Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 116–123

Ferrocenyl-QUINAP: a planar chiral *P*,*N*-ligand for palladium-catalyzed allylic substitution reactions

Ralf J. Kloetzing and Paul Knochel*

Department of Chemistry and Biochemistry, Ludwig-Maximilians-University, Butenandtstrasse 5-13, 81377 Munich, Germany

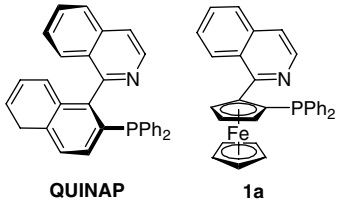
Received 2 November 2005; accepted 1 December 2005

Abstract—The new planar chiral *P*,*N*-ligands **1a** and **1b** were prepared via a straightforward enantioselective synthesis using a Negishi cross-coupling and a sulfoxide/lithium exchange. Ligand **1a** was successfully applied to Pd-catalyzed allylic alkylation (86% ee) and amination (83% ee) reactions.

1. Introduction

Enantioselective synthesis using metal complexes with chiral ligands has been a growing field of interest in organic chemistry over the past decades.[1] *P*,*N*-Ligands are the most widely used heterodentate ligands,[2] and they can be classified according to their elements of chirality.[2b] Various ligands with central,[3] axial,[4] and planar[5] chirality have been reported. A ferrocene scaffold allows a unique combination of planar and central chirality.[6] However, in many cases the configuration of the stereogenic center in the side chain directs the configuration of the planar chirality. Thus, these elements of chirality cannot be varied independently. Herein, we have designed a new planar chiral ferrocene-based *P*,*N*-ligand **1a**, which only possesses a plane of chirality. This allows us to look at the effect of the planar chirality on the performance of ferrocenyl ligands without the interference of a stereogenic center in the side chain. The structure of this planar chiral 1,2-disubstituted ferrocenyl ligand **1a** is related to the axial chiral QUINAP ligand,[7] which is one of the most successful *P*,*N*-ligands and has found widespread application in asymmetric catalysis (Scheme 1).[8] For example, QUINAP is an excellent ligand for the copper-catalyzed enantioselective three-component synthesis of chiral propargyl amines which was recently developed in our laboratory (Scheme 2).[9]

A drawback for the use of QUINAP is its difficult resolution via diastereomeric Pd-complexes.[7a] Recently,



Scheme 1. Design of the new ligand.

Carreira has reported a readily available diastereomeric biaryl *P*,*N*-ligands (PINAP), which can replace QUINAP for several applications including the synthesis of propargyl amines described above.[4a]

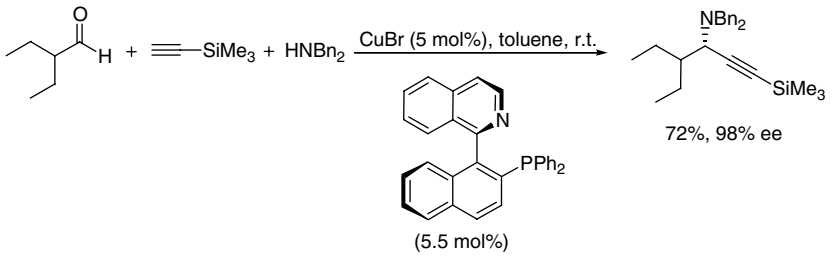
Herein, we report the synthesis of a new *P*,*N*-ligand **1a** as a QUINAP analogue bearing a plane of chirality instead of an axis of chirality. As an advantage, we expect that the planar chiral ferrocene exhibits a higher stability toward racemization and should therefore be configurationally stable. Furthermore, this approach allows a stereoselective synthesis avoiding resolution processes. It has recently been shown that a planar chiral ferrocenyl diphosphine can serve as a BINAP analogue as it forms axially chiral complexes upon complexation to transition metals.[10]

2. Synthesis

The new *P*,*N*-ligand **1a** was readily prepared by a straightforward enantioselective synthesis using Kagan's sulfoxide[11] **2**. It offers a general possibility of controlling

* Corresponding author. Tel.: +49 (0)89 2180 77681; fax: +49 (0)89 2180 77680; e-mail: paul.knochel@cup.uni-muenchen.de

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.12.001



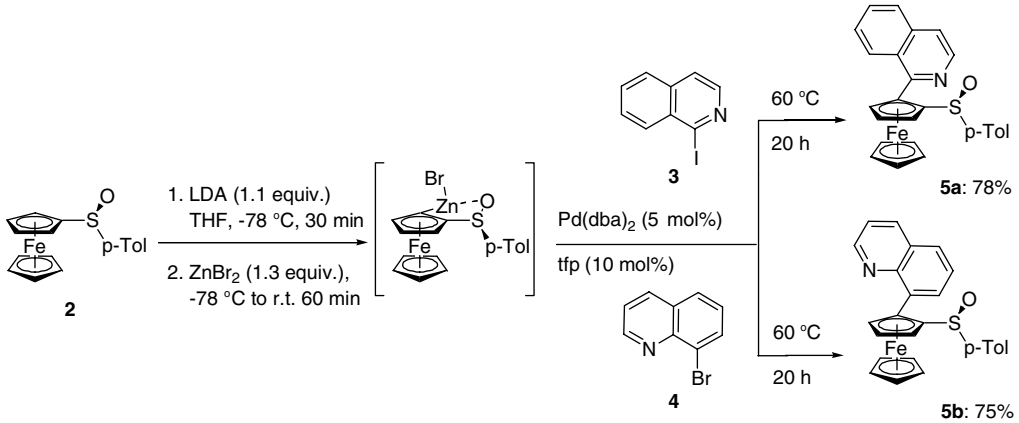
Scheme 2. Application of QUINAP: enantioselective three-component synthesis of propargyl amines.

the planar chirality of 1,2-disubstituted ferrocenes by a directed *ortho*-lithiation with LDA, which proceeds with 98% de.[12] The resulting ferrocenyllithium was transmetalated to zinc and a subsequent Negishi cross-coupling[13] with 1-iodoisoquinoline[14] **3** furnished intermediate **5a** in 78% yield (Scheme 3). Similarly, ferrocenyl sulfoxide **5b** was prepared using 8-bromoquinoline[15] **4** in 79% yield.

