ORGANIC LETTERS

2011
Vol. 13, No. 13
3300–3303

Simple *N*-Sulfinyl-Based Chiral Sulfur–Olefin Ligands for Rhodium-Catalyzed Asymmetric 1,4-Additions

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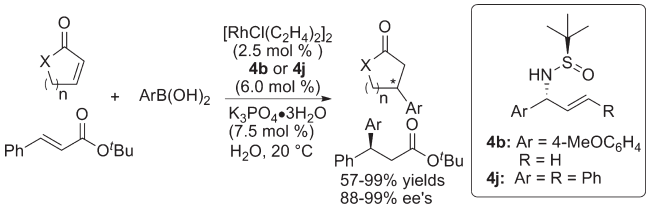
Received April 11, 2011

ABSTRACT



A variety of *N*-sulfinyl-based chiral sulfur–olefin ligands has been successfully developed for the first time for rhodium-catalyzed highly efficient and enantioselective 1,4-additions. The ease of synthesis and needless consideration of the carbon chirality makes this novel type of ligands attractive for asymmetric catalysis.

Chiral *tert*-butanesulfinamide as an important and inexpensive reagent has attracted considerable attention since Ellman and co-workers reported the first approach to obtain its enantiomerically pure form in 1997.[1,2] Besides its diverse applications in synthetic chemistry, *tert*-butanesulfinamide has also been incorporated in chiral ligands.[1d] For example (Figure 1), in 2001, Ellman and co-workers developed the first *N*-sulfinyl-based chiral ligands **1a**–**c** for a copper-catalyzed asymmetric Diels–Alder reaction, and this type of ligand was believed to bind with copper through oxygen atoms.[3] Subsequently, *P*,*N*-sulfinyl imine ligand **2** was also explored and subjected to Pd and Ir-catalyzed asymmetric alkylation and hydrogenation by Ellman's group.[4] Very recently, Qin and co-workers reported the development of biaryl *P*,*N*-sulfinyl imine ligands **3a**,**b** and their application in Pd-catalyzed asymmetric addition of arylboronic acids to *N*-benzylisatin.[5] Moreover, some chiral ligands as well as organocatalysts possessing acidic N–H as binding element have also been developed.[6] In these reported ligands, either nitrogen or

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10.1021/ol2009494
Published on Web 05/27/2011

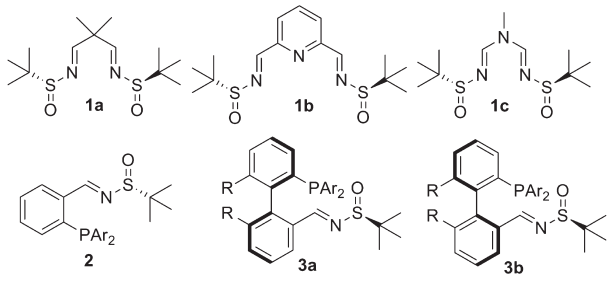

Figure 1. Representative *N*-sulfinyl-based chiral ligands for metal-catalyzed asymmetric reactions.

oxygen acts as the coordination atom. However, to the best of our knowledge, few chiral ligands with the sulfur of *tert*-butanesulfinamide as the coordination atom have been developed for asymmetric catalysis, even though the chirality is actually at sulfur, which will probably provide a better chiral environment.[7−9] Exploring novel *N*-sulfinyl-based chiral sulfur ligands is therefore of great interest.

As one type of lately emerging ligand, chiral olefin ligands have witnessed significant progress since the pioneering contribution by Hayashi and Carreira.[10,11] Both chiral diene[12] and hybrid ligands combined olefins with heteroatoms such as phosphorus[13] and nitrogen[14] have been well developed. However, other coordination atoms except P and N have seldom been incorporated in chiral olefin ligands. As part of our interest in exploring new, effective, and accessible chiral olefin ligands, in our previous work, a variety of acyclic chiral diene ligands as well as P/olefin ligands has been developed for Rh- or Pd-catalyzed asymmetric additions or allylic alkylation.[15] Inspired by the perfect character of *tert*-butanesulfinamide, we envision that the combination of *tert*-butanesulfinamide and olefin in chiral ligands will provide an excellent opportunity for the development of novel *N*-sulfinyl-based chiral sulfur−olefin ligands. Herein, we wish to report our efforts on this subject.

