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Sulfoxide–Alkene Hybrids: A New Class of Chiral Ligands for the Hayashi–Miyaura Reaction

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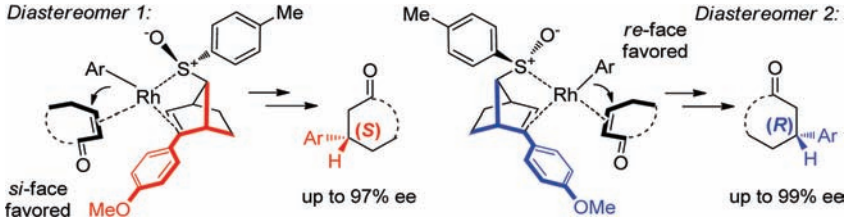
ABSTRACT



Sulfoxide–alkene hybrids are introduced as a new class of chiral heterodentate ligands for the Hayashi–Miyaura reaction. The synthesis of these ligands was achieved without the use of protecting groups. A chiral resolution was performed via simple column-chromatographic separation of the diastereomeric ligands. Both diastereomers proved to be excellent ligands in Rh-catalyzed 1,4-addition reactions, furnishing chiral products with high enantioselectivities and, remarkably, opposite stereoconfigurations.

The Rh-catalyzed 1,4-addition of boronic acids to enones, also known as the Hayashi–Miyaura reaction,[1] has been well established as an important and versatile tool for the enantioselective Michael addition.[2] Chiral dienes[3] and most recently chiral bissulfoxides[4] have proven very effective for achieving high levels of enantioselectivity in this type of reaction. The easy preparation[5] and resolution of chiral diastereomeric sulfoxides, which can be performed via simple column chromatographic separation,[4a–c,6] led us to envision novel modular hybrid ligands that combine both alkenes and sulfoxides as coordinative elements.

So far, *tert*-butylsulfinylphosphines represent the only class of chiral sulfoxide-based hybrid ligands employed in the Hayashi–Miyaura reaction,[7] and alkene hybrid ligands are restricted to either phosphorus[8] or nitrogen[9] as second coordinating moiety. Herein, we report the preparation and use of the first chiral sulfoxide–alkene hybrid ligands in the Hayashi–Miyaura reaction with a direct comparative study on the relative influences of the alkenyl and sulfoxide group on the reactivity and enantioselectivity of the Rh(I) catalyst.

Inspired by Hayashi's well-studied phosphorus–olefin hybrid ligand,[8e,i] we designed a straightforward, protective-group free synthesis of **1** and **2** from norbornene (**3**) in four steps (Scheme 1). Thus, the functionalization of **3** with NBS (*N*-bromosuccinimide) in H_2O and subsequent Swern oxidation[8e,i] furnished bromo ketone **4** in 55% yield. $LaCl_3 \cdot 2LiCl$-mediated addition[10] of 4-anisylmagnesium bromide to **4** followed by acidic elimination of H_2O using MsOH (methanesulfonic acid) directly gave the racemic alkene **5** with 67% overall yield without unnecessary protection–deprotection steps. Br/Li exchange on **5** using *t*-BuLi, subsequent transmetalation with $MgCl_2$, and quenching with (−)-menthyl (*S*)-*p*-toluenesulfinate (**6**; Andersen sulfinate)[11] furnished the two diastereomeric ligands **1** and **2** with 72% yield and 99% ee,[12] which could be easily separated via column chromatographic purification.[13] No preparative HPLC separation was required.[8e,i]

^1H and ^{13}C NMR experiments on the Rh-complexes of **1** and **2** obtained by reacting them with $[(coe)_2RhCl]_2$[14] (coe: cyclooctene; 0.5 equiv) in 1,4-dioxane-d_8 clearly proved the coordination of both the alkene and the sulfoxide moiety

(1) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(2) For selected reviews, see: (a) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (b) Hayashi, T. *Russ. Chem. Bull.* **2003**, *52*, 2595. (c) Hayashi, T. *Synlett* **2001**, 879.

