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Design of Chiral Sulfoxide–Olefins as a New Class of Sulfur-Based Olefin Ligands for Asymmetric Catalysis

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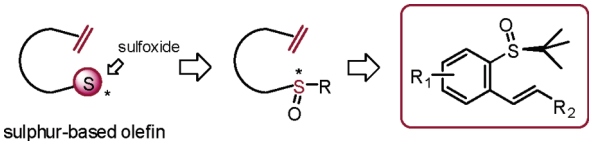
ABSTRACT



The design and development of a novel class of chiral sulfur–olefin hybrid ligands with high synthetic feasibility are described. These new sulfoxide–olefin ligands showed excellent catalytic activities and enantioselectivities (up to 98% ee) in rhodium-catalyzed asymmetric 1, 4-addition reactions of aryl boronic acids to α,β-unsaturated carbonyl compounds.

In transition-metal-mediated asymmetric catalysis, chiral ligands play an essential role in efforts to achieve excellent stereoselectivity. For this reason, design and discovery of novel effective chiral ligands remain an important focus of modern synthetic chemistry.[1] Recently, chiral olefins have attracted considerable attention as new steering ligands and have evoked great interest from the chemical society.[2−5] Nevertheless, despite the fact that heteroatom–olefin hybrid ligands generally exhibit increased coordination ability to transition metals, their development and use in asymmetric catalysis is far less extensive than that of diene ligands; only rare examples of pnictogen-based olefin analogues have been disclosed in the literature.[6] On the other hand, catalytic asymmetric transformations applying sulfur-based ligands have been more intensively investigated in recent years.[7] Compared to the phosphorus- or nitrogen-containing ligands, chiral sulfur ligands present advantages of easy synthesis, high stability, and special *S*-stereogenic control. Therefore, it is reasoned that a structurally proper olefin containing heteroatomic sulfur could possibly act as a previously unexplored sulfur-olefin hybrid class ligand, which should offer new opportunities for asymmetric applications. Very recently, we discovered that simple and readily available chiral sulfinamide-olefins can display great catalytic activities and enantioselectivities in rhodium-catalyzed 1,4-addition reactions.[8]

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(2) For two pioneering references, see: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

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(4) For selected very recent examples on chiral dienes in asymmetric catalysis, see: (a) Luo, Y.; Carnell, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750. (b) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795. (c) Shintani, R.; Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3969. (d) Nishimura, T.; Wang, J.; Nagaosa, M.; Okamoto, K.; Shintani, R.; Kwong, F.; Yu, W.; Chan, A. S. C.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 464. (e) Nishimura, T.; Kawamoto, T.; Nagaosa, M.; Kumanmoto, H.; Hayashi, T. *Angew.Chem., Int. Ed.* **2010**, *49*, 1638. (f) Nishimura, T.; Maeda, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7324. (g) Nishimura, T.; Makino, H.; Nagaosa, M.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 12865. (h) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168. (i) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373. (j) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 3820. (k) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7872. (l) Cao, Z.-P.; Du, H.-F. *Org. Lett.* **2010**, *12*, 2602. (m) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2011**, *13*, 788. (n) Li, Q.; Dong, Z.; Yu, Z.-X. *Org. Lett.* **2011**, *13*, 1122. (o) Wang, Y.-Z.; Hu, X.-C.; Du, H.-F. *Org. Lett.* **2010**, *12*, 5482.

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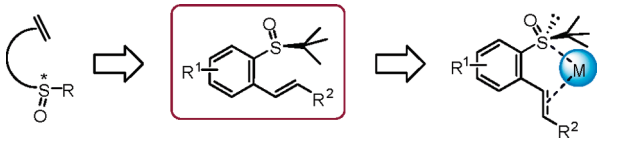
Chiral sulfoxides are an intriguing class of molecules.[9] During recent years, they have been successfully utilized as chiral ligands in various kinds of transition-metal-catalyzed asymmetric reactions.[9a,b,10] The sulfinyl group is perfectly featured with both an intrinsic stereogenic center and binding site to metals. Inspired by these elegant works, we envisioned probing sulfinyl-based olefin ligands. To fulfill this idea, one simple design is to assemble molecules that have both sulfinyl and olefin groups attached to a benzene ring in a 1,2-fashion. As outlined in Scheme 1,

