directing group. With this design consideration, we have chosen the system developed by Kagan et al.[4g] using sulfoxide **6** as starting material. Here, the sulfoxide group is easily interchanged with electrophiles. In previous studies, we applied the palladium-catalyzed Negishi coupling[1] in order to synthezise the ferrocenyl−aryl bond. However, for introducing amino- or hydroxy-substituted arenes, use of the less basic Suzuki conditions[5] seemed to be more appropriate. Ferrocenyl boronic acid **7** was easily prepared by diastereoselective ortho lithiation of the optically pure ferrocenyl sulfoxide **6** with LDA and concomitant trapping of the anion with trimethyl borate. After acidic workup, chiral ferrocenyl boronic acid **7** could be isolated in quantitative yield without the need for further purification.[6]

SCHEME 1. Synthesis of Ferrocenyl Boronic Acid 7



6 **7**

TABLE 1. Suzuki Cross-Coupling between Arylhalogenides and Boronic Acid 7



7 **8a-h** **9a, 9c-h** **9b**

entry[a]	electrophile **8**, R	solvent/temp	product	yield (%)
1	**8a**, Br	DME/85 °C	**9a**:**9b** = 3:1[b]	32
2	**8a**, Br	toluene/110 °C	**9a**	54
3	**8b**, I	toluene/110 °C	**9b**	45
4	**8c**, OH	toluene/110 °C	**9c**	50
5	**8d**, OMe	toluene/110 °C	**9d**	69
6	**8e**, OBn	toluene/110 °C	**9e**	49
7	**8f**, NH_2	toluene/110 °C	**9f**	33
8	**8g**, NHAc	toluene/110 °C	**9g**	85
9	**8h**, NO_2	toluene/110 °C	**9h**	78

[a] Conditions: 5−8 mol % Pd, 3.0 M NaOH (aqueous), reflux 2−6 h. [b] Determined by analysis of the 300 MHz ^{1}H NMR spectrum.

The Suzuki coupling was optimized using 2-bromo iodobenzene as an electrophile. During initial experiments, it was observed that no coupling took place under standard anhydrous coupling conditions using, e.g., Pd(OAc)$_2$, Pd(PPh$_3$)$_4$, or PdCl$_2$(dppf), and bases such as K_2CO_3, K_3PO_4, or K^{t}OBu in different solvents. Only starting material, along with varying amounts of the deborated ferrocene, was isolated. The use of a 3.0 M aqueous solution of sodium hydroxide as a base in DME at 85 °C finally gave the desired coupling product, to our surprise, however, accompanied by the dicoupling product **9b** in a total yield of 32% (entry 1, Table 1). Switching the solvent to toluene gave solely the pure monocoupling product in 54% yield (entry 2, Table 1). Employing 1,2-diiodobenzene as an electrophile in toluene, it was possible to isolate the pure dicoupling product in 45% yield (entry 3, Table 1). With the optimized conditions in hand, it was possible to carry out a range of Suzuki couplings on different sterically hindered ortho-substituted aromatic ethers and amines with moderate to good yields and with complete diastereo- and atroposelectivity, as outlined in entries 4−9, Table 1. No other diastereoisomer or rotamer could be detected according to ^{1}H NMR indicating a de > 98% (vide infra).

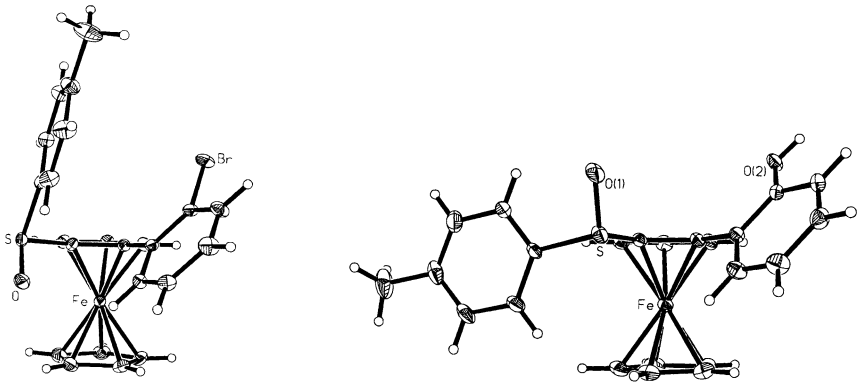
To our knowledge, this is the first reported coupling of aryl halogenides to ferrocene monoboronic acid deriva-

(3) For a recent review, see: Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.

(4) (a) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P. Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389. (b) Riant, O.; Samual, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835. (c) Riant, O.; Samual, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem.* **1997**, *62*, 6733. (d) Ganter, C.; Wagner, T. *Chem. Ber.* **1995**, *128*, 1157. (e) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10. (f) Rebière, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem.* **1993**, *105*, 644. (g) Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511.

(5) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. For review, see: (b) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457. (c) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(6) This compound is shelf stable and can be stored for months without decomposition.



9a **9c**

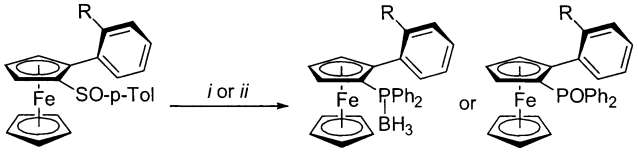
FIGURE 1. View of the two ligand precursors **9a** and **9c**. Displacement ellipsoids are drawn at the 50% probability level.[8]

tives using Suzuki conditions.[7] The coupling procedure can easily be scaled up to, e.g., 10 mmol without loss in yields.

The crystal structures of aryl ferrocenyl sulfoxides **9a** and **9c** show an orientation of the ortho substituents above the upper cyclopentadienyl ring of the ferrocene molecule (Figure 1), indicating a hindered rotation around the biarylic linkage.

To complete the synthesis of the two parental ligand structures, the diphenylphosphino group should be introduced via selective removal of the sulfoxide with *t*-BuLi followed by trapping of the lithiated ferrocenes with Ph_2PCl or alternatively with Ph_2POCl.

TABLE 2. Introduction of Phosphine Substituent on Sulfoxides 9a,d,e,g



9 **10** **11**

entry	substrate **9** − R	electrophile	product **10** or **11**	yield (%)[c]
1[a]	**9a**, Br	Ph_2PCl		none
2[b]	**9a**, Br	Ph_2POCl	**11a**	16
3[a]	**9d**, OMe	Ph_2PCl	**10a**	81
4[b]	**9d**, OMe	Ph_2POCl	**11b**	32
5[a,d]	**9e**, OBn	Ph_2PCl	**10b**	60
6[a]	**9g**, NHAc	Ph_2PCl		none
7[b]	**9g**, NHAc	Ph_2POCl	**11c**	42

[a] (i) *t*-BuLi (1,2−2,5 equiv), −78 °C THF, then Ph_2PCl (1.2−2.5 equiv) in THF, BH_3-THF (2.5 equiv) −78 °C → rt. [b] (ii) *t*-BuLi, −78 °C, THF, then Ph_2POCl in THF, −78 °C → rt. [c] Yields of isolated products after chromatography. [d] Product was fully characterized as the deborated compound (*S*)-**1e**.

The initial reactions using model bromo compound **9a** showed that the diphenylphosphinyl chloride might be the best electrophile for these reactions. No product was isolated using chloro diphenylphosphine as an electrophile, whereas 16% of **11a** was isolated using the more electrophilic phosphinyl chloride (entries 1 and 2, Table 2). Turning the attention to the synthesis of (*S*)-**1c**, the lithiation of **9c** was carried out with an extra equivalent of *t*-BuLi. However, none of the desired product could be isolated and only the sulfoxide cleavage product was isolated. Using the methyl protected analogue **9d** afforded a suitable precursor **10a** for (*S*)-**1c** in good yield (81%) (entry 3, Table 2). Surprisingly, the application of diphenylphosphinyl chloride as an electrophile in this reaction only gave 32% yield of **11b** (entry 4, Table 2). Similarly, the reaction of benzyl ether **9e** gave compound **10b** in good yield using the diphenylphosphine chloride as electrophile (entry 5, Table 2).