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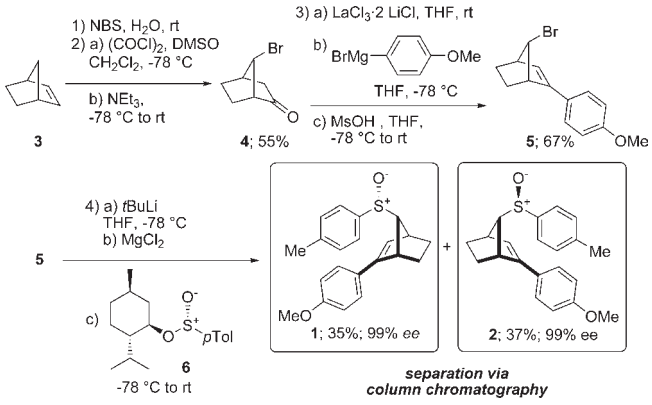
Scheme 1. Synthesis and Chiral Resolution of Ligands **1** and **2**



to the Rh atom with the signals for the respective C-atoms shifted upfield and split into doublets.[15]

To test the efficacy and scope of **1** as a chiral ligand in the Hayashi–Miyaura reaction, we prepared the Rh complex **7** by treating **1** with $[(coe)_2RhCl]_2$ (0.5 equiv) and a stoichiometric amount of $CsOH \cdot H_2O$ in 1,4-dioxane and water. The resulting in situ formed catalyst **7** (2.5 mol %) was then directly used without isolation in the 1,4-addition reactions of various aryl- and alkenylboronic acids to cyclic α,β-unsaturated carbonyl compounds (Table 1). The expected chiral addition products **8**–**10** were obtained with 61–99% yield and high enantioselectivities (82–97% ee) using only a slight excess of the respective boronic acid (1.2 equiv). The addition of arylboronic acids to cyclohex-2-enone typically proceeded with enantioselectivities between 90 and 93% ee. The (*S*)-configured products were obtained preferentially.[16] Lower stereoselectivities were observed with sterically more demanding (**8c**; 89% ee; entry 3) or electron-rich arylboronic acids (**8f**; 88% ee and **8i**; 82% ee; entries 6 and 9). The reactions of (*E*)-styryl- and (*E*)-4-methylstyrylboronic acid with cyclohex-2-enone gave the chiral addition products **8n**–**o** with 61–66% yields and high enantiomeric excesses (92–95% ee; entries 14 and 15). With cyclopent-2-enone as substrate, even higher enantioselectivities were achieved (**9a**–**i**; 94–97% ee; entries 16–24). In this case, switching from aryl- to alkenylboronic acids did not result in a deterioration of the yield (**9i**; entry 24). The use of heterocyclic *N*-benzyl maleimide as substrate led to the chiral (*S*)-configured addition products **10a**–**c** with good yields (84–88%) and high enantioselectivities (88–97% ee; entries 25–27).

Next, we examined diastereomeric **2** and its performance as a chiral ligand in the Rh-catalyzed Hayashi–-Miyaura reaction (Table 2). To our delight, we found that the corresponding Michael adducts were produced with equally high enantioselectivities and yields (79–92%; 90–99% ee), but remarkably, the absolute configurations of the products were opposite to those obtained with **1**, clearly hinting at predominant stereocontrol through the chiral environment around the alkenyl moiety.

(3) For reviews, see: (a) Shintani, R.; Hayashi, T. *Aldrichim. Acta* **2009**, *42*, 31. (b) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (c) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *6*, 3873. Articles: (d) Luo, Y.; Carnell, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750. (e) Hu, X.; Cao, Z.; Liu, Z.; Wang, Y.; Du, H. *Adv. Synth. Catal.* **2010**, *352*, 651. (f) Wang, Y.; Hu, X.; Du, H. *Org. Lett.* **2010**, *12*, 5482. (g) Wang, Z.-Q.; Feng, C.-G.; Zhang, S.-S.; Xu, M.-H.; Lin, G.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 5780. (h) Gendrineau, T.; Genet, J.-P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486. (i) Shintani, R.; Ichikawa, Y.; Takatsu, K.; Chen, F.-X.; Hayashi, T. *J. Org. Chem.* **2009**, *74*, 869. (j) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588. (k) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744. (l) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (m) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387. (n) Sörgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589. (o) Feng, C.-G.; Wang, Z.-Q.; Shao, C.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 4101. (p) Feng, C.-G.; Wang, Z.-Q.; Tian, P.; Xu, M.-H.; Lin, G.-Q. *Chem.—Asian J.* **2008**, *3*, 1511. (q) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331. (r) Berthon-Gelloz, G.; Hayashi, T. *J. Org. Chem.* **2006**, *71*, 8957. (s) Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673. (t) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503. (u) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873. (v) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508.

(4) (a) Chen, Q.-A.; Dong, X.; Chen, M.-W.; Wang, D.-S.; Zhou, Y.-G.; Li, Y.-X. *Org. Lett.* **2010**, *12*, 1928. (b) Bürgi, J. J.; Mariz, R.; Gatti, M.; Drinkel, E.; Luan, X.; Blumentritt, S.; Linden, A.; Dorta, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 2768. (c) Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172. (d) Chen, J.; Lang, F.; Zhang, X.; Cun, L.; Zhu, J.; Deng, J.; Liao, J. *J. Am. Chem. Soc.* **2010**, *132*, 4552.