Scheme 1. Chiral Sulfoxide–Olefin Ligand Proposal

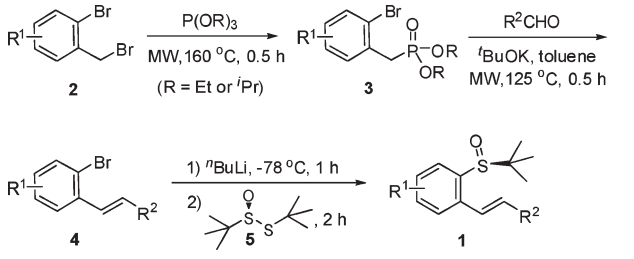


upon coordination to the metal, the sulfinyl functionality can be expected to serve as a nice stereodirecting group, thus providing effective asymmetric inductions. Herein, we disclose the first example of chiral sulfinyl-based olefin ligands and their potential in asymmetric catalysis.

Initially, to examine whether the use of a designed ligand could lead to catalysis in asymmetric reactions, compound **1a** ($R^1 = R^2 = H$) was first prepared using 2-bromobenzaldehyde as the starting material in two steps,[11] and we evaluated it in Rh-catalyzed conjugate addition of phenyl boronic acid to 2-cyclohexenone. The reaction proceeded smoothly at 60 °C in the presence of **1a** (3.3 mol %) under aqueous K_3PO_4/dioxane and went to completion in 30 min,[12] giving the corresponding product in 98% yield, albeit with low enantioselectivity (8% ee).

When the corresponding sulfoxide ligand where the vinyl group in **1a** has been hydrogenated was used, the reaction did not occur even after 6 h. This result clearly indicates the necessity for the olefin donor to be present on the ligand. Encouraged by these findings, we decided to synthesize a series of new sulfoxide–olefin ligands bearing different R^1 and R^2 substitutents.

Scheme 2. Synthesis of Sulfoxide–Olefin Ligands **1**



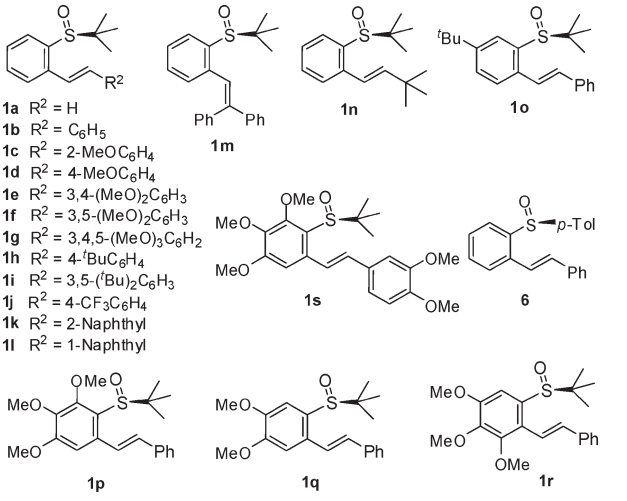


Figure 1. Sulfoxide–olefin ligands with diverse structures.

As illustrated in Scheme 2, the synthesis of structurally diverse sulfoxide-olefin ligands can generally be accomplished in three concise steps. Horner–Wadsworth–Emmons reaction of the resulting phosphonate **3** with the corresponding

(5) For our recent work involving on chiral diene ligands in asymmetric catalysis, see: (a) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (b) Feng, C.-G.; Wang, Z.-Q.; Tian, P.; Xu, M.-H.; Lin, G.-Q. *Chem. Asian J.* **2008**, *3*, 1511. (c) Feng, C.-G.; Wang, Z.-Q.; Shao, C.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 4101. (d) Wang, Z.-Q.; Feng, C.-G.; Zhang, S.-S.; Xu, M.-H.; Lin, G.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 5780. (e) Wang, L.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Synthesis* **2010**, 3263. (f) Zhang, S.-S.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 5546. (g) Yang, H.-Y.; Xu, M.-H. *Chem. Commun* **2010**, *46*, 9223.