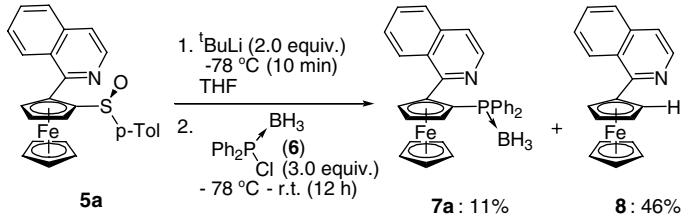
We thought to use a sulfoxide/lithium exchange for further functionalization of the ferrocenes **5a** and **5b**. Usually, *tert*-butyllithium is used for this exchange reaction giving complete conversion after 10 min at −78 °C.[16] However, the reaction of sulfoxide **5a** with *tert*-butyllithium gave only minimal amounts of product **7a** due to the formation of 1-ferrocenylisoquinoline **8** as a by-product (Scheme 4).

To optimize the sulfoxide/lithium exchange on *ortho*-substituted ferrocenyl sulfoxides, we have examined various reaction conditions and used several lithium reagents for performing the sulfoxide/lithium exchange on the chiral sulfoxide **9** using iodine as electrophile (Scheme 5).

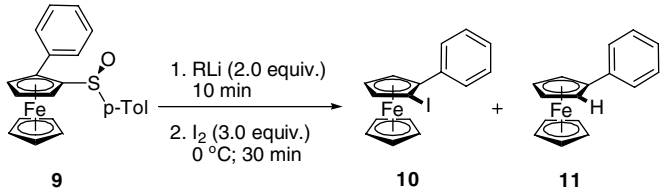
Table 1 shows that the ratio of the desired product **10** and the protonated by-product **11** obtained after sulfoxide/lithium exchange with *tert*-butyllithium is highly dependent on the temperature. While at −90 °C (entry 1) an unfavorable ratio was obtained, with the results improving when the temperature was raised to −30 °C leading to a ratio of 95:5 (entry 3). At a higher temperature (0 °C, entry 4), a larger amount of protonated by-product **11** was formed. Interestingly, an acceptable ratio of the desired product and protonated by-product was obtained, if the reaction was performed with an inverse addition at −78 and −50 °C (entries 5 and 6). Further lithium reagents were tested for this reaction. Very unfavorable results were obtained with *n*-butyllithium (entry 7), due to the acidic protons in the resulting sulfoxide. By using phenyllithium, the reaction proceeded unexpectedly well (entry 8). Sulfoxide **9** was converted to the lithium-reagent within 10 min at −78 °C and the desired product **10** was obtained in 87% yield



Scheme 3. *ortho*-Lithiation of sulfoxide **2** and cross-coupling.



Scheme 4. Sulfoxide/lithium exchange with isoquinoline derivative **5a**.



Scheme 5. Optimization of the sulfoxide/lithium exchange.

Table 1. Sulfoxide/lithium exchange with *t*-BuLi

Entry	RLi	Temperature (°C)	Addition	**10**:**11**[a]	Yield of **10** (%)
1	*t*-BuLi	−90	Normal	85:15	73
2	*t*-BuLi	−60	Normal	93:7	83
3	*t*-BuLi	−30	Normal	95:5	86
4	*t*-BuLi	0	Normal	43:57	—
5	*t*-BuLi	−78	Inverse	94:6	75
6	*t*-BuLi	−50	Inverse	93:7	79
7	*n*-Bu	−78	Inverse	50:50	44
8	PhLi	−78	Inverse	95:5	87

[a] Determined by ^{1}H NMR.

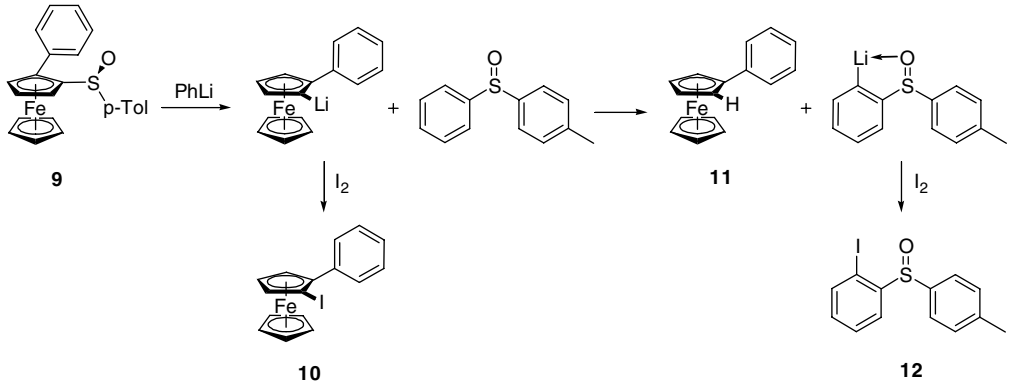
along with the formation of only 5% of the protonated by-product **11**. The competitive deprotonation of the resulting *p*-tolyl phenyl sulfoxide at the *ortho*-position may be responsible for the formation of this by-product (Scheme 6).

The isolation of iodosulfoxide **12** could not be accomplished. Instead of *p*-tolyl iodophenyl sulfoxide **12**, a statistical mixture of iodides of diphenyl sulfoxide, *p*-tolyl phenyl sulfoxide and di-*p*-tolyl sulfoxide was found. These sulfoxides were formed by sulfoxide/lithium exchange with excess phenyllithium. Thus, *p*-tolyllithium was used to perform the sulfoxide/lithium exchange on chiral sulfoxide **9**. The reaction mixture was warmed up to 0 °C and the protonated product **11** isolated in quantitative yield. The iodosulfoxide **13** was isolated from the reaction mixture and ^{1}H NMR spectroscopic analysis confirmed the *ortho*-substitution (Scheme 7).

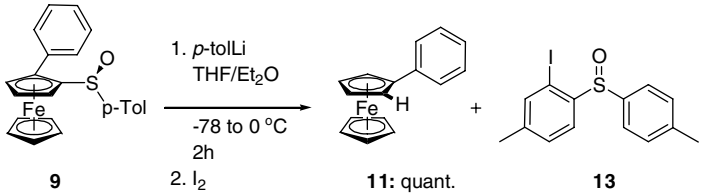
In summary, these experiments on the sulfoxide/lithium exchange with chiral sulfoxide **9** could show that the high reactivity of the resulting sulfoxides for *ortho*-lithiation can cause the undesired formation of the protonated by-product **11**.

The sulfoxide/lithium exchange and the subsequent reaction with iodine proceeds with complete retention of configuration concerning the planar chirality. This was proven by the iodine/lithium exchange on iodide **10** and reaction with paraformaldehyde (Scheme 8). The enantiomers of the resulting alcohol **14** were separated by HPLC.[17] The enantiomeric excess was determined to be 99%.