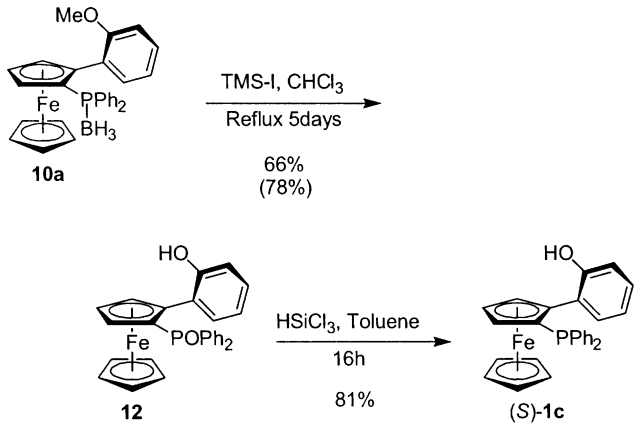
For the synthesis of P,N ligand (*S*)-**1d**, three possible strategies were investigated starting out with the nitrogen-containing compounds **9f**−**h**. Compound **9f**, having a free amino group on the aryl substituent, would again lead directly to (*S*)-**1d**. Once more, trapping the ferrocenyllithium anion(s) with either Ph_2PCl or $Ph_2P(O)Cl$ yielded only the corresponding hydrolyzed product. Compound **9h** with a free nitro group led to a complex addition mixture, which was not analyzed further. Acetamido complex **9g**, however, reacted smoothly with the electrophilic $Ph_2P(O)Cl$ giving diphenylphosphine oxide **11c** in acceptable yield (entry 7, Table 2). The results in entries 6 and 7 (Table 2) are directly opposite to those of entries 3 and 4 (Table 2), showing another balance between the rates of phosphorylation using the more electrophilic $Ph_2P(O)Cl$ and the less sterically hindered phosphorus in Ph_2PCl.

Due to the relatively low yield of **11a**, conversion of this compound into targets (*S*)-**1c** and (*S*)-**1d** was no

(7) Only one reported procedure using ferrocene-1,1′-diboronicacid, see: Knapp, R.; Rehahn, M. *J. Organomet. Chem.* **1993**, *452*, 235.

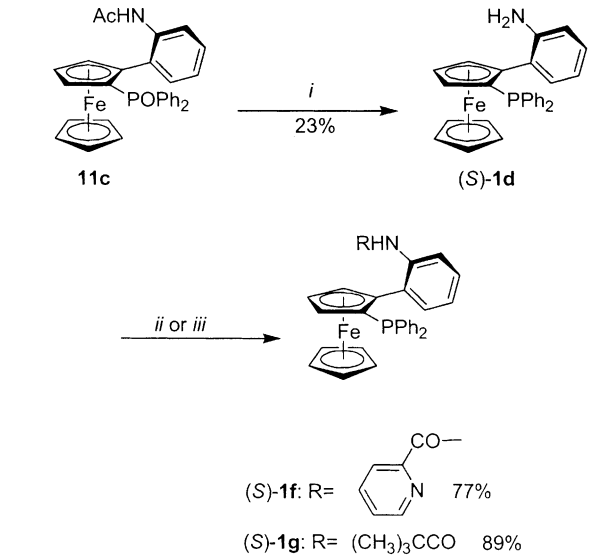
(8) Crystal data for **9a**: orthorhombic, $P2_12_12_1$, a = 7.3980(1) Å, b = 13.8760(1) Å, c = 22.1070(1) Å, V = 2269.39(4) Å^3, Z = 4, D_{calcd} = 1.526 g/cm^3, μ = 2.533 mm^{-1} (Mo Kα), T = 120(2) K, θ range 2.90−35.01, 41 276 reflections, 8430 unique reflections, 7566 observed reflections ($I \geq 2\sigma(I)$), Flack factor = 0.001(7), 307 parameters, $R1(F)$ = 0.0305 (observed data), $wR_2(F^2)$ = 0.0958 (all data), min/max residual electron density = −0.706/0.587 e/Å^3. Crystal data for **9c**: orthorhombic, $P2_12_12_1$, a = 7.9520(3) Å, b = 12.4400(6) Å, c = 19.4130(6) Å, V = 1920.39(13) Å^3, Z = 4, D_{calcd} = 1.440 g/cm^3, μ = 0.909 mm^{-1} (Mo Kα), T = 120(2) K, θ range 2.66−35.04, 51994 reflections, 8452 unique reflections, 8128 observed reflections ($I \geq 2\sigma(I)$), Flack factor = 0.016(8), 244 parameters, $R1(F)$ = 0.0290 (observed data), $wR_2(F^2)$ = 0.0767 (all data), min/max residual electron density = −0.728/0.524 e/Å^3. Crystal data for **12**: monoclinic, $P2_1$, a = 9.009(2) Å, b = 12.086(2) Å, c = 9.979(2) Å, β = 92.45(3)°, V = 1085.52(4) Å^3, Z = 2, D_{calcd} = 1.463 g/cm^3, μ = 0.792 mm^{-1} (Mo Kα), T = 120(2) K, θ range 2.04−29.60, 7628 reflections, 5273 unique reflections, 4739 observed reflections ($I \geq 2\sigma(I)$), Flack factor = −0.023(14), 289 parameters, $R1(F)$ = 0.0392 (observed data), $wR_2(F^2)$ = 0.0935 (all data), min/max residual electron density = −0.337/0.433 e/Å^3.

SCHEME 2. Synthesis of Ligand Precursor (*S*)-1c



longer an attractive strategy. Instead, the syntheses were completed with the other phosphine derivatives. The final steps in the synthesis of (*S*)-**1c** and (*S*)-**1d** now solely involved deprotection and reduction protocols. Cleavage of the methyl ether bond in **10a** with trimethylsilyl iodide was successful; however, the reaction was accompanied by deboration and oxidation of the phosphine, giving **12** in good yields (78% based on recovered starting material) (Scheme 2). The oxidation is presumably caused by iodine, which is generated under the reaction conditions.[9] Standard reduction of phosphine oxide **12** with $HSiCl_3$ gave parent *o*-OH-phenyl-MOPF ligand (*S*)-**1c** in very good yield (Scheme 2). It should be mentioned that other demethylation agents such as BBr_3, BCl_3, and BF_3-Et_2O all were ineffective. Similarly, the hydrogenolysis of **10b** using a palladium on charcoal catalyst was fruitless.

SCHEME 3. Synthesis and Derivatization of Ligand Precursor (*S*)-1d[a]



[a] Reagents and conditions: (i) Toluene, $HSiCl_3$ (13 equiv), Et_3N (22 equiv), reflux 48 h. (ii) DCC (5.0 equiv) 2-picolinic acid (4.0 equiv), CH_2Cl_2 20 °C, 16 h. (iii) $(CH_3)_3CCOCl$ (1.5 equiv), Et_3N (2.2 equiv), CH_2Cl_2 20 °C, 16 h.

The novel *o*-NH_2-phenyl-MOPF ligand (*S*)-**1d** was prepared in a single step from **11c** by reduction of the phosphine oxide and simultaneous cleavage of the acetyl group with $HSiCl_3$, affording (*S*)-**1d** in acceptable yield.

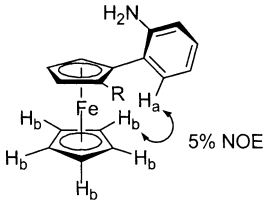
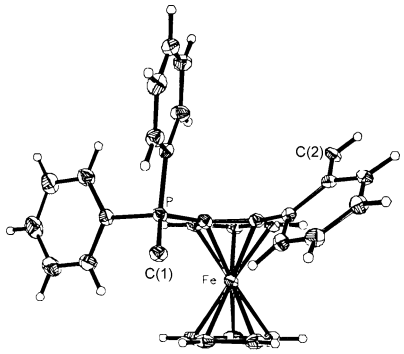


FIGURE 2. NOE study of ligand **1d**.