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(7) (a) *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008. (b) *Chiral Sulfur Ligands: Asymmetric Catalysis*; Pellissier, H., Ed.; Royal Society of Chemistry: Cambridge, U.K., 2009. (c) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. (d) Pellissier, H. *Tetrahedron* **2007**, *63*, 1297.

(8) Jin, S.-S.; Wang, H.; Xu, M.-H. *Chem. Commun.* 2011, 47, DOI: 10.1039/c1cc12322j.

(9) (a) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651. (b) Hiroi, K.; Sone, T. *Curr. Org. Synth.* **2008**, *5*, 305. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559. (d) Carreño, M. C.; Hernández-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Commun.* **2009**, 6129.

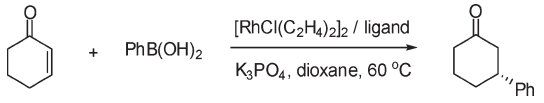
(10) For recent leading examples, see: (a) Mariz, R.; Luan, X. J.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172. (b) Burgi, J. J.; Mariz, R.; Gatti, M.; Drinkel, E.; Luan, X.-J.; Blumentritt, S.; Linden, A.; Dorta, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 2768. (c) Mariz, R.; Poater, A.; Gatti, M.; Drinkel, E.; Buergi, J.; Luan, X.-J.; Blumentritt, S.; Linden, A.; Cavallo, L.; Dorta, R. *Chem.—Eur. J.* **2010**, *16*, 14335. (d) Chen, J.; Chen, J.-M.; Lang, F.; Zhang, X.-Y.; Cun, L.-F.; Zhu, J.; Deng, J.-G.; Liao, J. *J. Am. Chem. Soc.* **2010**, *132*, 4552. (e) Chen, Q.-A.; Dong, X.; Chen, M.-W.; Wang, D.-S.; Zhou, Y.-G.; Li, Y.-X. *Org .lett.* **2010**, *12*, 1928. (f) Lang, F.; Li, D.; Chen, J.-M.; Chen, J.; Li, L.-C.; Cun, L.-F.; Zhu, J.; Deng, J.-G.; Liao, J. *Adv. Synth. Catal.* **2010**, *352*, 843.

(11) See the Supporting Information for details.

(12) The reaction was found to be slow at room temperature or 40 °C.

aldehyde under microwave irridation for 30 min afforded mainly *trans*-stilbene derivatives **4** in good yields. Treatment of **4** with ^{n}BuLi at −78 °C, followed by addition of (*S*)-thiosulfinate **5**, led to the desired molecules[13] (see Figure 1 for representative structures).

Table 1. Ligand Screening[a]

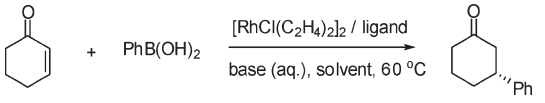


entry	ligand	yield[b] (%)	ee[c] (%)
1	**1a**	98	8 (*S*)
2	**1b**	99	90 (*R*)
3	**1c**	99	83 (*R*)
4	**1d**	93	86 (*R*)
5	**1e**	99	90 (*R*)
6	**1f**	93	80 (*R*)
7	**1g**	90	86 (*R*)
8	**1h**	99	87 (*R*)
9	**1i**	99	85 (*R*)
10	**1j**	95	89 (*R*)
11	**1k**	98	90 (*R*)
12	**1l**	4	48 (*R*)
13	**1m**		
14	**1n**	trace	N.D[d]
15	**1o**	81	70 (*R*)
16	**1p**	99	95 (*R*)
17	**1q**	99	93 (*R*)
18	**1r**	99	91 (*R*)
19	**1s**	99	88 (*R*)
20	**6**[e]	99	12[f] (*R*)

[a] Reaction conditions: $PhB(OH)_2$ (0.5 mmol), 2-cyclohexenone (0.25 mmol), $[Rh(C_2H_4)_2Cl]_2$ (3 mol %, 1.5 mg), ligand (3.3 mol %), and K_3PO_4 (1.5 M aq, 83 μL, 0.5 equiv) in dioxane (0.5 mL) at 60 °C for 0.5 h. [b] Isolated yield. [c] Determined by HPLC analysis on a Daicel Chiralcel OJ-H column; the absolute configuration was determined by comparison with known data. [d] Not determined. [e] The optical purity of this ligand was low (48% ee). [f] A retained 25% ee can be obtained if a optically pure **6** could be used.