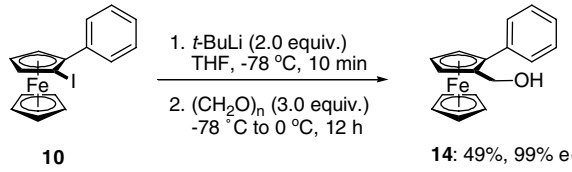
Applying these findings to isoquinoline derivative **5a**, it was shown that phenyllithium is the appropriate reagent for the sulfoxide/lithium exchange on heterocyclic substrates (Scheme 9).



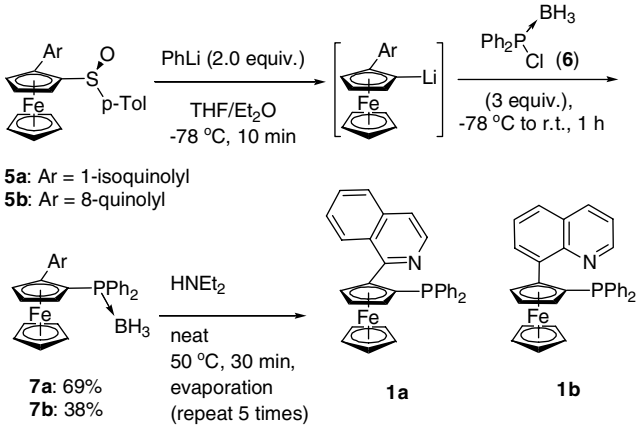
Scheme 6. Formation of the protonated by-product **11**.



Scheme 7. Proton source for the formation of the protonated by-product **11**.



Scheme 8. Synthesis of alcohol **12** for demonstration of enantiomeric purity.

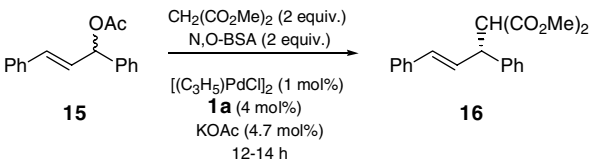


Scheme 9. Synthesis of the borane complexes **7a** and **7b** via the optimized sulfoxide/lithium exchange and deprotection.

The resulting lithium compound was reacted with $Ph_2PCl{\cdot}BH_3$ **6**. The reaction with this electrophile is faster and more efficient compared to the unprotected chlorodiphenylphosphine. Thus, product **7a** was isolated in 69% yield. Similarly, the reaction of ferrocene **5b** leads to borane complex **7b** in 38% yield. The stable borane protected *P*,*N*-ligands **7a** and **7b** can be handled in air and purified by conventional column chromatography. The borane complexes **7a** and **7b** were deprotected by treatment with diethylamine[18] giving the ligands **1a** and **1b** in pure form and quantitative yield. ^{1}H NMR experiments at various temperatures were performed with ligand **1a** and the borane-complex **7a**. No coalescence was observed over a broad range of temperature (+100 to −80 °C) in DMSO-d_6 or acetone-d_6.

3. Catalysis

We herein report the results obtained with ligand **1a** in preliminary experiments on the Pd-catalyzed allylic substitution. The reaction was performed with 1,3-diphenylallyl acetate **15** under standard Trost[19] conditions. The catalyst was preformed in situ from allylpalladium(II) chloride dimer as Pd-precursor (1 mol %) and ligand **1a** (4 mol %) giving a ligand/Pd ratio of 2:1 (Scheme 10).



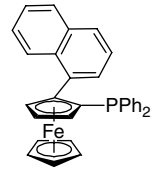
Scheme 10. Allylic alkylation with ligand **1a**.

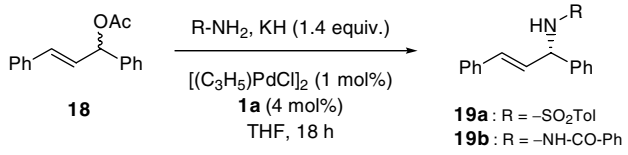
Table 2. Pd-catalyzed allylic alkylation with ligand **1a**

Entry	Solvent	*T* (°C)	Ligand (mol %)	Yield[a] (%)	Enantioselectivity[b] (% ee)
1	CH_2Cl_2	22	4.0	49	69
2	CH_2Cl_2/toluene 1:3	22	4.0	59	73
3	Toluene	22	4.0	99	86
4	Toluene/*n*-hexane 3:2	22	4.0	91	56
5	THF	22	4.0	94	59
6	Toluene	0	4.0	29	84
7	Toluene	22	2.0	88	72

[a] Isolated yield after purification by column chromatography.
[b] Determined by HPLC (Daicel Chiralcel OD-H).

Table 2 shows the important influence of the solvent on the selectivity of the catalyst. Ligand **1a** gave moderate enantioselectivity and low conversion in CH_2Cl_2. Both selectivity and reactivity were increased by using a mixture of CH_2Cl_2 and toluene. The best results were obtained in pure toluene (entry 3, 99%, 86% ee) showing the adverse effect of chlorinated solvents on ligand **1a**. Reducing the solvent polarity by adding *n*-hexane lowered the catalyst solubility. In a toluene/*n*-hexane mixture 3:2, the catalyst was still soluble but gave low enantioselectivity (entry 4). In THF, the catalyst is less selective than in toluene (entry 5). Low reaction temperature reduced the catalyst activity substantially, but the selectivity remained almost unchanged (entry 6). With a ligand load of 2 mol % instead of the previously used 4 mol % and a ligand/Pd ratio of 1:1, the product was obtained only with a moderate enantiomeric excess (entry 7). Pd-black precipitated during the reaction, indicating that a stable catalytic system is only formed with a ligand/Pd ratio of 2:1. This result could indicate that ligand **1a** acts as a monodentate ligand without participation of the nitrogen donor. Monophosphine **17**[16c] was therefore used for the performance of the allylic alkylation under the same reaction conditions (Scheme 10, toluene, 22 °C). However, no conversion was observed with monophosphine **17** indicating that the nitrogen donor is important for the formation of an active catalyst. Ligand **1a** was also employed for the Pd-catalyzed allylic amination (Scheme 11).





Scheme 11. Allylic amination with ligand **1a**.

