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A Diastereomeric Pair of Sulfoxide-containing Chiral MOP-type Ligands: Preparation and Application to Rhodium-catalyzed Asymmetric 1,4-Addition Reactions

Takashi Hoshi,* Masataka Fujita, Shouta Matsushima, Hisahiro Hagiwara, and Toshio Suzuki
Department of Applied Chemistry and Chemical Engineering, Niigata University, Nishi-ku, Niigata 950-2181, Japan

E-mail: hoshi@gs.niigata-u.ac.jp

(R,S_S)-Sulfoxide-MOP (**L2**) and (R,R_S)-sulfoxide-MOP (**L3**) were developed as a diastereomeric pair of sulfoxide-containing chiral MOP-type ligands. These two ligands also represent the first monosulfoxide analogues of BINAP. The chiral ligand **L2** was successfully applied to the highly enantioselective rhodium-catalyzed 1,4-addition between α,β-unsaturated ketones or esters and arylboronic acids, and exhibited a broad substrate scope when the reaction was performed using 1.5 mol% Rh in cyclohexane/H_2O (10:1) at 40 °C under mild basic conditions.

Keywords: Sulfoxide ligand | Rhodium catalyst | 1,4-Addition

The use of chiral non-C_2-symmetric bidentate ligands containing strong and weak donor heteroatom pairs in transition-metal-catalyzed enantioselective processes has proven to be a powerful strategy for controlling the stereochemistry-determining step through the different trans influence of the two ligating heteroatoms. Among such ligands, P,S-ligands are especially attractive, because the extra chirality on sulfur generated by coordination to the metal center (sulfur chirality) can be utilized as an additional stereocontrol element.[1] Consequently, the labile metal-bound substrate is positioned trans to the stronger phosphorus donor and adjacent to the stereogenic sulfur center. We have previously reported the development of sulfide-containing MOP-type ligands, such as (*R*)-sulfide-MOP (**L1**) and its various analogues (Figure 1, left), and their application to the highly enantioselective palladium-catalyzed allylic alkylation of indoles with 1,3-diphenylpropenyl acetate.[2] However, because the stereogenic sulfur center generated at the metal-bound sulfide donor has the potential to undergo inversion owing to its low energy barrier,[3] the erosion of enantioselectivity must be considered when using sulfides as donor ligands in metal-catalyzed asymmetric processes. Sulfoxides, which possess many potentially attractive features as chiral ligands,[1c,4] resist sulfur inversion owing to their inherent central chirality with a high inversion barrier. Furthermore, when the chiral sulfoxide also contains additional chirality in the ligand backbone, a pair of diastereomers is generated, and their different stereochemistry can be used as a control element to influence the reactivity and enantioselectivity of catalytic asymmetric processes. Herein, we report the development of a new class of MOP-type ligands,[5,6] (R,S_S)-sulfoxide-MOP (**L2**) and (R,R_S)-sulfoxide-MOP (**L3**), as a pair of diastereomeric sulfoxide-containing chiral P,S-ligands (Figure 1, center and right). These two non-C_2-symmetric bidentate ligands also represent the first monosulfoxide analogues of BINAP.[7] In the presence of **L2**, the rhodium-catalyzed asymmetric 1,4-addition of α,β-unsaturated ketones and esters with arylboronic acids proceeded smoothly in generally high yields and excellent enantioselectivities under mild conditions.[8,9]