(5) For reviews, see: (a) Wojaczyńska, E.; Wojaczyński, J. *Chem. Rev.* **2010**, *110*, 4303. (b) Carmen Carreño, M.; Hernández-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Commun.* **2009**, 6129. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559. (d) Toru, T., Bolm, C., Eds. *Organosulfur Chemistry in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2008. (e) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichim. Acta* **2005**, *38*, 93. (f) Fernandéz, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651.

(6) (a) Thaler, T.; Geittner, F.; Knochel, P. *Synlett* **2007**, 2655. (b) Clayden, J.; Kubinski, P. M.; Sammiceli, F.; Helliwell, M.; Diorazio, L. *Tetrahedron* **2004**, *60*, 4387. (c) Clayden, J.; Mitjans, D.; Youssef, L. H. *J. Am. Chem. Soc.* **2002**, *124*, 5266.

(7) Lang, F.; Li, D.; Chen, J.; Chen, J.; Li, L.; Cun, L.; Zhu, J.; Deng, J.; Liao, J. *Adv. Synth. Catal.* **2010**, *352*, 843.

(8) (a) Drinkel, E.; Briceño, A.; Dorta, R.; Dorta, R. *Organometallics* **2010**, *29*, 2503. (b) Grugel, H.; Minuth, T.; Boysen, M. M. K. *Synthesis* **2010**, 3248. (c) Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2009**, *11*, 4212. (d) Mariz, R.; Briceño, A.; Dorta, R.; Dorta, R. *Organometallics* **2008**, *27*, 6605. (e) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130. (f) Stemmler, R. T.; Bolm, C. *Synlett* **2007**, 1365. (g) Kasák, P.; Arion, V. B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3084. (h) Piras, E.; Läng, F.; Rüegger, H.; Stein, D.; Wörle, M.; Grützmacher, H. *Chem.—Eur. J.* **2006**, *12*, 5849. (i) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611.

(9) Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143.

(10) (a) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497. (b) Metzger, A.; Gavryushin, A.; Knochel, P. *Synlett* **2009**, 1433.

(11) (a) Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93. For preparation, see:(b) Klunder, J. M.; Sharpless, K. B. *J. Org. Chem.* **1987**, *52*, 2598. (c) Watanabe, Y.; Mase, N.; Motoaki, T.; Toru, T. *Tetrahedron: Asymmetry* **1999**, *10*, 737.

(12) Transmetalation with $MgCl_2$ prior to the reaction with the sulfinate was necessary to prevent epimerization at the chiral sulfur. See the Supporting Information for details.

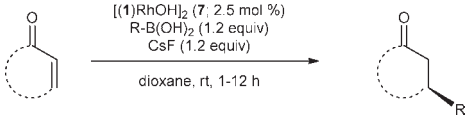
(13) Flash column chromatography: purification/separation of the diastereomeric sulfoxide ligands from byproducts: (a) SiO_2, *n*-pentane/acetone 2:1; separation of the two diastereomeric sulfoxide ligands: (b) SiO_2, CH_2Cl_2/EtOAc 2:1.

(14) van der Ent, A.; Onderdelinden, A. L. *Inorg. Synth.* **1990**, *28*, 90.

(15) See the Supporting Information for details.

(16) Comparison with HPLC data from references 3d,3o, 4b, and 8i.

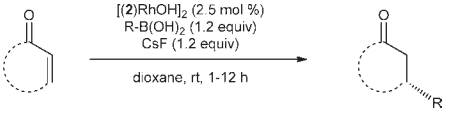
Table 1. Enantioselective 1,4-Addition of Boronic Acids to Various Electron-deficient Alkenes Using **1** as Chiral Ligand