Table 3. Pd-catalyzed allylic amination

Entry	–R	*T* (°C)	Yield[a] (%)	Enantioselectivity[b] (% ee)
1	$-SO_2Tol$	22	15	71
2		40	83	77
3	–NH–CO–Ph	22	77	57
4		40	80	83

[a] Isolated yield after purification by column chromatography.
[b] Enantioselectivity determined by HPLC (Daicel Chiralcel OD), (+)-enantiomer for both substrates.

Table 3 shows the results of allylic aminations yielding amines **19a** and **19b** at different temperatures. As for the allylic alkylation, the catalyst displays a higher selectivity and better reactivity at elevated temperature. The differences in reactivity are less remarkable for the more nucleophilic reagent benzoyl hydrazine (entries 3 and 4) giving allyl hydrazone **19b**.

4. Conclusion

In conclusion, we have reported the straightforward synthesis of the new planar chiral *P*,*N*-ligands **1a** and **1b**. We optimized the sulfoxide/lithium exchange by using PhLi as a more selective reagent. Ligand **1a** was used in Pd-catalyzed allylic substitution reactions. The allylic alkylation proceeds with quantitative yield and 86% ee. The enantioselectivity with QUINAP was higher (98% ee)[7a] thus illustrating the unpredictable nature of ligand design. The allylic amination with two different nucleophiles gave 77% and 83% ee. Remarkably, the Pd-catalyst with ligand **1a** is more efficient and selective at higher temperature. Further experiments extending the scope of the *P*,*N*-ligands to other transition metal catalyzed reactions are currently underway in our laboratories.

5. Experimental

All reactions were carried out under argon using standard Schlenk techniques. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 or AMX 600 instrument. ^{31}P NMR spectra were recorded on a VARIAN Mercury 200 instrument. Chemical shifts (δ) are given as ppm relative to the residual solvent peak. IR spectra were recorded on a PERKIN ELMER 1420 Infrared Spectrometer. Mass spectra were recorded on a FINNIGAN MAT 95 Q spectrometer. Optical rotations were measured on a PERKIN ELMER 241 polarimeter. Column chromatography was performed on MERCK silica gel 60 (230–400 mesh ASTM). Enantiomeric excesses were determined by HPLC. Chiralcel OD-H and OD (Daicel Chemical Industries) columns were used with *n*-heptane/*i*-propanol as a mobile phase and detection by a diode array UV–vis detector at 214 nm. BuLi was titrated prior to use according to the method of Paquette.[20] $ZnBr_2$ was used as 1.7 M solution prepared by drying $ZnBr_2$ (3.78 g, 15.0 mmol) under vacuum for 6 h at 140 °C and dissolving the cold salt in dry THF (8.8 mL). THF and diethyl ether were dried with sodium/benzophenone, toluene was dried with sodium, and dichloromethane was dried with CaH_2 and distilled.

5.1. Diasteroselective *ortho*-lithiation and cross-coupling

5.1.1. (S_{Fc},*S*)-[2-(1-Isoquinolinyl)-ferrocen-1-yl]-*p*-tolylsulfoxide 5a. Sulfoxide **2** (1.95 g, 6.00 mmol) in THF (60 mL) was cooled to −78 °C. LDA (6.60 mmol) was added and the mixture stirred for 30 min at −78 °C. A solution of $ZnBr_2$ in THF (1.7 M, 7.80 mmol) was added. It was warmed up to 22 °C and stirred for 1 h. The solvent was removed under reduced pressure. For the cross-coupling reaction, bis(dibenzylideneacetone)palladium(0) (173 mg, 0.30 mmol), tris-*o*-furylphosphine (139 mg, 0.60 mmol) and 1-iodoisoquinoline (2.14 g, 8.40 mmol) in THF (10 mL) were stirred for 5 min at 22 °C. The above prepared zinc reagent was added in THF (25 mL). The mixture was heated to 60 °C for 20 h. After the addition of satd NH_4Cl soln, the mixture was extracted with diethyl ether (150 mL). The organic layer was washed with water and brine and dried over $MgSO_4$. Purification by flash chromatography (*n*-pentane/diethyl ether 2:1, 1% triethylamine) afforded the sulfoxide **5a** as red solid (78%, 2.11 g, 4.67 mmol). Mp: 79–81 °C. $[\alpha]_D = +131.3$ (*c* 0.34, THF). Mp: 79–81 °C IR: (KBr): $\tilde{\nu} = 3051$ (w), 2922 (w), 1623 (m), 1343 (w), 1038 (m), 823 (m) cm^{-1}. ^1H NMR: (300 MHz, C_6D_6): δ 8.77 (d, $J = 5.6$ Hz, 1H), 8.06 (d, $^3J = 8.1$ Hz, 1H), 7.88 (d, $^3J = 8.0$ Hz, 2H), 7.50 (d, $^3J = 8.1$ Hz, 1H), 7.36–7.25 (m, 2H), 7.22–7.13 (m, 1H), 6.94 (d, $^3J = 8.0$ Hz, 2H), 4.57 (dd, $^3J = 2.6$ Hz, $^4J = 1.3$ Hz, 1H), 4.32 (s, 5H), 4.28 (dd, $^3J = 2.6$ Hz, $^4J = 1.3$ Hz, 1H), 4.17 (dd, $^3J = 2.6$ Hz, 1H), 2.10 (s, 3H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 156.0, 142.0 (CH), 141.3, 141.0, 136.3, 129.6 (CH), 129.2 (CH), 128.1, 127.0 (CH), 126.9 (CH), 126.8 (CH), 125.6 (CH), 119.7 (CH), 97.1, 87.7, 72.8 (CH), 71.5 (CH), 69.0 (CH), 68.4 (CH), 21.4 (CH_3). EI MS: (70 eV): *m*/*z* (%) = 451 (14) [M^+], 435 (100) [M^+−O], 312 (73), 279 (19). HR EI MS: for $^{12}C_{26}{}^1H_{21}{}^{56}Fe\,{}^{14}N{}^{32}S{}^{16}O$: calcd: 451.0693, found: 451.0694.