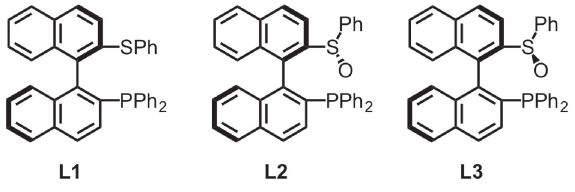
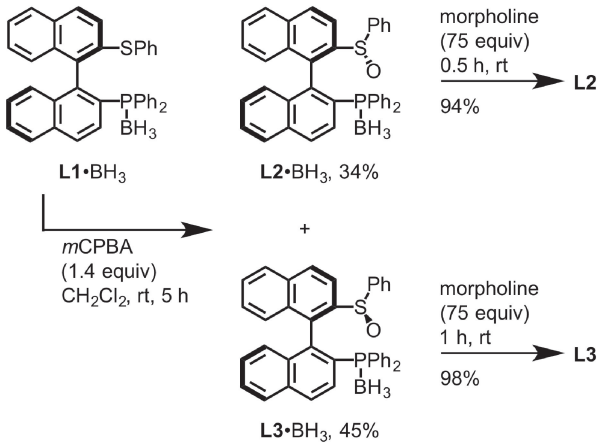


Figure 1. (*R*)-Sulfide-MOP (**L1**), (R,S_S)-sulfoxide-MOP (**L2**), and (R,R_S)-sulfoxide-MOP (**L3**).

(R,S_S)-Sulfoxide-MOP (**L2**) and (R,R_S)-sulfoxide-MOP (**L3**) were prepared in enantiomerically and diastereomerically pure form via the route depicted in Scheme 1. The *m*CPBA oxidation of BH_3-protected (*R*)-sulfide-MOP (**L1**·BH_3)[2] generated the corresponding sulfoxides **L2**·BH_3 and **L3**·BH_3 as a mixture of diastereomers, which were readily separated by simple column chromatography to afford 34% and 45% isolated yields of **L2**·BH_3 and **L3**·BH_3, respectively. Deprotection of each diastereomer using morpholine as a BH_3 scavenger furnished the corresponding sulfoxide-MOP ligands **L2** and **L3** in almost quantitative yields. The relative stereochemistry of **L2** and **L3** was determined via the single-crystal XRD analysis of the **L2**·$PtCl_2$ and **L3**·$PtCl_2$ complexes (Figure 2). The sulfur-bound phenyl groups of **L2**·$PtCl_2$ and **L3**·$PtCl_2$, which would be expected to possess geometries similar to those of the rhodium complexes generated in the catalytic cycle, were found to occupy the quasi-axial and quasi-equatorial positions, respectively.

The rhodium-catalyzed asymmetric arylation of electron-deficient alkenes, such as α,β-unsaturated carbonyl compounds, with arylboronic acids, has emerged as one of the most convenient and reliable carbon–carbon bond-forming processes for creating benzylic stereocenters.[8,9] Therefore, we selected this important transformation as a test reaction for evaluating **L2** and



Scheme 1. Synthesis of sulfoxide-MOP ligands **L2** and **L3**.

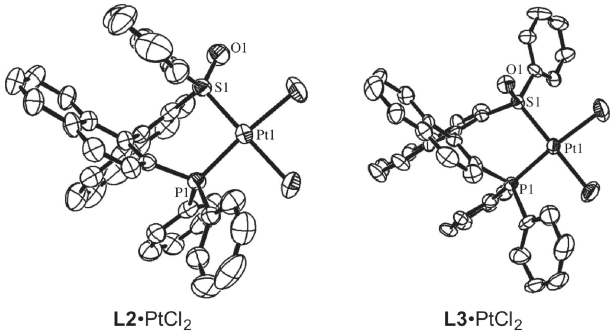
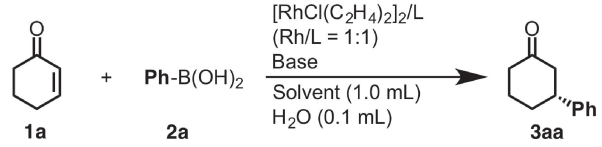


Figure 2. ORTEP diagrams of **L2**·$PtCl_2$ (left) and **L3**·$PtCl_2$ (right). Ellipsoids are shown at 50% probability, and hydrogen atoms are omitted for clarity.