The amino functionality can easily be derivatized by, e.g., coupling 2-picolinic acid or pivaloyl chloride using standard methods (Scheme 3). These novel compounds (*S*)-**1f** and (*S*)-**1g** are suitable starting points as ligands in asymmetric catalysis (vide infra).[10]

To clarify the conformation of the aryl-ferrocenyl system, we investigated compound (*S*)-**1d** by one- and two-dimensional NMR. ^1H NMR revealed one relatively deshielded proton, which is the arylic ortho proton H_a next to the biarylic linkage (see Figure 2).

A similar deshielding caused by the anisotropy effect from the ferrocene structure was seen in other complexes. A NOE effect of 5% was observed between this proton H_a and the nonsubstituted Cp-ring protons H_b on the ferrocene. The same dipolar interactions were observed in the two-dimensional NOESY spectrum (See Supporting Information). It is also noteworthy that no observable NOE effects were observed between H_a and the substituents on the upper Cp-ring in the NOESY spectrum. These data suggest that the complex exists in a locked conformation in solution with the *ortho*-amino substituent situated above the ferrocene structure, as shown in the drawings. For compound (*S*)-**1c**, we were not able to deduced the orientation of the hydroxy group by two-dimensional NOESY. Instead, a crystal structure of compound **12** was obtained, which confirmed the expected orientation of the hydroxy group above the upper cyclopentadienyl ring (Figure 3).



12

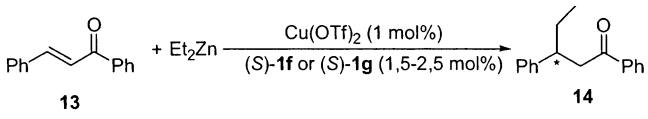
FIGURE 3. Crystal structure of compound **12**. Displacement ellipsoids are drawn at the 50% probability level.[8]

Recently, considerable progress has been achieved in the asymmetric copper-catalyzed conjugate addition of

(9) Iodine is known to oxidize phosphines quite readily. See, e.g.: Han, J. W.; Jang, H. Y.; Chung, Y. K. *Tetrahedron: Asymmetry* **1999**, *10*, 2853.

(10) Katsuki, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto H., Eds.; Springer: New York, 1999.

TABLE 3. Copper-Catalyzed Asymmetric Addition to *trans*-Chalcone 13

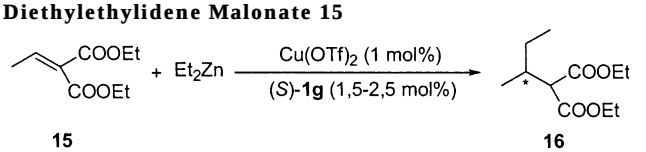


13 14

entry	ligand	solvent	temp	reaction time	yield (%)[d]	ee (%)[e]
1[a]	(*S*)-**1f**	CH_2Cl_2	0 °C	14 h	22	50
2[a]	(*S*)-**1f**	toluene	0 °C	14 h	15	0
3[a]	(*S*)-**1f**	Ph-CF_3	0 °C	24 h	49	43
4[b]	(*S*)-**1g**	toluene	0 °C	24 h	68	58
5[b]	(*S*)-**1g**	CH_2Cl_2	0 °C	20 h	5	8
6[b]	(*S*)-**1g**	toluene	rt	20 h	57	52
7[c]	(*S*)-**1g**	toluene	rt	20 h	95	56

[a] Conditions: 1 mol % $Cu(OTf)_2$, 2.5 mol % ligand (*S*)-**1f**, 1.3 equiv of Et_2Zn. [b] Conditions: 1 mol % $Cu(OTf)_2$, 1.5 mol % ligand (*S*)-**1g**, 1.3 equiv of Et_2Zn. [c] Conditions: 1 mol % $Cu(OTf)_2$, 2.5 mol % ligand (*S*)-**1g**, 1.3 equiv of Et_2Zn. [d] Yields of isolated products after silica gel chromatography. [e] Ee determined by HPLC analysis.

TABLE 4. Copper-Catalyzed Asymmetric Addition to Diethylethylidene Malonate 15



15 16

entry	ligand	solvent	temp	conversion (%)[c]	yield (%)	ee (%)[f]
1[a]	(*S*)-**1g**	toluene	0 °C	>98	56[d]	55
2[a]	(*S*)-**1g**	CH_2Cl_2	0 °C	>98	98[e]	5
3[a]	(*S*)-**1g**	toluene	−20 °C	>98	98[e]	36
4[a]	(*S*)-**1g**	toluene	rt	>98	81[d]	55
5[b]	(*S*)-**1g**	toluene	rt	>98	66[d]	56
6[a]	(*S*)-**1g**	Ph-CF_3	rt	42	nd	53

[a] Conditions: 1 mol % $Cu(OTf)_2$, 1.5 mol % ligand (*S*)-**1g**, 1.3 equiv of Et_2Zn, 14−20 h. [b] Conditions: 1 mol % $Cu(OTf)_2$, 2.5 mol % ligand (*S*)-**1g**, 1.3 equiv of Et_2Zn, 48 h. [c] Determined by ^1H NMR analysis of the crude product. [d] Yields of isolated products after chromatography. [e] Yields of isolated products after standard aqueous workup and concentration in vacuo (purity of >98% according to GC). [f] Ee determined by GC analysis.

diethyl zinc to enones.[3] Pfaltz et al.[11] and Zhang[12] have applied P,N ligand systems in the asymmetric Michael addition, whereas Feringa and co-workers[13] developed the monodentate phosphorus amidite ligands. In all ligand systems, the chirality is based on the C_2-symmetrical axially chiral binaphthalene structure. However, further development in this reaction is still needed in order to extend the scope of the reaction toward synthetically important substrates (vide infra).

With the novel P,N ferrocene ligands (*S*)-**1f** and (*S*)-**1g** in hand, we tested the copper-catalyzed conjugate addition of diethyl zinc to a linear enone system *trans*-chalcone **13** (Table 3). Using 1 mol % $Cu(OTf)_2$ and 1.5−2.5 mol % (*S*)-**1f** or (*S*)-**1g** as a catalyst allowed product **14** to be isolated in moderate to excellent yield and up to 58% ee.

As evident from Table 3, the yield and selectivity in the catalytic reactions are solvent dependent. Ligand (*S*)-**1g** seemed to be the most promising ligand and was further investigated with the more reactive and "difficult" substrate diethylethylidene malonate (Table 4).[14] Enantioselectivities of up to 56% and excellent yields were obtained for product **16**. For both substrates **13** and **15**, the copper:ligand (*S*)-**1g** ratio only had minimal impact on the enantioselectivity. This result compares well with the only successful precedent for asymmetric addition of dialkyl zinc to noncyclic alkylidene malonates.[14]

The results are encouraging, and even higher selectitvities are potentially obtainable through simple optimization of the R-substituent on the amino functionality. Currently, we have no information on the catalytically active species in this reaction, apart from our assumption that the ligands act as bidentate entities.

In conclusion, we have succeeded in developing a novel Suzuki-based coupling procedure for the synthesis of chiral aryl-ferrocenyl compounds. The methodology opens up the construction of complexes with base-sensitive aryl groups due to the low basicity of the Suzuki reagents. Herein, we have presented the synthesis of two parent structures (*S*)-**1c** and (*S*)-**1d**, which can serve as precursors for a range of chiral ligands employing a simple combinatorial approach to ligand synthesis using the free hydroxyl or amino group on the ligands as handles. To illustrate the simple derivatization technique, two simples derivatives (*S*)-**1f** and (*S*)-**1g** were synthesized by standard peptide coupling chemistry. Moreover, the two derivatives have been tested in the asymmetric addition of diethylzinc to a "problematic" substrate, with equal success to other known ligands. We anticipate that by variation of the coupling components, greater selectivities can be obtained.