At the outset of our studies, a variety of *N*-sulfinyl-based chiral sulfur−olefin ligands containing terminal or internal olefins was synthesized in high yields and diasteroselectivities according to the well established methodology by condensation of aldehyde or chalcone with (*R*)-*tert*-butanesulfinamide followed by addition with a vinyl Grignard reagent or reduction with DIBAL-H.[1,16,17] Selected chiral ligands are listed in Figure 2, and it is worth noting that some of them are already well-known compounds, but none of them has been utilized as an effective ligand for asymmetric catalysis.

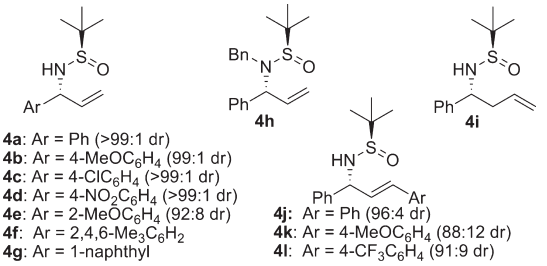

Figure 2. Selected *N*-sulfinyl-based chiral sulfur−olefin ligands.

To test the possibility for application of these novel ligands in asymmetric catalysis, ligand **4a** was subjected to Rh(I)-catalyzed 1,4-addition[18] of phenylboronic acid (**6a**) to 2-cyclohexenone (**5a**) in the presence of $K_3PO_4 \cdot 3H_2O$ with water as solvent at ambient temperature for 3 h (Scheme 1). We were pleased to find that this reaction proceeded smoothly to give the desired adduct **7a** in 99%

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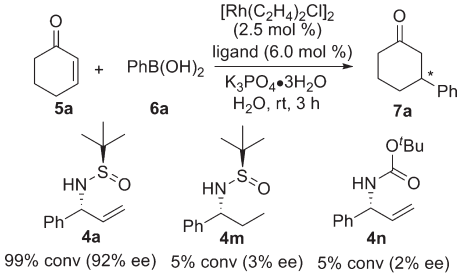
Scheme 1. Rh(I)-Catalyzed Asymmetric Addition of Phenylboronic Acid (**6a**) to 2-Cyclohexenone (**5a**)



conversion with 92% ee. Control experiments employing **4m** and **4n** as ligands were also conducted under the same conditions. However, only trace amount of racemic product was obtained, which suggests that both sulfinyl and olefin moieties are essential for the observed high reactivity and enantioselectivity.

Table 1. Evaluation of Chiral Ligands[a]

entry	ligand	conv[b] (%)	ee[c] (%)	entry	ligand	conv[b] (%)	ee[c] (%)
1	**4a**	99	92	8	**4h**	80	81
2	**4b**	>99	93	9	**4i**	83	27
3	**4c**	92	92	10	**4j**	84	−94
4	**4d**	99	87	11	**4k**	85	−95
5	**4e**	99	91	12	**4l**	50	−82
6	**4f**	96	90	13[d]	**4b**	>99	92
7	**4g**	98	87	14[e]	**4b**	>99	84

[a] All of the reactions were carried out with 2-cyclohexenone (**5a**) (0.20 mmol), phenylboronic acid (**6a**) (0.30 mmol), $K_3PO_4 \cdot 3H_2O$ (0.015 mmol), $[RhCl(C_2H_4)_2]_2$ (0.005 mmol), ligand (0.012 mmol) in water (1.0 mL), and dioxane (0.04 mL) under argon for 3 h unless other stated. [b] The conversion was determined by crude ^1H NMR. [c] The ee was determined by chiral HPLC. [d] 2.5 mol % of catalyst. [e] 1.0 mol % of catalyst.