5.1.2. (S_{Fc},*S*)-[2-(8-Quinolinyl)-ferrocen-1-yl]-*p*-tolylsulfoxide 5b. Prepared according to the procedure described above (Section 5.1.1) from sulfoxide **2** (486 mg, 1.50 mmol) in THF (15 mL), LDA (1.65 mmol), and $ZnBr_2$ in THF (1.7 M, 1.15 mmol). For the cross-coupling reaction, bis(dibenzylideneacetone)palladium(0) (43.1 mg, 0.075 mmol), tris-*o*-furylphosphine (34.8 mg, 0.150 mmol) and 8-bromoquinoline (437 mg, 2.10 mmol) in THF (2.5 mL), and the above prepared zinc reagent THF (6 mL) were used. Purification by flash chromatography (*n*-pentane/diethyl ether 2:1) afforded sulfoxide **5b** as a red solid (75%, 511 mg, 1.13 mmol). $[\alpha]_D = +360.9$ (*c* 0.44, THF). Mp: 195–197 °C (decomp.) IR: (KBr): $\tilde{\nu} = 3085$ (w), 3046 (w), 1636 (m), 1611 (m), 1596 (m), 1496 (m), 1042 (s), 826 (s), 801 (s), 494 (s) cm^{-1}. ^1H NMR: (600 MHz, C_6D_6): δ 9.15 (d, $J = 7.4$ Hz, 1H), 8.69–8.64 (m, 1H), 7.57 (d, $J = 9.7$ Hz, 1H), 7.53 (d, $J = 7.9$ Hz, 2H), 7.51–7.46 (m, 1H), 7.42 (d, $J = 8.1$ Hz, 1H), 6.82–6.77 (m, 1H), 6.66 (d, $J = 7.9$ Hz, 2H), 5.33–5.28 (m, 1H), 4.53–4.49 (m, 1H), 4.34 (s, 5H), 4.33–4.30 (m, 1H), 1.86 (s, 3H).

^{13}C NMR: (151 MHz, C_6D_6): δ 149.0 (CH), 147.3, 142.4, 139.2, 135.7 (CH), 135.2, 134.9 (CH), 128.6 (CH), 128.3, 127.5 (CH), 126.1 (CH), 125.1 (CH), 120.4 (CH), 96.2, 86.7, 76.5 (CH), 71.5 (CH), 70.9 (CH), 68.9 (CH), 20.8 (CH_3). EI MS: (70 eV): m/z (%) = 451 (18) [M^+], 435 (100) [M^+−O], 370 (74), 312 (54), 191 (31). HR EI MS: for $^{12}C_{26}{}^{1}H_{21}{}^{56}Fe{}^{14}N{}^{32}S{}^{16}O$: calcd: 451.0693, found: 451.0675.

5.2. Sulfoxide–lithium exchange

5.2.1. (S_{Fc})-1-Iodo-2-phenylferrocene (optimized procedure) 10. A pre-cooled solution of sulfoxide **9** (120 mg, 0.300 mmol) in THF (3 mL) was added to a solution of PhLi in diethyl ether (0.60 mmol)[21] at −78 °C. After 10 min, a solution of iodine (228 mg, 0.90 mmol) in THF (3 mL) was added and the mixture was warmed to rt. After 10 min, a satd soln of $Na_2S_2O_3$ was added. The mixture was extracted with diethyl ether. The combined organic phases were washed with brine and dried over $MgSO_4$. Purification by flash chromatography (*n*-pentane/diethyl ether 100:3) afforded iodide **10** (101 mg, 0.26 mmol, 87%) as an inseparable mixture with phenylferrocene **11** (3.4 mg, 0.013 mmol). The ratio was determined by ^{1}H NMR. $[\alpha]_D = -6.9$ (*c* 0.64, acetone). IR: (KBr): $\tilde{\nu}$ = 3090 (m), 3056 (m), 2921 (m), 1602 (m), 1107 (m), 904 (s), 822 (s), 762 (s), 698 (s), 546 (m), 499 (m) cm^{-1}. ^{1}H NMR: (300 MHz, C_6D_6): Iodide **10**: δ 7.73–7.67 (m, 2H), 7.19–7.05 (m, 3H), 4.35 (dd, J = 2.5, 1.5 Hz, 1H), 4.19 (dd, J = 2.5, 1.5 Hz, 1H), 3.91 (dd, J = 2.5 Hz), 3.90 (s, 5H). Separate signals of phenylferrocene **11**: 4.47 (dd, J = 2.0 Hz, 2H), 4.06 (dd, J = 2.0 Hz, 2H), 3.85 (s, 5H). ^{13}C NMR: (75 MHz, C_6D_6): δ 137.8, 130.0 (CH), 128.1, 127.2 (CH), 89.4, 76.5 (CH), 72.7 (CH), 69.5 (CH), 68.3 (CH), 43.4. EI MS: (70 eV): m/z (%) = 388 (100) [M^+], 260 (15), 203 (24), 139 (15). HR EI MS: for $^{12}C_{16}{}^{1}H_{13}{}^{127}I{}^{56}Fe$: calcd: 387.9411, found: 387.9412.

5.2.2. (2-Iodo-4-methylphenyl)(4-methylphenyl)sulfoxide 13. A pre-cooled solution of sulfoxide **9** (292 mg, 0.729 mmol) in THF (4 mL) was added to a solution of *p*-TolLi in diethyl ether (0.80 mmol)[22] at −78 °C. After 2 h at 0 °C, a solution of iodine (406 mg, 1.60 mmol) in THF (1 mL) was added and the mixture stirred for 20 min at 0 °C. A satd soln of $Na_2S_2O_3$ was added and the mixture extracted with diethyl ether. The combined organic phases were washed with brine and dried over $MgSO_4$. Purification by flash chromatography (*n*-pentane/diethyl ether 100:3–1:1) afforded phenylferrocene **11** in quantitative yield and (2-iodo-4-methylphenyl)(4-methylphenyl)sulfoxide **13** as second fraction (93 mg, 0.26 mmol, 37%). IR: (KBr): $\tilde{\nu}$ = 3047 (w), 2921 (m), 2862 (w), 1584 (m), 1456 (m), 1096 (m), 1080 (m), 1017 (s), 807 (s) cm^{-1}. ^{1}H NMR: (300 MHz, C_6D_6): δ 8.07 (d, ^3J = 8.0 Hz, 1H), 7.74 (d, ^3J = 8.4 Hz, 2H), 7.22 (d, ^4J = 0.9 Hz, 1H), 6.83–6.76 (m, 3H), 1.86 (s, 3H), 1.69 (s, 3H). ^{13}C NMR: (75 MHz, C_6D_6): δ 146.8, 143.7, 142.9, 141.4, 140.0 (CH), 130.2 (CH), 129.9 (2CH), 126.9 (CH), 126.7 (2CH), 93.7, 21.1 (CH_3), 20.4 (CH_3). EI MS: (70 eV): m/z (%) = 356 (100) [M^+], 340 (14) [M^+−O], 308 (41), 249 (49), 229 (89), 214 (44), 122 (62). HR EI MS: for $^{12}C_{14}{}^{1}H_{13}{}^{56}Fe{}^{127}I{}^{16}O{}^{32}S$: calcd: 355.9732, found: 355.9731.