Experimental Section

General Methods. All reactions were carried out under an atmosphere of either argon or nitrogen in flame- or oven-dried glassware with magnetic stirring. All solvents and reagents were distilled prior to use. THF was distilled from sodium/benzophenone under nitrogen. Dichloromethane and toluene were distilled from CaH_2. *t*-BuLi (1.5 or 1.7 M solution in pentane), *n*-BuLi (1.6 M solution in hexane), BH_3−THF (1 M solution in THF), and $SiHCl_3$ were purchased and used without further purification. Purification of reaction products was carried out by flash chromatography using silica gel (0.040−0.063 mm, 230−400 mesh). Analytical thin-layer chromatography was performed on silica gel plates. Ferrocenes could be seen directly as yellow-brown spots.

^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature in $CDCl_3$. Coupling constants are given in hertz. Enantiomeric purities were determined by GC analysis using a Chrompack Chiralsil-Dex CB Column or analytical high-performance liquid chromatography (HPLC) using a Daicel OD-H column.

Synthesis of (S_P,S_S)-2-(Borono)-1-(*p*-tolylsulfinyl)ferrocene (7). To a stirred suspension of sulfoxide (*S*)-**6** (4.1 g,

(11) (a) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429. (b) Esher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879.

(12) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518.

(13) (a) De Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374. (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.

(14) Products from this reaction could serve as simple precursors for chiral β-branched caroboxylic acids after decarboxylation. Known ligands such as the phosphorus amidites used by Feringa et al.[13] for asymmetric conjugated addition, however, only give low ee in this reaction, e.g., using *O*,*O*′-(*S*)-(1,1′-dinaphthyl-2,2′-diyl)-*N*,*N*′-di-(*R*,*R*)-1-phenylethylphosphoramidate as a ligand and $Cu(OTf)_2$ resulted in 4% ee. For an examination of a range of chiral ligands in this reaction giving up to 65% ee, see: Alexakis, A.; Benhaim, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1151.

12.6 mmol) in THF (130 mL) at −78° C under nitrogen was added LDA (30.3 mL, 0.5 M, 15.2 mmol) dropwise via syringe pump. The resulting orange-red solution was stirred at −78 °C for 30 min before $B(OMe)_3$ (4.25 mL, 37.9 mmol) in THF (10 mL) was added slowly via syringe. After stirring for 20 min at −78 °C, the resulting yellow solution was slowly warmed to room temperature and then diluted with CH_2Cl_2 (100 mL). The organic phase was subsequently washed with saturated NH_4Cl (aqueous) and brine and finally dried over $MgSO_4$. Concentration in vacuo afforded 4.6 g (99%) of pure (S_P,S_S)-**7** as a yellow amorphous powder: $[\alpha]^{20}_D$ +492° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.38 (d, J = 8.5, 2H), 7.19 (d, J = 8.5, 2H), 6.92 (bs, 2H), 4.84 (m, 1H), 4.69 (m, 1H), 4.62 (m, 1H), 4.46 (s, 5H), 2.35 (s, 3H); ^{13}C NMR (75 MHz) δ 141.9, 141.1, 129.8, 124.17, 97.1, 77.6, 73.7, 73.2, 69.9, 70.9 (s, 5C), 69.9, 67.9, 21.3; MS (EI) *m*/*z* 368 [M$^+$]. Anal. Calcd for $C_{17}H_{17}FeBO_3S$: C, 55.48; H, 4.66. Found: C, 55.20; H, 4.96.

General Procedure for Coupling of 2-Substituted Aryliodides. (S_P,S_S)-2-(2-Bromophenyl)-1-(*p*-tolylsulfinyl)ferrocene (9a) (Entry 2, Table 1). To a 250 mL high-necked Schlenk flask were added (S_P,S_S)-**7** (2.27 g, 6.17 mmol), $Pd(dppf)Cl_2$ (361.2 mg, 0.494 mmol), and 2-bromo iodobenzene (2.1 g, 7.42 mmol). The flask was evacuated and flushed with nitrogen three times. Toluene (100 mL) and NaOH (aqueous) (4.1 mL, 3.0 M) were transferred, and the resulting suspension was warmed to 110 °C, giving a homogeneous solution. After 2 h of stirring at 110 °C, the solution was slowly cooled to room temperature and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography on silica gel (2/1 hexane/ethyl acetate), yielding 1.59 g (54%) of (S_P,S_S)-**9a** as a red/yellow amorphous powder. Crystallized from toluene/hexane: $[\alpha]^{20}_D$ +177° (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.18 (m, 1H), 7.38−7.30 (m, 4H), 7.28−7.22 (m, 3H), 4.68 (m, 1H), 4.52 (m, 1H), 4.48 (m, 1H), 4.37 (s, 5H), 2.32 (s, 3H); ^{13}C NMR (75 MHz) δ 140.5, 140.2, 135.6, 135.0, 132.1, 128.9 (s, 2C), 128.7, 126.3, 125.7, 124.3 (s, 2C), 95.2, 89.2, 74.1, 71.1 (s, 5C), 69.6, 68.1, 21.3; MS (EI) *m*/*z* 478 [M$^+$]. Anal. Calcd for $C_{23}H_{19}FeBrOS$: C, 57.65; H, 4.00. Found: C, 57.36; H, 3.94.

(S_P,S_S, S_P,S_S)-1,2-Bis[(*p*-tolylsulfinyl)ferrocenyl]benzene (9b) (Entry 3, Table 1). According to the general procedure, sulfoxide (S_P,S_S, S_P,S_S)-**9b** was obtained as a yellow amorphous powder after flash chromatography, yield 45%: $[\alpha]^{20}_D$ −54° (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.10 (m, 2H), 7.68 (d, J = 8.2, 4H), 7.44 (m, 2H), 7.30 (d, J = 8.2, 4H), 4.10 (s, 10H), 4.09 (m, 2H), 4.03 (m, 2H), 3.82 (m, 2H), 2.45 (s, 6H); ^{13}C NMR (75 MHz) δ 141.0 (s, 2C), 140.4 (s, 2C), 135.3, 133.4, 129.5 (s, 4C), 126.7 (s, 2C), 125.2 (s, 4C), 94.5 (s, 2C), 90.6, 74.1, 70.89 (s, 10C), 68.75 (s, 4C), 66.87 (s, 4C), 21.50 (s, 2C); MS (EI) *m*/*z* 722 [M$^+$]; HRMS (EI) calcd for $C_{40}H_{34}Fe_2O_2S_2$ 722.0699, found 722.0735.

(S_P,S_S)-2-(2-Hydroxyphenyl)-1-(*p*-tolylsulfinyl)ferrocene (9c) (Entry 4, Table 1). According to the general procedure, sulfoxide (S_P,S_S)-**9c** was obtained as a red/yellow amorphous powder after flash chromatography, yield 50%: $[\alpha]^{20}_D$ +452° (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz) δ 9.10 (bs, 1H), 7.18−7.04 (m, 3H), 6.99−6.80 (m, 4H), 6.62 (m, 1H), 4.55 (m, 1H), 4.45 (m, 1H), 4.42 (s, 6H), 2.18 (s, 3H); ^{13}C NMR (75 MHz) δ 154.4, 140.8, 139.2, 133.0, 129.2, 129.1 (s, 2C), 128.2, 125.2, 124.3 (s, 2C), 119.8, 91.8, 83.8, 73.6, 71.4, 71.0 (s, 5C), 68.9, 21.2; MS (EI) *m*/*z* 416 [M$^+$]; HRMS (EI) calcd for $C_{23}H_{20}FeO_2S$ 416.0533, found 416.0526.