entry	product	yield (%)[a]	ee (%)[b]
1	**8a:** R = Ph	98	92
2	**8b:** R = 2-Et-C_6H_4	99	92
3	**8c:** R = 1-naphthyl	96	89 (*S*)[c]
4	**8d:** R = 2-MeO-C_6H_4	90	90
5	**8e:** R = 2-F-C_6H_4	88	90
6	**8f:** R = 2,3-CH_2O_2-C_6H_3	86	88
7	**8g:** R = 3-MeO-C_6H_4	93	90
8	**8h:** R = 3-Cl-C_6H_4	90	90
9	**8i:** R = 4-MeO-C_6H_4	85	82 (*S*)[c]
10	**8j:** R = 4-PhO-C_6H_4	90	93
11	**8k:** R = 4-Cl-C_6H_4	84	93
12	**8l:** R = 4-F-C_6H_4	89	92
13	**8m:** R = 4-F_3C-C_6H_4	80	93
14	**8n:** R = (*E*)-PhCH=CH	66	95
15	**8o:** R = (*E*)-4-MeC_6H_4-CH=CH	61	92
16	**9a:** R = Ph	85	96 (*S*)[c]
17	**9b:** R = 1-naphthyl	99	94
18	**9c:** R = 2-MeO-C_6H_4	96	96
19	**9d:** R = 3-Cl-C_6H_4	99	96
20	**9e:** R = 4-MeO-C_6H_4	88	94
21	**9f:** R = 4-Me-C_6H_4	92	96
22	**9g:** R = 4-Cl-C_6H_4	99	96
23	**9h:** R = 4-F_3C-C_6H_4	93	97
24	**9i:** R = (*E*)-PhCH=CH	94	95
25	**10a:** R = Ph	84	88[d] (*S*)[c]
26	**10b:** R = 4-MeO-C_6H_4	88	92[d] (*S*)[c]
27	**10c:** R = 3,5-Me_2-C_6H_3	85	97[d] (*S*)[c]

[a] Isolated yield of analytically pure product. [b] Determined via chiral HPLC analysis. [c] Absolute configurations determined by comparison with reported chiral HPLC data.[16] [d] Reaction time: 12 h. Compound racemizes when stored at room temperature.

Table 2. Enantioselective 1,4-Addition of Boronic Acids to Various Electron-Deficient Alkenes Using **2** as Chiral Ligand

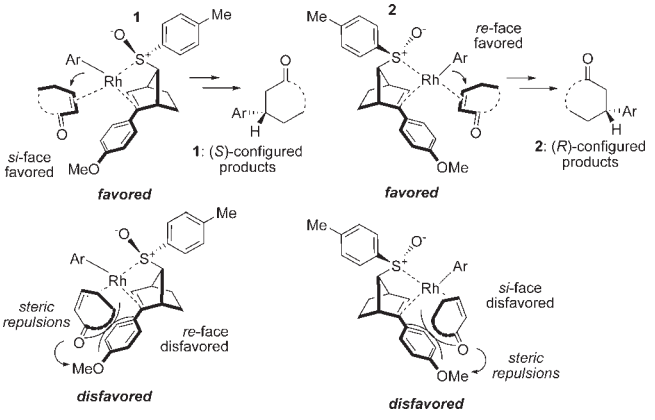


entry	product	yield (%)[a]	ee (%)[b]
1	**11a:** R = Ph	87	92
2	**11b:** R = 1-naphthyl	92	92 (*R*)[c]
3	**11c:** R = 4-MeO-C_6H_4	82	92 (*R*)[c]
4	**11d:** R = 4-F_3C-C_6H_4	85	90
5	**12a:** R = 1-naphthyl	82	96
6	**12b:** R = 4-Cl-C_6H_4	79	93
7	**12c:** R = 4-F_3C-C_6H_4	83	95
8	**13:** R = 3,5-Me_2-C_6H_3	80	96[d] (*R*)[c]
9	**14:** R = Ph	92	99[e]

[a] Isolated yield of analytically pure product. [b] Determined via chiral HPLC analysis. [c] Absolute configurations determined by comparison with reported chiral HPLC data.[16] [d] Reaction time: 12 h. Compound racemizes when stored at room temperature. [e] Reaction time: 12 h.

Moreover, the addition of phenylboronic acid to heterocyclic Cbz-protected 2,3-dihydropyridin-4(1*H*)-one furnished **14** with 92% yield and 99% ee (entry 9). To rationalize the opposite stereochemical outcomes obtained with the diastereomeric ligands **1** and **2**, we propose the model outlined in Scheme 2. Since sulfinyl groups are known to be strong σ-donors to Rh,[4b] a *trans*-configuration of the aryl group and the alkene moiety of the ligand in the complex can be assumed as it is reported for the related phosphine−olefin hybrid ligands.[8e] The stereoselectivity is controlled by the chiral environment around the alkenyl unit, which forces the substrate via steric interactions to bind to the Rh complex with its *si* face in the case of **1** and with its *re* face in the case of **2**. Despite a strong coordination of the sulfinyl group to Rh the central chirality at the sulfur has only a minor influence on the observed enantioselectivities.