5.2.3. (S_{Fc})-1-Hydroxymethyl-2-phenylferrocene 14. (S_{Fc})-1-Iodo-2-phenylferrocene **10** (165 mg, 0.391 mmol) in THF (4 mL) was cooled to −78 °C. *t*-BuLi (1.5 M in pentane, 0.52 mL, 0.78 mmol) was added and the mixture stirred for 10 min at −78 °C. Paraformaldehyde (23 mg, 0.78 mmol) was added as a suspension in THF (1 mL) via PTFE-cannula. The mixture was stirred for 12 h while it was allowed to warm to 0 °C. Satd NH_4Cl soln was added and the mixture extracted with diethyl ether. The combined organic phases were washed with brine and dried over $MgSO_4$. Purification by flash chromatography (*n*-pentane/diethyl ether 2:1) afforded the alcohol **14** (49%, 56 mg, 0.19 mmol). The enantiomeric excess was determined to be 99% by HPLC (OD, 92% *n*-heptane, 8% *i*-propanol, 0.8 mL/min); retention time (min): 24.9 (R_{Fc}), 29.5 (S_{Fc}).[17] $[\alpha]_D = +201.0$ (*c* 0.59, acetone). IR: (KBr): $\tilde{\nu}$ = 3091 (m), 2923 (m), 1601 (m), 1506 (w), 1460 (m), 1384 (m), 1106 (m), 1002 (s), 765 (s), 701 (s) cm^{-1}. ^{1}H NMR: (300 MHz, C_6D_6): δ 7.70–7.64 (m, 2H), 7.23–7.07 (m, 3H), 4.46 (dd, J = 12.0, 6.6 Hz, 1H), 4.35 (dd, J = 2.4, 1.7 Hz, 1H), 4.31 (dd, J = 12.0, 3.2 Hz, 1H), 4.13 (dd, J = 2.4, 1.7 Hz, 1H), 4.00 (dd, J = 2.4 Hz, 1H), 3.85 (s, 5H), 1.19 (dd, J = 12.0, 3.2 Hz, 1H). ^{13}C NMR: (75 MHz, C_6D_6): δ 137.8, 129.2 (CH), 128.4, 126.6 (CH), 87.9, 85.5, 70.9 (CH), 70.2 (CH), 70.1 (CH), 67.6 (CH), 59.9 (CH_2). EI MS: (70 eV): m/z (%) = 292 (100) [M^+], 154 (64), 135 (25). HR EI MS: for $^{12}C_{17}{}^{1}H_{16}{}^{56}Fe{}^{16}O$: calcd: 292.0551, found: 292.0535.

5.2.4. (S_{Fc})-[2-(1-Isoquinolinyl)ferrocen-1-yl]diphenylphosphine borane complex 7a. A pre-cooled solution of sulfoxide **5a** (715 mg, 1.58 mmol) in THF (20 mL) was added to a solution of PhLi (3.17 mmol)[21] at −78 °C. After 10 min a solution of $Ph_2PCl{\cdot}BH_3$ is added. This solution had been prepared by adding borane in THF (1 M, 4.8 mL, 4.8 mmol) to a solution of chlorodiphenylphosphine (0.87 mL, 1.05 g, 4.75 mmol) in diethyl ether (3 mL) at rt and by stirring for 30 min. The mixture was then stirred for 5 min at −78 °C and then for 60 min at 22 °C. Water (0.3 mL) and triethylamine (0.25 mL) were added and the mixture was evaporated under reduced pressure. The remaining red oil was dissolved in CH_2Cl_2 (5 mL) and filtered through a pad of silica gel (50 mL) with *n*-pentane/CH_2Cl_2 (1:1). Evaporation of the filtrate afforded the crude product which was purified by flash chromatography (*n*-pentane/diethyl ether 7:1) to yield **7a** as a red crystalline solid (69%, 555 mg, 1.09 mmol).

$[\alpha]_D = +229.3$ (*c* 1.22, THF). Mp: 193–194 °C (decomp.) IR: (KBr): $\tilde{\nu}$ = 3051 (w), 2390 (m), 1622 (m), 1436 (w), 1107 (w), 1063 (m), 824 (m), 742 (m), 696 (m) cm^{-1}. ^{1}H NMR: (300 MHz, $CDCl_3$): δ 8.21 (d, ^3J = 8.3 Hz, 1H), 8.02 (d, J = 5.8 Hz, 1H), 7.71 (d, ^3J = 8.3 Hz, 1H), 7.67–7.44 (m, 5H), 7.41–7.29 (m, 6H), 7.24–7.16 (m, 2H), 4.98–4.93 (m, 1H), 4.66–4.71 (m, 1H), 4.47 (s, 5H), 4.40–4.35 (m, 1H), 1.82–0.35 (br s, 3H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 155.2, 141.3 (CH), 135.9,

133.1 (CH, $J = 8.8$ Hz), 132.8 (CH, $J = 9.4$ Hz), 131.8 ($J = 28.5$ Hz), 130.8, 130.2 (CH, $J = 2.0$ Hz), 129.9 (CH, $J = 2.4$ Hz), 129.2 (CH), 127.9 (CH, $J = 9.4$ Hz), 127.7 (CH, $J = 10.3$ Hz), 127.0 (CH), 126.6 (CH), 126.1 (CH), 119.5 (CH), 91.3 ($J = 7.6$ Hz), 75.3 (CH, $J = 6.1$ Hz), 74.9 (CH, $J = 8.8$ Hz), 71.6 (CH), 71.0 ($J = 65$ Hz), 70.7 (CH, $J = 7.8$ Hz). ^{31}P NMR: (81 MHz, $CDCl_3$): δ +17.9 (br s). EI MS: (70 eV): m/z (%) = 511 (0.5) [M^+], 497 (40) [M^+-BH_3], 420 (100), 222 (26). HR EI MS: for $^{12}C_{31}{}^{1}H_{27}{}^{11}B^{56}Fe^{14}N^{31}P$: calcd: 511.1324, found: 511.1311.