With various sulfoxide−olefin ligands in hand, we then turned our attention to survey their catalytic performance (Table 1). In comparison with **1a** bearing a terminal olefin, most of ligands (**1b**−**k**) with an R^2 substitutent attached to the double bond showed dramatically improved enantioselectivities while maintaining the same high catalytic activity (entries 2−11). Among them, ligands **1b**, **1e**, and **1k** performed equally well and gave a promising 90% ee (entries 2, 5, and 11). When **1l** was applied to the reaction, the yield became very low, and the ee value decreased to only 48% (entry 12), suggesting that a sterically very bulky R^2 would disfavor the coordination and induction. To understand whether the *trans*-stilbene structure is crucial, ligands **1m** and **1n** derived from benzophenone and pivaladehyde respectively were examined.[14] As a result, the use of these two ligands seriously hampered the reaction, giving no or only trace amount of products (entries 13 and 14). We also investigated the substitution effect (R^1) on the central benzene ring moiety (**1o**−**s**, entries 15−19), to our delight, the introduction of multimethoxy groups (**1p**, **1q**, and **1r**) was beneficial (entries 16−18), the best selectivity of 95% ee was obtained when ligand **1p** was employed (entry 16). Notably, replacing the *tert*-butyl sulfinyl group in **1b** with *p*-tolylsulfinyl led to a much lower reaction stereocontrol (entry 20).

Table 2. Optimization of the Reaction Conditions[a]



entry	ligand	base	solvent	yield[b] (%)	ee[c] (%)
1	**1b**	K_3PO_4	dioxane	99	90
2	**1b**	K_3PO_4	CH_2Cl_2	98	75
3	**1b**	K_3PO_4	toluene	98	67
4	**1b**	K_3PO_4	MeOH	89	88
5	**1b**	K_3PO_4	THF	93	91
6	**1b**	KOH	dioxane	90	88
7	**1b**	KF	dioxane	94	92
8	**1b**	Na_2CO_3	dioxane	91	92
9	**1b**	K_2CO_3	dioxane	97	92
10	**1b**	K_2HPO_4	dioxane	96	93
11	**1b**	K_2CO_3	THF	97	93
12	**1b**	K_2HPO_4	THF	97	94
13	**1p**	K_2HPO_4	THF	99	97
14	**1q**	K_2HPO_4	THF	99	94
15	**1r**	K_2HPO_4	THF	99	93

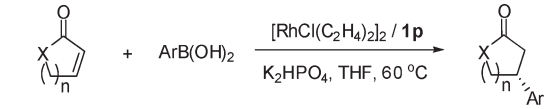
[a] Reaction conditions: $PhB(OH)_2$ (0.5 mmol), 2-cyclohexenone (0.25 mmol), $[Rh(C_2H_4)_2Cl]_2$ (3 mol %, 1.5 mg), ligand (3.3 mol %), and base (1.5 M aq, 83 μL, 0.5 equiv) in the indicated solvent (0.5 mL) at 60 °C for 0.5 h. [b] Isolated yield. [c] Determined by HPLC analysis on a Daicel Chiralcel OJ-H column.

Given the encouraging results, the reaction conditions were further explored (Table 2). The easily available sulfoxide−olefin **1b** was first chosen as a model ligand (entries 1−11). The use of a noncoordinating solvent such as CH_2Cl_2 or toluene provided low enantioselectivities (entries 2 and 3). When THF was used, a slightly better enantioselectivity was observed (entry 5). A careful survey of inorganic bases led to the identification of K_2HPO_4 as the best additive, affording the addition product with 94% ee in THF (entry 12). Gratifyingly, an excellent enantioselectivity of 97% ee was obtained by using the previously recognized optimal ligand **1p** (entry 13).