(S_P,S_S)-2-(2-Methoxyphenyl)-1-(*p*-tolylsulfinyl)ferrocene (9d) (Entry 5, Table 1). According to the general procedure, sulfoxide **9d** was obtained as a yellow amorphous powder after flash chromatography, yield 69%: $[\alpha]^{20}_D$ −29° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.99 (dd, J = 7.6, 1.8, 1H), 7.61 (d, J = 8.2, 2H), 7.31−7.21 (m, 3H), 7.01 (m, 1H), 6.82 (d, J = 8.2, 1H), 4.74 (m, 1H), 4.41 (m, 1H), 4.20 (m, 1H), 4.15 (s, 5H), 3.70 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz) δ 157.4, 140.8, 140.8, 133.7, 129.0 (s, 2C), 128.7, 125.3 (s, 2C), 123.56, 120.2, 110.9, 93.9, 86.1, 73.8, 70.9 (s, 5C), 68.9, 68.2, 55.4, 21.4; MS (EI) *m*/*z* 430 [M$^+$]. Anal. Calcd for $C_{24}H_{22}FeO_2S$: C, 66.98; H, 5.15. Found: C, 66.77; H, 5.20.

(S_P,S_S)-2-(2-Benzyloxyphenyl)-1-(*p*-tolylsulfinyl)ferrocene (9e) (Entry 6, Table 1). According to the general procedure, sulfoxide **9e** was obtained as a yellow amorphous powder after flash chromatography, yield 49%: $[\alpha]^{20}_D$ +44° (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.09 (dd, J = 7.7, 1.7, 1H), 7.54 (d, J = 8.4, 2H), 7.40−7.15 (m, 8H), 7.06 (m,1H), 6.87 (d, J = 8.4, 1H), 4.87 (m, 2H), 4.80 (m, 1H), 4.41 (m, 1H), 4.23 (m, 1H), 4.14 (s, 5H), 2.38 (s, 3H); ^{13}C NMR (75 MHz) δ 156.7, 140.7, 140.6, 137.1, 134.1, 128.9, 128.6, 128.4 (s, 2C), 127.7, 127.4 (s, 2C), 125.2 (s, 2C), 124.2, 120.7, 112.8, 93.8, 85.8, 77.2, 74.0, 70.9 (s, 5C), 70.6, 68.9, 68.5, 21.4; MS (EI) *m*/*z* 506 [M$^+$]. Anal. Calcd for $C_{30}H_{26}FeO_2S$: C, 71.15; H, 5.17. Found: C, 71.25; H, 5.15.

(S_P,S_S)-2-(2-Aminophenyl)-1-(*p*-tolylsulfinyl)ferrocene (9f) (Entry 7, Table 1). According to the general procedure, sulfoxide **9f** was obtained as a yellow amorphous powder after flash chromatography, yield 33%: $[\alpha]^{20}_D$ +41° (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.78 (m, 1H), 7.63 (m, 2H), 7.29 (m, 2H), 7.14 (m, 1H), 6.84 (m, 1H), 6.63 (m, 1H), 4.61 (m, 1H), 4.47 (m, 1H), 4.24 (m, 6H), 3.71 (bs, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz) δ 146.0, 141.0, 140.2, 133.6, 129.1 (s, 2C), 128.7, 125.1 (s, 2C), 118.5, 117.6, 115.4, 94.4, 88.5, 72.7, 70.7 (s, 5C), 69.1, 67.6, 21.4; MS (EI) *m*/*z* 415 [M$^+$]; HRMS (EI) calcd for $C_{23}H_{21}FeNOS$ 415.0693, found 415.0694.

(S_P,S_S)-2-(2-Acetamidophenyl)-1-(*p*-tolylsulfinyl)ferrocene (9g) (Entry 8, Table 1). According to the general procedure, sulfoxide **9g** was obtained as a yellow amorphous powder after flash chromatography, yield 85%: $[\alpha]^{20}_D$ −151° (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.68 (bs, 1H), 7.11 (dd, J = 8.0, 17.8, 2H), 7.49 (d, J = 8.2, 2H), 7.34 (m, 1H), 7.22 (d, J = 8.2, 2H) 7.16 (m, 1H), 4.47 (m, 1H), 4.43 (m, 1H), 4.35 (s, 5H), 4.23 (m, 1H), 2.40 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz) δ 168.9, 141.6, 139.0, 137.0, 135.8, 133.5, 129.3 (s, 2C), 128.7, 126.7, 125.5, 125.0 (s, 2C), 124.9, 124.4, 93.4, 88.6, 74.1, 70.9 (s, 5C), 69.0, 68.5, 24.1, 21.4; MS (EI) *m*/*z* 519 [M$^+$]. Anal. Calcd for $C_{25}H_{23}FeNO_2S$: C, 65.65; H 5.07; N 3.06. Found: C, 65.68; H, 5.06; N, 3.28.

(S_P,S_S)-2-(2-Nitrophenyl)-1-(*p*-tolylsulfinyl)ferrocene (9h) (Entry 9, Table 1). According to the general procedure, sulfoxide **9h** was obtained as a yellow amorphous powder after flash chromatography on silica gel, yield 78%: $[\alpha]^{20}_D$ +211° (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.43 (dd, J = 1.3, 8.0, 1H), 7.59−7.47 (m, 2H), 7.33 (m, 1H), 7.19 (d, J = 8.6, 2H), 6.99 (d, J = 8.6, 2H), 4.70 (m, 1H), 4.48 (m, 1H), 4.42 (s, 5H), 4.36 (m, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz) δ 150.4, 140.1, 140.1, 136.7, 131.0, 129.7, 128.8 (s, 2C), 128.0, 124.3 (s, 2C), 123.0, 95.0, 85.0, 71.7, 71.4 (s, 5C), 71.2, 69.0, 21.2; MS (EI) *m*/*z* 445 [M$^+$]. Anal. Calcd for $C_{23}H_{19}FeNO_3S$: C, 62.03; H 4.30; N 3.15. Found: C, 61.98; H, 4.32; N, 3.00.

(*S*)-2-(2-Bromophenyl)-1-(diphenylphosphinyl)ferrocene (11a) (Entry 2, Table 2). Compound **11a** was prepared according to the above-described procedure in 16% yield as a yellow amorphous powder: $[\alpha]^{20}_D$ −79° (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.34 (d, J = 7.2 Hz, 1H), 7.79 (m, 2H), 7.58−7.37 (m, 5H), 7.31−7.13 (m, 5H), 6.90 (m, 1H), 4.84 (m, 1H), 4.50 (m, 1H), 4.46 (s, 5H), 4.00 (m, 1H); ^{13}C NMR (75 MHz) δ 136.0, 135.9, 134.2 (d, J_{C-P} = 106.4, 1C), 133.1 (d, J_{C-P} = 107.4, 1C), 131.6, 131.6 (d, J_{C-P} = 3.2, 2C), 131.5 (d, J_{C-P} = 3.8, 2C), 131.3 (d, J_{C-P} = 2.8, 1C), 130.9 (d, J_{C-P} = 2.7, 1C), 128.3, 128.0 (d, J_{C-P} = 12.0, 2C), 127.6 (d, J_{C-P} = 12.4, 2C), 126.3, 125.1, 92.7 (d, J_{C-P} = 10.4, 1C), 75.5 (d, J_{C-P} = 9.4, 1C), 75.5 (d, J_{C-P} = 112, 1C), 74.6 (d, J_{C-P} = 14.6, 1C), 71.2 (s, 5C), 69.2 (d, J_{C-P} = 11.3, 1C); ^{31}P NMR δ 28.26; MS (EI) *m*/*z* 542 [M$^+$]; HRMS (EI) calcd for $C_{28}H_{22}BrFeOP$ 539.9941, found 539.9934.