5.2.5. (S_{Fc})-[2-(8-Quinolinyl)ferrocen-1-yl] diphenylphosphine borane complex 7b. Prepared according to the procedure described above (Section 5.2.3) from sulfoxide **5b** (181 mg, 0.400 mmol) in THF (5 mL), PhLi (0.800 mmol),[21] and $Ph_2PCl{\cdot}BH_3$ were added. This solution had been prepared from borane in THF (1 M, 1.2 mL, 1.2 mmol) and chlorodiphenylphosphine (0.22 mL, 265 mg, 1.20 mmol). Due to solubility problems it was not possible to pre-cool the solution of sulfoxide **5b** to −78 °C. It was slowly added to the PhLi solution. Purification by flash chromatography (*n*-pentane/diethyl ether 5:1) yielded **7b** as a red crystalline solid (38%, 77 mg, 0.15 mmol). $[\alpha]_D = -3.7$ (*c* 0.54, THF). Mp: 190–191 °C (decomp.) IR: (KBr): $\tilde{\nu} = 3056$ (w), 2398 (m), 1636 (m), 1436 (m), 1107 (m), 1062 (m), 828 (m), 792 (m), 742 (s), 700 (s) cm^{-1}. ^{1}H NMR: (600 MHz, C_6D_6): δ 8.61–8.57 (m, 1H), 8.33 (d, $J = 7.5$ Hz, 1H), 8.05–7.98 (m, 2H), 7.63–7.57 (m, 2H), 7.57–7.52 (m, 1H), 7.33 (d, $J = 7.5$ Hz, 1H), 7.20 (dd, $J = 7.5$ Hz, 1H), 7.12–7.07 (m, 3H), 6.91–6.86 (m, 1H), 6.83–6.74 (m, 3H), 4.78–4.75 (m, 1H), 4.53–4.50 (m, 1H), 4.45 (s, 5H), 4.39–4.36 (m, 1H), 2.4–1.8 (br m, 3H). ^{13}C NMR: (151 MHz, C_6D_6): δ 149.1 (CH), 148.5, 135.6 (CH), 135.5, 134.9 (CH), 133.8 (CH, $J = 9.3$ Hz), 133.6 (CH, $J = 10.7$ Hz), 132.8 ($J = 58$ Hz), 131.1 ($J = 57$ Hz), 130.4 (CH), 130.0 (CH), 128.2–127.4 (m), 125.9 (CH), 120.5 (CH), 92.9 ($J = 8.2$ Hz), 77.4 (CH, $J = 7.0$ Hz), 74.2 (CH, $J = 10.4$ Hz), 71.7, 71,3 (CH), 70.5 (CH, $J = 7.0$). ^{31}P NMR: (81 MHz, $CDCl_3$): δ +18.7 (br s). EI MS: (70 eV): m/z (%) = 511 (0.5) [M^+], 497 (100) [M^+-BH_3], 420 (87), 354 (28), 248 (37). HR EI MS: for $^{12}C_{31}{}^{1}H_{27}{}^{11}B^{56}Fe^{14}N^{31}P$: calcd: 511.1324, found: 511.1367.

5.3. Deprotection

The borane complexes **7a** and **7b** (10.2 mg, 40.0 μmol) were dissolved in diethylamine (1 mL) and stirred at 50 °C. After 30 min, the volatile compounds were evaporated under reduced pressure. This procedure was carried out five times. The deprotection was monitored by ^{31}P NMR. The ligand was ready for use for metal catalysis after the final evaporation.

5.3.1. (S_{Fc})-[2-(1-Isoquinolinyl)ferrocen-1-yl]diphenylphosphine 1a. ^{1}H NMR: (300 MHz, acetone-d_6): δ 8.77 (d, $J = 8.3$ Hz, 1H), 8.16 (d, $J = 5.5$ Hz, 1H), 7.88 (d, $J = 8.3$ Hz, 1H), 7.75–7.53 (m, 6H), 7.45–7.38 (m, 2H), 7.25–7.09 (m, 5H), 5.13–5.07 (m, 1H), 4.67–4.60 (m, 1H), 4.14 (s, 5H), 4.02–3.95 (m, 1H). ^{31}P NMR: (81 MHz, $CDCl_3$): δ −18.6 (s).

5.3.2. (S_{Fc})-[2-(8-Quinolinyl)ferrocen-1-yl] diphenylphosphine 1b. ^{31}P NMR: (81 MHz, C_6D_6): δ −19.4 (s).

5.4. Catalysis

5.4.1. Allylic alkylation. The freshly deprotected ligand **1a** (Section 5.3) and allylpalladium(II) chloride (dimer, 1.6 mg, 4.4 μmol, 0.87 mol %) were dissolved in toluene (3 mL) and stirred for 15 min at rt 3-acetoxy-1,3-diphenylpropene (126 mg, 0.50 mmol) in toluene (1 mL), *N*,*O*-bistrimethylsilylacetamide (0.25 mL, 210 mg, 1.01 mmol), dimethyl malonate (0.11 mL, 130 mg, 0.96 mmol) and potassium acetate (2.3 mg, 23 μmol, 4.6 mol %) were then added. The reaction was followed by thin layer chromatography (*n*-pentane/diethyl ether 6:1). After 10 h, satd NH_4Cl soln was added and the mixture extracted with dichloromethane (60 mL). The organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (*n*-pentane/diethyl ether 5:1) to obtain pure product **16** (161 mg, 0.496 mmol, 99%, 86% ee) The enantiomeric excess was determined by HPLC (OD-H, 97% *n*-heptane, 3% *i*-propanol, 0.4 mL/min); retention time (min): 21.5 (*R*), 23.1 (*S*). The spectral properties were in accordance with the literature.[6i]

5.4.2. Allylic amination. *p*-Tosylamin (157 mg, 0.917 mmol) or benzoyl hydrazine (125 mg, 0.917 mmol) was added to a suspension of KH (28.5 mg, 0.711 mmol) in THF (3 mL) and stirred for 2 h at rt. The freshly deprotected ligand **1a** (Section 5.3) and allylpalladium(II) chloride (dimer, 1.6 mg, 4.4 μmol, 0.87 mol %) were dissolved in THF (1 mL) and stirred for 15 min at rt. 3-Acetoxy-1,3-diphenylpropene (126 mg, 0.50 mmol) in THF (1 mL) and the suspension of potassium amide were added. The reaction was followed by thin layer chromatography (*n*-pentane/diethyl ether 2:1). After 14 h at 40 °C, work-up and purification were performed according to the procedure described above (Section 5.4.1) and the pure products **19a** (151 mg, 0.415 mmol, 83%, 77% ee) or **19b** (131 mg, 0.399 mmol, 80%, 83% ee) obtained. The enantiomeric excess was determined by HPLC (OD, **19a**: 90% *n*-heptane, 10% *i*-propanol, 0.5 mL/min); retention time (min): 30.4, 45.2; **19b**: 95% *n*-heptane, 5% *i*-propanol, 0.6 mL/min; retention time (min): 85.2, 104.8. The spectral properties were in accordance with the literature.[10]

Acknowledgements

R.J.K. thanks the Stiftung Stipendien-Fonds des VCI (Frankfurt) and the Bundesministerium für Bildung und Forschung, for a scholarship. We thank Chemetall (Frankfurt), for the generous gift of chemicals.