Scheme 2. Tentative Stereochemical Model Explaining the Opposite Configurations of the Addition Products Obtained with Ligands **1** and **2**

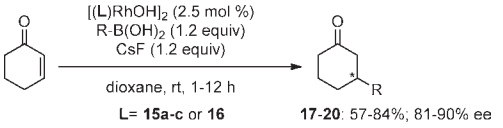


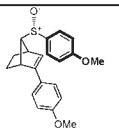
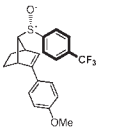
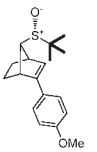
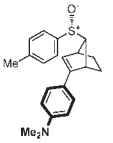
Finally, we examined the influence of electronic and steric modulations at the sulfoxide−olefin hybrid ligand on reactivity and enantioselectivity of the Rh complex in the Hayashi−Miyaura reaction. For this purpose, we

prepared the analogues **15a**−**c** bearing different sulfinyl moieties using subsequent addition of the corresponding Grignard reagents to (*S*)-TMPOO (*N*-tosylmethylphenyl-1,2,3-oxathiazolidine 2-oxide).[17] To investigate the role of the alkenyl moiety, we prepared **16** with a more electron-rich 4-dimethylaniline substituent at the C=C double bond. These ligands were then submitted to the Rh-catalyzed 1,4-addition of various arylboronic acids to cyclohexen-2-one (Table 3). Both increasing and reducing the electron-density at the sulfoxide (**15a**,**b**) led to an overall deterioration of yield and enantioselectivity (entries 1−7 of Table 3). Interestingly, the use of electron-poor arylboronic acids as nucleophiles proved advantageous to yield and enantioselectivity with both ligands (entries 4 and 7). A negative effect of electron-rich arylboronic acids on the stereoselectivity was also found with **1** as ligand (entries 6 and 9 of Table 1). With ligand **15c** bearing a sterically highly congested *t*Bu group at the sulfoxide no reaction took place at all (entry 8 of Table 3). This is probably due to a loss of coordination between the sulfinyl group and Rh. The alkenyl moiety alone is not sufficient for efficiently binding to the Rh center, thus underlining the vital role of the sulfinyl group for chelation and formation of the reactive complex. An increase of the electron-density at the C=C bond (**16**) led only to a deterioration of yields, without impairing the enantioselectivities (entries 9 and 10).

In summary, we have developed a concise, protective-group free synthesis of sulfoxide−alkene hybrid ligands. Chiral resolution is achieved via simple column chromatographic separation of the diastereomeric ligands, which can both be used in the Hayashi−Miyaura reaction, furnishing the chiral products with excellent yields, equally high enantioselectivities. and opposite stereoconfigurations. Experiments with analogues of **1** and **2** displaying different steric and electronic properties showed that coordination of the sulfinyl group represents a crucial factor for efficient chelation and formation of the reactive Rh complex. Although efficient binding of the alkenyl moiety to the Rh center is less important for the reaction to proceed, its chiral environment dictates the stereochemical outcome.

Table 3. Enantioselective 1,4-Addition of Boronic Acids to Cyclohex-2-enone Using Analogues **15a**−**c** and **16** as Chiral Ligands



entry	ligand	product	yield (%)[a]	ee (%)[b]
1	 **15a**	**17a:** R = 4-MeO-C_6H_4	57	83 (*R*)[c]
2		**17b:** R = 4-Me-C_6H_4	63	88
3		**17c:** R = Ph	69	81
4		**17d:** R = 4-F-C_6H_4	73	90
5	 **15b**	**18a:** R = 4-MeO-C_6H_4	77	84 (*R*)[c]
6		**18b:** R = Ph	84	87
7		**18c:** R = 4-F_3C-C_6H_4	83	87
8	 **15c**	**19:** R = Ph	no reaction	-
9	 **16**	**20a:** R = 3-MeO-C_6H_4	79	89
10		**20b:** R = 1-naphthyl	62	90 (*S*)[c]

[a] Isolated yield of analytically pure product. [b] Determined via chiral HPLC analysis. See the Supporting Information for details. [c] Absolute configurations determined by comparison with reported chiral HPLC data.[16]

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Supporting Information Available. Experimental procedures and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) (a) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Su, X.; Wilkinson, H. S.; Lu, Z.-H.; Magiera, D.; Senanayake, C. H. *Tetrahedron* **2005**, *61*, 6386. (b) Han, Z.; Krishnamurthy, D.; Grover, P.; Wilkinson, H. S.; Fang, Q. K.; Su, X.; Lu, Z.-H.; Magiera, D.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2032.