(*S*)-2-(2-Methoxyphenyl)-1-[diphenylphosphino(borane)]ferrocene (10a) (Entry 3, Table 2). To a stirred solution of sulfoxide **9d** (2.57 g, 5.97 mmol) in THF (30 mL) at −78 °C under nitrogen was added *t*-BuLi (4.6 mL, 1.7 M (hexane), 7.76 mmol, 1.3 equiv) dropwise via syringe. After 5

min of stirring at −78 °C, the deep red solution was treated with Ph_2PCl (1.82 g, 7.76 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h at −78 °C followed by the addition of BH_3−THF (17.9 mL, 1.0 M, 17.9 mmol). After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h before quenching with NaOH (aqueous) (30 mL, 2.0 M). The organic phase was collected and diluted with CH_2Cl_2 (50 mL) and subsequently washed with brine and water and dried ($MgSO_4$). Filtration and concentration in vacuo afforded the crude product, which was purified by flash chromatography on silica gel (97/3 hexane/EtOAc) yielding 2.37 g (81%) of **10a** as a yellow amorphous powder: $[\alpha]^{20}_D$ −39° (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.62 (m, 2H), 7.50−7.27 (m, 7H), 7.24−7.08 (m, 3H), 6.69 (m, 1H), 6.55 (m, 1H), 4.57 (m, 1H), 4.52 (m, 1H), 4.42 (m, 1H), 4.31 (s, 5H), 3.23 (s, 3H) 1.8−0.6 (m, 3H); ^{13}C NMR (75 MHz) δ 157.9, 134.3, 133.1 (d, J_{C-P} = 5.8, 2C), 133.0 (d, J_{C-P} = 6.3, 2C), 131.9 (d, J_{C-P} = 59.2, 1C), 130.5 (d, J_{C-P} = 58.0, 1C), 130.4 (d, J_{C-P} = 2.6, 1C), 130.2 (d, J_{C-P} = 2.6, 1C), 128.6, 127.9 (d, J_{C-P} = 10.5, 2C), 127.8 (d, J_{C-P} = 10.5, 2C), 124.0, 119.5, 109.2, 91.8 (d, J_{C-P} = 9.3, 1C) 76.1 (d, J_{C-P} = 7.3, 1C), 73.9 (d, J_{C-P} = 9.9, 1C), 70.8 (s, 5C), 70.0 (d, J_{C-P} = 7.3, 1C), 69.8 (d, J_{C-P} = 64.4, 1C) 54.2; ^{31}P NMR δ 17.11; HRMS (EI) calcd for $C_{29}H_{28}BFeOP$ 490.1320, found 490.1314. Anal. Calcd for $C_{29}H_{28}BFeOP$: C, 71.06; H, 5.76. Found: C, 70.94; H, 5.62.

(*S*)-2-(2-Methoxyphenyl)-1-(diphenylphosphinyl)ferrocene (11b) (Entry 4, Table 2). Compound **11b** was prepared according to the above-described procedure as a yellow amorphous powder in 32% yield: $[\alpha]^{20}_D$ −57° (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.96 (dd, *J* = 1.7, 7.6, 1H), 7.68 (m, 2H), 7.44−7.30 (m, 5H), 7.17 (m, 1H), 7.06 (m, 2H), 6.96 (m, 1H), 6.73 (m, 1H), 6.45 (d, *J* = 8.3, 1H), 4.63 (m, 1H), 4.39 (m, 1H), 4.30 (s, 5H), 3.99 (m, 1H), 3.41 (s, 3H); ^{13}C NMR (75 MHz) δ 157.1, 134.7 (d, J_{C-P} = 107, 1C), 134.3, 133.8 (d, J_{C-P} = 107, 1C), 131.5 (d, J_{C-P} = 9.6, 2C), 131.4 (d, J_{C-P} = 9.8, 2C), 131.0 (d, J_{C-P} = 2.0, 1C), 130.6 (d, J_{C-P} = 2.0, 1C), 128.2, 127.8 (d, J_{C-P} = 12.0, 2C), 127.4 (d, J_{C-P} = 12.2, 2C), 124.4, 119.7, 109.5, 89.7 (d, J_{C-P} = 10.5, 1C), 75.4 (d, J_{C-P} = 9.4, 1C), 74.1 (d, J_{C-P} = 15.0, 1C), 70.7 (s, 5C), 69.6 (d, J_{C-P} = 10.9, 1C), 54.8 (quart. C_p not observed); ^{31}P NMR δ 29.16; MS (EI) *m*/*z* 492 [M^+]; HRMS (EI) calcd for $C_{29}H_{25}FeO_2P$ 492.0942, found 492.0949.

(*S*)-2-(2-Benzyloxyphenyl)-1-[diphenylphosphino]ferrocene (1e) (Entry 5, Table 2). To a stirred solution of sulfoxide **9e** (0.967 g, 1.91 mmol) in THF (40 mL) at −78 °C under nitrogen was added *t*-BuLi (1.35 mL, 1.7 M, 2.29 mmol, 1.3 equiv) dropwise via syringe. After 5 min of stirring at −78 °C, the deep red solution was treated with Ph_2PCl (1.82 g, 7.76 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h at −78 °C followed by the addition of BH_3−THF (5.7 mL, 1.0 M, 5.73 mmol). After complete addition, the reaction mixture was warmed to room temperature and then stirred for 2 h before quenching with NaOH (aqueous) (30 mL, 2.0 M). The organic phase was collected and diluted with CH_2Cl_2 (50 mL) and subsequently washed with brine and water and dried ($MgSO_4$). Filtration and concentration in vacuo afforded the crude product, which was further purified by flash chromatography on silica gel (97/3 hexane/EtOAc) yielding 644 mg of compound **10b** (60%). The product was immediately deborated with DABCO in toluene (20 mL) to afford 551 mg of **1e**. $[\alpha]^{20}_D$ −134° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.11 (m, 1H), 7.64−7.52 (m, 2H), 7.44−7.27 (m, 8H), 7.19−6.95 (m, 7H), 6.78 (dd, *J* = 1.0, 8.2, 1H), 4.97 (d, *J* = 12.4, 1H), 4.83 (m, 1H), 4.81 (d, *J* = 12.4, 1H), 4.43 (m, 1H), 4.06 (s, 5H), 3.80 (m, 1H); ^{13}C NMR (75 MHz) δ 156.8 (s, 1C), 139.8 (d, J_{C-P} = 11.4, 1C), 138.4 (d, J_{C-P} = 10.3, 1C), 137.5, 135.13 (d, J_{C-P} = 21.8, 2C), 133.9 (d, J_{C-P} = 8.3, 1C), 132.2 (d, J_{C-P} = 17.1, 2C), 128.9, 128.4 (s, 2C), 128.1, 127.0 (d, J_{C-P} = 4.2, 2C), 127.6 (d, J_{C-P} = 5.8, 2C), 127.4, 127.3, 126.6, 126.0, 120.2, 112.3, 90.7 (d, J_{C-P} = 22.9, 1C), 76.9 (d, J_{C-P} = 9.4, 1C), 74.3 (d, J_{C-P} = 3.6, 1C), 70.6 (d, J_{C-P} = 4.2, 1C), 70.2 (s, 5C), 69.9, 69.4; ^{31}P NMR δ −20.65; MS (EI) *m*/*z* 552 [M^+]. Anal. Calcd for $C_{35}H_{29}FeOP$: C, 76.10; H, 5.29. Found: C, 75.81; H, 5.18.