References

1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.
2. For general reviews, see: (a) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497; (b) Chelucci, G.; Orrù,

G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471; (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
3. (a) Chelucci, G.; Muroni, D.; Manca, I. *J. Mol. Catal. A* **2005**, *225*, 11; (b) Bueno, A.; Moreno, R. M.; Moyano, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1763; (c) Laurent, R.; Caminade, A.-M.; Majoral, J.-P. *Tetrahedron Lett.* **2005**, *46*, 6503; (d) Tsarev, V. N.; Konkin, S. I.; Shyryaev, A. A.; Davankova, V. A.; Gavrilov, K. N. *Tetrahedron: Asymmetry* **2005**, *16*, 1737; (e) Liu, D.; Dai, Q.; Zhang, X. *Tetrahedron* **2005**, *61*, 6460; (f) Guiu, E.; Claver, C.; Benet-Buchholz, J.; Castillón, S. *Tetrahedron: Asymmetry* **2004**, *15*, 3365; (g) Lyle, M. P. A.; Narine, A. A.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 5060; (h) Mino, T.; Segawa, H.; Yamashita, M. *J. Organomet. Chem.* **2004**, *689*, 2833; (i) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941.
4. (a) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971; (b) Connolly, D. J.; Lacey, P. M.; McCarthy, M.; Saunders, C. P.; Carroll, A.-M.; Goddard, R.; Guiry, P. J. *J. Org. Chem.* **2004**, *69*, 6572; (c) Botman, P. N. M.; David, O.; Amore, A.; Dinkelaar, J.; Vlaar, M. T.; Goubitz, K.; Fraanje, J.; Schenk, H.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3471; (d) Korostylev, A.; Gridnev, I.; Brown, J. M. *J. Organomet. Chem.* **2003**, *680*, 329.
5. (a) García Manchenõ, O.; Gómez Arrayás, R.; Carretero, J. C. *Organometallics* **2005**, *24*, 557; (b) Tao, B.; Fu, G. C. *Angew. Chem.* **2002**, *41*, 3892.
6. (a) Togni, A.; Hayashi, T. *Ferrocenes: Homogenous Catalysis, Organic Synthesis, Material Science*; VCH: Weinheim, 1995; (b) Perseghini, M.; Togni, A. *Sci. Synth.* **2002**, *1*, 889; for recent reviews on ferrocene ligands, see: (c) Atkinson, R. C. J.; Gibson, V. C.; Long, N. J. *Chem. Soc. Rev.* **2004**, *33*, 313; (d) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101; for recent examples, see: (e) Hu, X.-P.; Chen, H.-L.; Zheng, Z. *Adv. Synth. Catal.* **2005**, *347*, 541; (f) Barbaro, P.; Bianchini, C.; Giambastiani, G. *Synthesis* **2005**, 2445; (g) Hu, X.; Dai, H.; Bai, C.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 1065; (h) Barbaro, P.; Bianchini, C.; Gambastiani, G.; Togni, A. *Tetrahedron Lett.* **2003**, *44*, 8279; (i) Kloetzing, R. J.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **2003**, *14*, 255.
7. (a) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743; (b) Alcock, N. W.; Hulmes, D. I.; Brown, J. M. *Chem. Commun.* **1995**, 395.
8. For examples, see: (a) Black, A.; Brown, J. M. *Chem. Commun.* **2005**, 5284; (b) Kalendra, D. M.; Duenes, R. A.; Morken, J. P. *Synlett* **2005**, 1749; (c) Miller, S. P.; Morgan, J. B.; Nepveux, F. J., V; Morken, J. P. *Org. Lett.* **2004**, *6*, 131; (d) Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *J. Am. Chem. Soc.* **2004**, *126*, 9200; (e) Chen, L.; Xiaodong, L.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174; (f) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702; (g) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535; (h) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493; (i) Brown, J. M.; Hulmes, D. I.; Layzell, T. P. *Chem. Commun.* **1993**, 1673; for a review on 1,1′-binaphthyl ligands, see: (j) Kocovsky, P.; Vyskocil, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213.
9. (a) Dube, H.; Gommermann, N.; Knochel, P. *Synthesis* **2004**, 2015; (b) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324; (c) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.
10. Lotz, M.; Kramer, G.; Knochel, P. *Chem. Commun.* **2002**, 2546.
11. Guillaneux, D.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 2502.
12. Rebiere, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 568.
13. (a) Knochel, P. In *Metal Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1997; p 406; (b) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.
14. The following procedure can be performed on the 20 mmol-scale: Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539.
15. Butler, J. L.; Gordon, M. *J. Heterocycl. Chem.* **1975**, *12*, 1015.
16. (a) Lotz, M.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4708; (b) Jensen, J. F.; Svendsen, B. Y.; la Cour, T. V.; Redersen, H. L.; Johannsen, M. *J. Am. Chem. Soc.* **2002**, *124*, 4558; (c) Pedersen, H. L.; Johannsen, M. *J. Org. Chem.* **2002**, *67*, 7982; (d) Jensen, J. F.; Søtofte, I.; Sørensen, H. O.; Johannsen, M. *J. Org. Chem.* **2003**, *68*, 1258; (e) Seitzberg, J. G.; Dissing, C.; Søtofte, I.; Norrby, P.-O.; Johannsen, M. *J. Org. Chem.* **2005**, *70*, 8332.
17. The racemic iodide was prepared from ferrocenyl phenyl sulfide by oxidation with *m*CPBA, Negishi cross-coupling and sulfoxide/lithium exchange with PhLi.
18. Imamoto, T.; Kusumoto, T.; Suzuki, N.; Sato, K. *J. Am. Chem. Soc.* **1985**, *107*, 5301.
19. Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
20. Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.
21. Prepared by adding *n*-BuLi (2.0 equiv) to iodobenzene in diethyl ether (4 mL/mmol iodobenzene) and stirring for 30 min at 0 °C.
22. Prepared by adding *n*-BuLi (2.0 equiv) to 4-iodotoluene in diethyl ether (4 mL/mmol 4-iodotoluene) and stirring for 30 min at 0 °C.