(13) During the addition reaction, a small degree of *S*-stereogenic racemization was observed; fortunately, in most cases, the ee's of ligands were > 98%. See the Supporting Information for detailed ee values. For a similar racemization discussion, see: Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.

(14) An attempt to synthesize the corresponding ligand **1b** with *cis*-stilbene structure was also carried out, and the product was obtained in a *cis*/*trans* ratio of 3:1. However, this *cis*-dominating ligand only gave the reaction in 50% yield and 35% ee, also suggesting the important effect of *trans*-stilbene structure on both yield and enantioselectivity.

Table 3. $[RhCl(C_2H_4)_2]_2$/**1p**-Catalyzed Asymmetric Conjugated Addition[a]



7a, X = CH_2, n = 2
7b, X = CH_2, n = 1
7c, X = O, n = 2

8

entry	**7**	Ar	**8**	yield[b] (%)	ee[c] (%)
1	**7a**	C_6H_5	**8a**	99	97
2	**7a**	4-MeC_6H_4	**8b**	99	96
3	**7a**	4-$MeOC_6H_4$	**8c**	99	95
4	**7a**	4-FC_6H_4	**8d**	94	98
5	**7a**	4-ClC_6H_4	**8e**	97	96
6	**7a**	3-MeC_6H_4	**8f**	96	97
7	**7a**	3-ClC_6H_4	**8g**	85	97
8	**7a**	3-$MeOC_6H_4$	**8h**	99	97
9	**7a**	2-MeC_6H_4	**8i**	31	94
10	**7a**	2-$MeOC_6H_4$	**8j**	53	96
11	**7a**	2-naphthyl	**8k**	99	97
12	**7a**	1-naphthyl	**8l**	97	98
13	**7b**	C_6H_5	**8m**	98	96
14	**7b**	4-MeC_6H_4	**8n**	99	96
15	**7b**	4-ClC_6H_4	**8o**	95	95
16	**7c**	C_6H_5	**8p**	91	96

[a] The reaction was carried out with 0.25 mmol of enone/ester **7**, 0.5 mmol of arylboronic acid in the presence of 3 mol % of $[RhCl(C_2H_4)_2]_2$, 3.3 mol % of ligand **1p**, and 1.5 M aq K_2HPO_4 (0.1 mL) in THF (1 mL) at 60 °C for 0.5–2 h. [b] Isolated yield. [c] Determined by HPLC analysis on Daicel chiral columns.

With the best ligand **1p**, we next examined the substrate scope of this rhodium-catalyzed asymmetric 1,4-addition under the above optimized conditions. As presented in Table 3, a wide range of arylboronic acids with varying electronic and steric demands were successfully reacted with α,β-unsaturated carbonyl compounds such as 2-cyclohexenone (**7a**), 2-cyclopentenone (**7b**), and 5,6-dihydro-2-pyranone (**7c**), giving the corresponding addition products **8** with excellent enantioselectivities (94–98% ee) in all cases. The nature of the substituent on the phenyl ring of the arylboronic acid had very little effect on the reaction stereoselectivity. Unlike in the previous observations with chiral olefin or related ligands,[15] it is worthy of note that the current catalytic system proved equally suitable for both six- and five-membered cyclic substrates. Unfortunately, when linear enone (*E*)-2-heptenone was subjected to react with phenylboronic acid, both low yield (34%) and selectivity (21% ee) were afforded.

In summary, we have developed an unprecedented new exciting class of sulfinyl-based olefin ligands for asymmetric catalysis. By taking advantage of inherent stereogenic elements in the scaffold of the sulfoxide, readily available chiral sulfoxide–olefins with simple molecular framwork have shown great catalytic activities and enantioselectivities as in rhodium-catalyzed asymmetric conjugate additions. This study revealed that the innovative *S*-stereogenic olefin ligands can also be as useful as other classical asymmetric ligands. Further development of more effective chiral sulfur–olefin hybrid ligands and their applications in other asymmetric reactions is currently underway in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data, and copies of NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) For selected examples, see refs 4k, 5b, 5c, 6h, and 10f.