(*S*)-2-(2-Acetamidophenyl)-1-(diphenylphosphinyl)ferrocene (11c) (entry 7, Table 2). In a typical procedure, a stirred solution of sulfoxide **9g** (1.0 g, 2.49 mmol) in THF (150 mL) at −78 °C under nitrogen was added *t*-BuLi (5.9 mL, 1.7 M (hexane), 9.96 mmol, 4.0 equiv) dropwise via syringe. After 5 min of stirring at −78 °C, the deep red solution was treated with Ph_2POCl (1.18 g, 4.98 mmol) dissolved in THF (10 mL). The reaction mixture was stirred for 1 h at −78 °C and then warmed to room temperature before the reaction was quenched with NaOH (aqueous) (30 mL, 2.0 M). The organic phase was collected and diluted with CH_2Cl_2 (50 mL) and subsequently washed with brine and water and dried ($MgSO_4$). Filtration and concentration in vacuo afforded the crude product, which was further purified by flash chromatography on silica gel (1/9 Et_2O/CH_2Cl_2 and 50/48/2 Et_2O/CH_2Cl_2/MeOH) yielding 532 mg (42%) of (*S*)-**11c** as a yellow amorphous powder: $[\alpha]^{20}_D$ −15.4° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 10.54 (bs, 1H), 8.08−7.85 (m, 2H), 7.80−7.63 (m, 3H), 7.63−7.30 (m, 6H), 7.30−7.12 (m, 2H), 6.91 (m, 1H), 4.55 (m, 2H), 4.39 (s, 5H), 3.89 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz) δ 169.3, 135.9, 134.5, 133.6 (d, J_{C-P} = 109, 1C), 132.2 (d, J_{C-P} = 7.8, 1C), 131.9 (d, J_{C-P} = 108, 1C), 132.0 (d, J_{C-P} = 2.7, 1C), 131.7, 131.7 (d, J_{C-P} = 10, 2C), 131.4 (d, J_{C-P} = 10, 2C), 128.2 (d, J_{C-P} = 12.4, 2C) 128.1, 128.1 (d, J_{C-P} = 12, 2C), 127.9 (d, J_{C-P} = 30, 1C), 125.7, 124.0, 90.6 (d, J_{C-P} = 10.4, 1C), 75.4 (d, J_{C-P} = 15.5, 1C), 75.2 (d, J_{C-P} = 9.5, 1C), 70.6 (s, 5C), 70.5 (d, J_{C-P} = 10.9, 1C), 25.22 (s, (*Z*)-amid), 24.61 (s, (*E*)-amid) (quart. C_p not observed); ^{31}P NMR δ 33.98; MS (EI) *m*/*z* 519 [M^+]; HRMS (EI) calcd for $C_{30}H_{26}FeNO_2P$ 519.1051, found 519.1058.

(*S*)-2-(2-Hydroxyphenyl)-1-(diphenylphosphinyl)ferrocene (12). To a stirred solution of **10a** (443 mg, 0.904 mmol) in $CHCl_3$ (45 mL) at room temperature under nitrogen was added TMS-I (361.8 mg, 1.808 mmol) dropwise via syringe. After 5 days of reflux, the reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel (9/1 CH_2Cl_2/Et_2O) yielding 287 mg (66%) of **12** along with 66 mg of recovered **10a**: $[\alpha]^{20}_D$ −50° (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz) δ 10.37 (s, 1H), 7.78−7.72 (m, 2H), 7.65−7.49 (m, 3H), 7.42−7.31 (m, 3H), 7.29−7.20 (m, 2H), 7.14 (m, 2H), 7.07 (dd, *J* = 1.8, 7.8, 1H), 6.72 (dt, *J* = 1.4, 7.4, 1H), 4.64 (m, 1H), 4.52 (m, 1H), 4.41 (s, 5H), 3.82 (m, 1H); ^{13}C NMR (75 MHz) δ 154.8, 133.5, 132.1 (d, J_{C-P} = 2.8, 1C), 132.0 (d, J_{C-P} = 9.9, 2C), 132.0 (d, J_{C-P} = 109.1, 1C), 131.8 (d, J_{C-P} = 109.7, 1C), 131.8 (d, J_{C-P} = 2.6, 1C), 131.5 (d, J_{C-P} = 10.4, 2C), 129.1, 128.2 (d, J_{C-P} = 12.5, 2C), 128.1 (d, J_{C-P} = 12.5, 2C), 124.6, 119.5, 109.2, 89.7 (d, J_{C-P} = 10.4, 1C), 75.4 (d, J_{C-P} = 9.9, 1C), 75.0 (d, J_{C-P} = 16.1, 1C), 70.8 (s, 5C), 70.8 (d, J_{C-P} = 114.8, 1C), 70.7 (d, J_{C-P} = 11.4, 1C); ^{31}P NMR δ 36.69; MS (EI) *m*/*z* 478 [M^+]; HRMS (EI) calcd for $C_{28}H_{23}FeO_2P$ 478.0785, found 478.0790. Anal. Calcd for $C_{28}H_{23}FeO_2P$: C, 70.31; H, 4.85. Found: C, 70.02; H, 4.94.

(*S*)-2-(2-Hydroxyphenyl)-1-(diphenylphosphino)ferrocene ((*S*)-1c). To a stirred solution of **12** (450 mg, 0.942 mmol), Et_3N (2.28 g, 22.58 mmol), and toluene (23 mL) at 0 °C under nitrogen was added $HSiCl_3$ (1.53 g, 11.3 mmol) via syringe. The temperature was raised to 110 °C and maintained for 16 h and then was quenched with NaOH (20 M, 20 mL) and diluted with CH_2Cl_2 (20 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to afford 350 mg (81%) of (*S*)-**1c** as a yellow amorphous powder: $[\alpha]^{20}_D$ −229° (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.66−7.55 (m, 2H), 7.47−7.37 (m, 3H), 7.31 (d, *J* = 2.4, 1H), 7.26−7.09 (m, 7H), 6.95 (dd, *J* = 1.1, 8.1, 1H), 6.75 (ddd, *J* = 1.3, 7.5, 8.8, 1H), 4.66 (m, 1H), 4.56 (m, 1H), 5.15 (s, 5H), 4.09 (m, 1H); ^{13}C NMR (75 MHz) δ 153.4, 139.4 (d, J_{C-P} = 9.3, 1C), 137.4 (d, J_{C-P} = 8.8, 1C), 135.2 (d, J_{C-P} = 21.8, 2C), 132.0 (d, J_{C-P} = 17.6, 2C), 131.9 (d, J_{C-P} = 5.2, 1C), 129.4 (d, J_{C-P} = 1.1, 1C), 128.9, 128.2 (d, J_{C-P} = 10.9, 2C), 128.1 (d, J_{C-P} = 8.3, 2C), 127.9, 121.2, 119.7, 115.9, 88.8 (d, J_{C-P} = 26.9,

1C), 76.4 (d, J_{C-P} = 11.7, 1C), 72.7 (d, J_{C-P} = 4.1, 1C), 71.6 (d, J_{C-P} = 4.2, 1C), 70.8, 70.2 (s, 5C); ^{31}P NMR δ −21.52; MS (EI) *m*/*z* 462 [M$^+$]; HRMS (EI) calcd for $C_{28}H_{23}FeOP$ 462.0836, found 462.0822.

(*S*)-2-(2-Aminophenyl)-1-(diphenylphosphino)ferrocene ((*S*)-1d). To a stirred solution of **11c** (535 mg, 1.03 mmol), Et_3N (2.33 g, 23.1 mmol), and toluene (20 mL) at 0 °C under nitrogen was added $HSiCl_3$ (1.87 g, 13.84 mmol) via syringe. The temperature was raised to 110 °C and maintained for 48 h before the reaction was quenched with NaOH (20 M, 20 mL) and the mixture diluted with CH_2Cl_2 (20 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (1/1 CH_2Cl_2/pentane and then 1/9 Et_2O/CH_2Cl_2) to afford 109 mg (23%) of (*S*)-**1d** as a yellow amorphous powder: $[\alpha]^{20}_D$ −190° (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.73 (dt, *J* = 1.5, 7.6, 1H), 7.56−7.44 (m, 2H), 7.35−7.28 (m, 3H), 7.11−7.97 (m, 5H), 6.93 (m, 1H), 6.67 (ddd, *J* = 1.1, 7.4, 8.7, 1H), 6.45 (dd, *J* = 1.0, 7.9, 1H), 4.60 (m, 1H), 4.38 (m, 1H), 4.04 (s, 5H), 3.84 (m, 1H), 3.68 (bs, 2H); ^{13}C NMR (75 MHz) δ 145.1, 139.7 (d, J_{C-P} = 11.5, 1C), 138.2 (d, J_{C-P} = 10.5, 1C), 135.0 (d, J_{C-P} = 21.3, 2C), 133.5 (d, J_{C-P} = 6.7, 1C), 132.1 (d, J_{C-P} = 18.2, 2C), 128.9 (d, J_{C-P} = 1.1, 1C), 128.0, 127.9 (d, J_{C-P} = 27.6, 2C), 127.8, 127.8 (d, J_{C-P} = 31.6, 2C), 120.7, 120.7, 117.6, 115.0, 92.3 (d, J_{C-P} = 24.9, 1C), 77.4 (d, J_{C-P} = 9.0, 1C), 77.1 (d, overlap with solvent, 1C), 72.0 (d, J_{C-P} = 3.7, 1C), 71.2 (d, J_{C-P} = 4.2, 1C), 70.3 (s, 5C); ^{31}P NMR δ −21.65; MS (EI) *m*/*z* 461 [M$^+$]. Anal. Calcd for $C_{28}H_{24}FeNP$: C, 72.90; H, 5.24; N, 3.04. Found: C, 72.66; H, 5.16; N, 2.92.