Table 1. Optimization of rhodium-catalyzed 1,4-addition of **1a** with **2a**[a]



Entry	Rh /mol%	L	Solvent Temp/°C	Base (mol%)	Time /h	Yield /%	ee /%[b]
1	3.0	**L2**	Dioxane RT	KOH (50)	15	1	85
2	3.0	**L2**	Toluene RT	KOH (50)	5	28	99
3	3.0	**L3**	Toluene RT	KOH (50)	25	0	—
4	3.0	**L1**	Toluene RT	KOH (50)	25	5	0
5	1.5	**L2**	Toluene 40	KOH (50)	2.5	71	97
6	1.5	**L2**	C_6H_{12} 40	KOH (50)	1.5	84	99
7	1.5	**L2**	C_6H_{12} 40	K_3PO_4 (50)	0.5	92	99
8	1.5	**L2**	C_6H_{12} 40	K_2CO_3 (50)	0.5	91	99
9	1.5	**L2**	C_6H_{12} 40	K_2CO_3 (10)	3	53	98
10	1.5	**L2**	C_6H_{12} 40	—	3	4	96

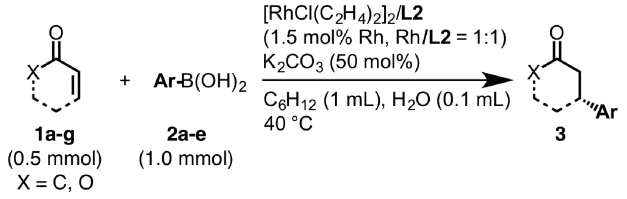
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.75 or 1.5 mol%), Ligand (1.5 or 3.0 mol%) in solvent (1 mL) and H_2O (0.1 mL). [b]Determined by HPLC analysis.

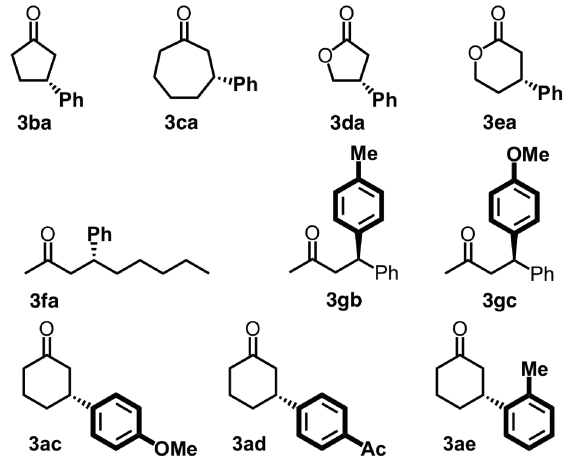
L3 as chiral ligands for asymmetric catalysis. During the survey of reaction conditions for the 1,4-addition of 2-cyclohexenone (**1a**) and phenylboronic acid (**2a**) (Table 1), we discovered that the use of **L2** with $[Rh(C_2H_4)_2Cl]_2$ as the rhodium source (3 mol% Rh, Rh/**L2** = 1:1) in dioxane/H_2O (10:1) with 50 mol% KOH at room temperature provided the arylation product **3aa** in only 1% yield, but fortunately with acceptable enantioselectivity (85% ee) (Table 1, Entry 1). Changing the solvent from dioxane to the more hydrophobic toluene led to significant improvements in both the yield (28%) and enantioselectivity (99% ee) (Table 1, Entry 2). In contrast, when **L3** was used under the same reaction conditions, **1a** remained unreacted and no arylation product was obtained, suggesting that the stereogenic sulfur center (sulfur chirality) plays an important role in controlling the catalysis (Table 1, Entry 3). The use of **L1** was also ineffective and the racemate was obtained in only 5% yield (Table 1, Entry 4). We then focused our efforts on optimizing the catalytic system based on **L2**. At a slightly elevated temperature (40 °C), the yield was remarkably improved to 71% despite the use of one-half of the amount of the rhodium catalyst (1.5 mol% Rh) (Table 1, Entry 5). Conducting the reaction in a mixture of cyclohexane and H_2O (10:1) afforded an 84% yield of **3aa** after 1.5 h (Table 1, Entry 6). The use of K_3PO_4 or K_2CO_3 instead of KOH led to the complete consumption of **1a** to achieve 92% and 91% yields of **3aa**, respectively (Table 1, Entries 7 and 8). In addition, the use of these weaker bases led to higher reaction rates, allowing the reaction to reach completion in 0.5 h. However, it was essential to perform the reaction under basic conditions, which is likely attributable to the generation of the active hydroxorhodium complex in the catalytic cycle (Table 1, Entries 9 and 10).[10,11]