Encouraged by this promising result, chiral ligands **4b**–**l** were subsequently subjected to Rh(I)-catalyzed 1,4-addition of phenylboronic acid (**6a**) to 2-cyclohexenone (**5a**) to search for more effective ligands. As shown in Table 1, all of these ligand-modified rhodium catalysts can promote this reaction to afford the desired product **7a** in 50−>99% conversions with 27−95% ee's (entries 1−12). For ligands bearing terminal olefins, different aryl groups had only a little impact on reactivities and enantioselectivities (Table 1, entries 1−7). When the N−H of ligand **4a** was replaced by N-Bn, or using homoallyl ligand **4i**, obviously lower conversions and ee's were obtained (Table 1, entries 1 vs 8 and 9). Ligands possessing internal olefins were also suitable for this reaction to give the desired product **7a** with the reverse absolute configuration (Table 1, entries 10−12). Further reducing the catalyst loading to 2.5 mol % and 1.0 mol %, the reactions still went efficiently but with a little lower ee's (Table 1, entries 13 and 14). Overall, ligands **4b** and **4j** proved to be most suitable for this reaction in terms of both reactivity and enantioselectivity.

Further studies on ligands **4b** and **4j** with different diastereomeric ratios were carried out to investigate the impact of the carbon chirality. Interestingly, it was found that no matter with high or low diastereomeric ratios, the Rh(I)-catalyzed asymmetric 1,4-addition of phenylboronic acid (**6a**) to 2-cyclohexenone (**5a**) gave the desired product **7a** with almost the same conversions and ee's (Figure 3). This result demonstrates that the sulfur chirality played a crucial role in the asymmetric induction. Especially, needless consideration of the carbon chirality during synthesis makes this type of ligands more practical.

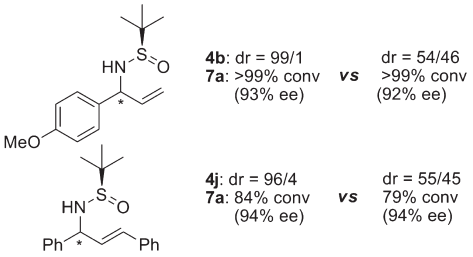
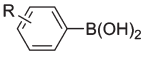
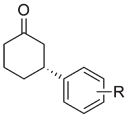
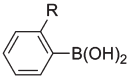
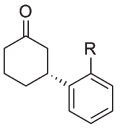
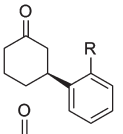
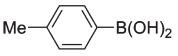
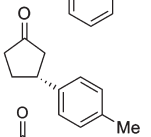
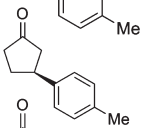
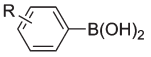
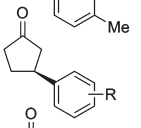
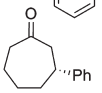
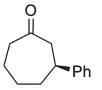
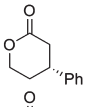
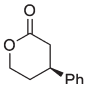


Figure 3. Impact of the carbon chirality for Rh(I)-catalyzed 1,4-addition of phenylboronic acid (**6a**) to 2-cyclohexenone (**5a**).

With the best ligands **4b** and **4j** in hand, we examined the substrate scope for this novel type of ligand in Rh(I)-catalyzed 1,4-additions. A variety of arylboronic acids and enones were subjected to this reaction under optimal conditions, and the results are summarized in Table 2. It was found that ligand **4b** was highly effective for the reactions between 2-cyclohexenone (**5a**) and *para*- or *meta*-substituted arylboronic acids to give the corresponding products in 57−99% yields with 89−95% ee's (Table 2, entries 3−8), but far less effective for *ortho*-substituted arylboronic acids (Table 2, entries 9 and 10). However, ligand **4j** was found to be more suitable for the asymmetric addition of *ortho*-substituted arylboronic acids to 2-cyclohexenone (**5a**) to afford the contrary configuration adducts with excellent ee's (Table 2, entries 9−10 vs 11−12). Moreover, ligand **4j** behaved an obvious advantage over **4b** to give up to 99% ee when using enones **5b**−**d** as substrates (Table 2, entries 13−20). The application of ligand **4j** can be also extended to the Rh(I)-catalyzed asymmetric addition of arylboronic acids to *tert*-butyl cinnamate (**8**) under the same conditions to give the desired products **9** in good yields and ee's without further optimization (Scheme 2).