(*S*)-2-[2-(*N*-2-Picolinylamino)phenyl]-1-(diphenylphosphino)ferrocene ((*S*)-1f). A suspension of DCC (5 equiv, 241.4 mg, 1.17 mmol), 4-DMAP (10 mol %, 3 mg, 0.0234 mmol), (*S*)-1d (95.1 mg, 0.234 mmol), and 2-picolinic acid (115.1 mg, 0.936 mmol) in CH_2Cl_2 (6 mL) was stirred for 16 h at room temperature under nitrogen. The reaction mixture was subsequently treated with water (2.5 mL) and acetic acid (0.02 mL) and then stirred for an additional 2 h. The solid residue was filtered off and washed with CH_2Cl_2 (10 mL). The combined organic phases were separated and washed with saturated NH_4Cl, dried over $MgSO_4$, and concentrated in vacuo. The yellow residue was further purified by flash chromatography on silica gel (1/1 CH_2Cl_2/pentane and then 1/9 Et_2O/CH_2Cl_2) yielding 101.7 mg (77%) of (*S*)-1f as a yellow amorphous powder: $[\alpha]^{20}_D$ −127° (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz) δ 10.19 (bs, 1H), 8.53 (m, 1H), 8.34 (dd, *J* = 1.4, 8.4, 1H), 8.22 (dt, *J* = 1.0, 8.0, 1H), 8.16 (dt, *J* = 1.6, 7.6, 1H), 7.87 (ddd, *J* = 1.7, 7.7, 9.6, 1H), 7.57−7.49 (m, 2H,), 7.44 (ddd, *J* = 1.2, 4.8, 6.0, 1H), 7.38 (m, 3H), 7.27 (ddd, *J* = 1.8, 7.6, 9.3, 1H), 7.18 (ddd, *J* = 1.4, 7.4, 8.9, 1H), 7.05−7.02 (m, 3H), 6.79 (m, 2H), 4.66 (m, 1H), 4.57 (m, 1H), 4.19 (s, 5H), 3.92 (m, 1H); ^{13}C NMR (75 MHz) δ 161.4, 150.3, 147.8, 138.5 (d, J_{C-P} = 11.5, 1C), 138.2 (d, J_{C-P} = 10.7, 1C), 137.4 (s, 2C), 137.9, 134.6 (d, J_{C-P} = 20.8, 2C), 133.6 (d, J_{C-P} = 6.2, 1C), 132.3 (d, J_{C-P} = 18.8, 2C), 130.1, 128.9, 128.1 (d, J_{C-P} = 7.3, 1C), 128.1, 127.8, 127.6 (d, J_{C-P} = 6.2, 1C), 126.1 (d, J_{C-P} = 1.0, 1C), 126.0, 123.2, 122.2, 119.6, 91.3 (d, J_{C-P} = 23.7, 1C), 79.2 (d, J_{C-P} = 8.9, 1C), 72.8 (d, J_{C-P} = 3.2, 1C), 71.5 (d, J_{C-P} = 4.2, 1C), 70.4 (s, 5C), (quart. C_p not observed); ^{31}P NMR δ −22.41; MS (EI) *m*/*z* 566 [M$^+$]; HRMS (EI) calcd for $C_{34}H_{27}FeN_2OP$ 566.1210, found 566.1220.

(*S*)-2-[2-(*N*-2-Pivaloylamino)phenyl]-1-(diphenylphosphino)ferrocene ((*S*)-1g). A stirred solution of (*S*)-**1d** (210 mg, 0.504 mmol), Et_3N (2.5 equiv, 127.5 mg, 1.26 mmol), and CH_2Cl_2 (10 mL) was treated with pivaloyl chloride (1.5 equiv, 91.3 mg, 0.756 mmol) via syringe at room temperature under nitrogen. After stirring for 16 h at room temperature, the reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Further purification by flash chromatography on silica gel (1/9 Et_2O/CH_2Cl_2) yielded 245 mg (89%) of (*S*)-**1g** as a yellow amorphous powder: $[\alpha]^{20}_D$ −176° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.16 (dt, *J* = 1.8, 7.4, 1H), 8.10 (dd, *J* = 1.7, 8.0, 1H), 7.55 (m, 2H), 7.40 (m, 4H), 7.24−7.05 (m, 5H), 6.99 (m, 2H), 4.55 (m, 2H), 4.18 (s, 5H), 3.94 (m, 1H), 1.16 (m, 9H); ^{13}C NMR (75 MHz) δ 175.7, 138.6 (d, J_{C-P} = 11.9, 1C), 137.5 (d, J_{C-P} = 10.4, 1C), 137.0, 134.5 (d, J_{C-P} = 20.8, 2C), 133.5 (d, J_{C-P} = 6.7, 1C), 132.1 (d, J_{C-P} = 19.2, 2C), 128.2 (d, J_{C-P} = 7.3, 1C), 128.1, 128.00, 127.9 (d, J_{C-P} = 6.3, 1C), 125.3 (d, J_{C-P} = 1.1, 1C), 122.9, 120.1, 91.0 (d, J_{C-P} = 24, 1C), 79.4 (d, J_{C-P} = 10.5, 1C), 71.8 (d, J_{C-P} = 3.2, 1C), 71.6 (d, J_{C-P} = 4.7, 1C), 70.7 (s, 5C), 39.7, 27.6 (s, 3C); ^{31}P NMR δ −22.82; MS (EI) *m*/*z* 546 [M$^+$]; HRMS (EI) calcd for $C_{33}H_{32}FeNOP$ 545.1571, found 545.1554.

General Procedure for Asymmetric 1,4-Conjugate Addition (Entry 7, Table 3). A solution of $Cu(OTf)_2$ (1 mol %, 1.4 mg, 3.83 μmol), ligand (*S*)-**1g** (2.5 mol %, 5.3 mg, 9.58 μmol), and toluene (2 mL) was stirred at room temperature for 0.5 h in a Schlenk tube under nitrogen. The catalyst solution was cooled to 0 °C and then treated with Et_2Zn (498 μL, 0.498 mmol, 1.0 M) dropwise via syringe. After 30 min of stirring at 0 °C, the catalyst system was treated with a solution of *trans*-chalcone **13** (79.8 mg, 0.383 mmol, 1.0 equiv) in toluene (1.3 mL) at 0 °C. The temperature was raised to room temperature; the reaction mixture was stirred for 20 h, and then quenched with saturated NH_4Cl. Dilution with Et_2O, separation of the phases, and subsequently extraction of the water phase with Et_2O followed by drying ($MgSO_4$), filtration, and concentration in vacuo afforded a light yellow residue. The residue was purified by flash chromatography on silica gel to afford 86.6 mg (95%) of 1,3-diphenyl-pentan-1-one **14**. Determination of enantiomeric excess of 1,3-diphenyl-pentan-1-one **14**[15] was carried out by HPLC with a chiralpak AD, 1/99 2-PrOH/hexane, and that of 2-*sec*-butyl malonic acid diethyl ester **16** was carried out on a GC apparatus equipped with a Chrompack Chiralsil-Dex CB Column.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **1c**, **1f**, **1g**, **9b**, **9c**, **9f**, and **11a**−**c** as well as two-dimensional NOESY spectrum of **1d** and X-ray crystal structure data for **9a**, **9c**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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