Under the developed optimum reaction conditions, we investigated the substrate scope of the rhodium-catalyzed 1,4-addition using (R,S_S)-sulfoxide-MOP (**L2**) (Table 2). Even though seven-membered cyclic ketone (**3ca**) and five-membered lactone (**3da**) were obtained in lower yields,[12] excellent ee values ranging from 94% to 97% were achieved for the reactions of five- to seven-membered cyclic enones or enoates (**1b**–**1d**), as observed for **1a** (Table 2, Entries 1–4). Acyclic enones bearing *n*-pentyl or phenyl substituents in the β-position with *trans*-olefin geometry were also applicable to the **L2**-based rhodium-catalyzed 1,4-addition reactions, although the former (**1f**) was converted with somewhat lower enantioselectivity (75% ee) relative to the latter (**1g**) and cyclic substrates (**1a**–**1e**) (Table 2, Entries 5–7). When **1a** was used as an olefinic substrate, electron-rich, electron-deficient, and bulky arylboronic acids (**2c**–**2e**) could also be successfully employed to achieve excellent enantioselectivities (Table 2, Entries 8–10). Even though the use of electronically or sterically deactivated boronic acids **2d** and **2e** led to 43% and 41% yields under standard reaction conditions, these low yields could be improved to 51% and 63% at a slightly elevated temperature (60 °C) with excellent enantioselectivities.[13,14]

In summary, we have developed (R,S_S)-sulfoxide-MOP (**L2**) and (R,R_S)-sulfoxide-MOP (**L3**) as a diastereomeric pair of sulfoxide-containing chiral MOP-type ligands. Ligand **L2** was successfully applied to the highly enantioselective rhodium-catalyzed 1,4-addition of various α,β-unsaturated ketones and esters with electron-rich, electronically neutral, electron-deficient, and bulky arylboronic acids using low catalyst loadings, and the reaction proceeded with short reaction times under mild basic conditions. The excellent enantioselectivity of **L2** in this transformation is promising for its application to other important rhodium-catalyzed asymmetric processes. Studies toward the use of the diastereomer **L3** as a chiral ligand are also underway in our laboratory.

Table 2. Substrate scope using **L2**[a]





Entry	Product	Time/h	Yield/%	ee/%[b]
1	**3ba**	0.5	92	97
2	**3ca**	1.5	52	94
3	**3da**	3	39	95
4	**3ea**	1	87	96
5	**3fa**	7	50	75
6	**3gb**	2	85	91
7	**3gc**	3	86	95
8	**3ac**	0.5	87	98
9	**3ad**	4	43	97
		(3)[c]	(51)[c]	(98)[c]
10	**3ae**	6	41	95
		(1.5)[c]	(63)[c]	(92)[c]

[a]Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.75 mol%), **L2** (1.5 mol%), K_2CO_3 (0.025 mmol) in cyclohexane (1 mL) and H_2O (0.1 mL) at 40 °C. [b]Determined by HPLC analysis. [c]60 °C.

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13 In contrast, the 1,4-addition reaction of **2a** to **1d** at 60 °C led to a decrease in the yield of **3da** from 39% to 25%.
14 We also performed the 1,4-addition reaction of **2e** to **1a** at a further elevated temperature (80 °C). However, both the yield and the ee value of **3ae** reduced to 41% and 86% ee, respectively.