In order to gain insight into the coordination mode of *N*-sulfinyl-based olefin ligands, a ^1H NMR study was carried out by mixing of ligand **4j** and $[RhCl(C_2H_4)_2]_2$ in $CDCl_3$. The spectrum suggested that there existed a strong coordination between olefin and rhodium, judged by the obvious upfield shifts of the olefin signals from $\delta = 6.8$ ppm and 6.2 ppm to $\delta = 5.0$ ppm and 4.3 ppm (see the Supporting Information). The coordination of sulfur atom and olefin

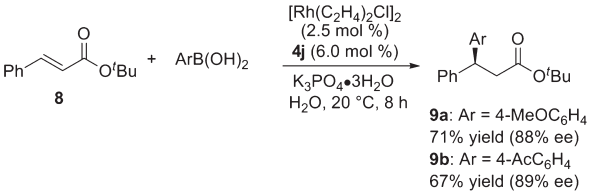
Table 2. Rhodium-Catalyzed Asymmetric 1,4-Additions[a]

entry	boronic acid (**6**)	ligand	product (**7**)	yield (%)[b]	ee (%)[c]
1	$PhB(OH)_2$ (**6a**)	**4b**		90	94
2	$PhB(OH)_2$ (**6a**)	**4j**		79	95
					
3	**6b**: R = 4-OMe	**4b**		99	93
4	**6c**: R = 4-F	**4b**		90	93
5	**6d**: R = 4-^{t}Bu	**4b**		80	94
6	**6e**: R = 3-Cl	**4b**		81	89
7	**6f**: R = 3-Me	**4b**		86	95
8	**6g**: R = 3,5-Me_2	**4b**		57	92
					
9		**4b**		81	40
10	**6h**: R = Cl **6i**: R = OMe	**4b**		92	37
11	**6h**: R = Cl	**4j**		98	97
12	**6i**: R = OMe	**4j**		90	95
13	 **6j**	**4b**		55	39
14	**6j**	**4j**		62	99
					
15	**6e**: R = 3-Cl	**4j**		62	93
16	**6k**: R = 2-F	**4j**		68	97
17	**6a**	**4b**		98	82
18	**6a**	**4j**		71	92
19	**6a**	**4b**		83	89
20	**6a**	**4j**		87	90

[a] All the reactions were carried out with enone **5** (0.40 mmol), arylboronic acid **6** (0.60 mmol), $K_3PO_4 \cdot 3H_2O$ (0.030 mmol), $[RhCl(C_2H_4)_2]_2$ (0.010 mmol), ligand (0.024 mmol) in water (2.0 mL), and dioxane (0.08 mL) under argon for 3 h. [b] Isolated yield. [c] The ee was determined by chiral HPLC.

to rhodium was further confirmed by X-ray analysis of an obtained single crystal formed between ligand **4j** and $[RhCl(C_2H_4)_2]_2$ (Figure 4).

Scheme 2. Rh(I)-Catalyzed Asymmetric Addition of Arylboronic Acids to *tert*-Butyl Cinnamate



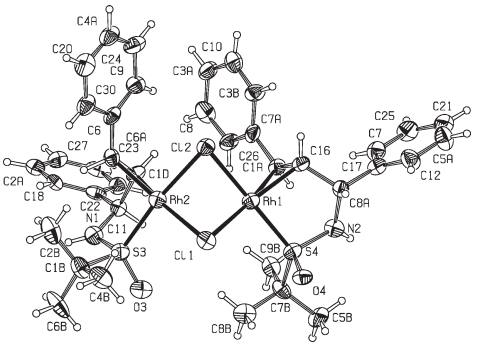


Figure 4. X-ray structure of [Rh**4j**Cl]$_2$ complex.

In summary, we described the development of a variety of *N*-sulfinyl-based chiral sulfur−olefin ligands for the first time by the combination of *tert*-butanesulfinamide and olefin moieties and their successful application in Rh(I)-catalyzed asymmetric 1,4-additions. The ease of synthesis and needless consideration of the carbon chirality make this type of ligand attractive and promising for asymmetric catalysis. Further exploring the application of chiral sulfur−olefin ligands in other transition-metal-catalyzed asymmetric reactions is underway in our laboratory.

Acknowledgment. We are grateful to financial support from the National Science Foundation of China (20802079, 21072194) and the National Basic Research Program of China (973 program, 2010CB833300).

Supporting Information Available. Procedure for the ligand synthesis and Rh-catalyzed 1,4-additions, characterization of ligands and adducts, X-ray data, and data for the determination of ee of adducts along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.