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Chiral Heterodisulfoxide Ligands in Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to Chromenones

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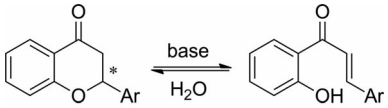
A new family of benzene-based chiral heterodisulfoxide ligands **L1**–**L5** was synthesized in a single step. These disulfoxide ligands were applied in the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to chromenones. The addition of diverse arylboronic acids to chromenones proceeds smoothly in up to 70% yield with up to 95% *ee*.

Introduction

Flavanones and their derivatives are a very important class of natural products that possess many notable pharmacological activities such as anti-inflammatory, antitumor, and antibacterial properties.[1] Synthetic methods for the construction of racemic flavanones have been extensively developed.[2] However, approaches to the stereoselective preparation of enantiomerically pure structural motifs are limited, and much attention has been paid to the production of a catalytic asymmetric strategy employing enzymes, organocatalysis, and metal-based catalysts.[3] Enzyme-catalyzed biosynthesis can generate chiral flavanones with very high enantioselectivity,[4] but other attempts, including the use of amino acids,[5] tartaric acid, or *N*-benzyl-1-phenylethylamine[6] and chiral cobalt–salen[7] complex catalyzed asymmetric oxa-Michael-type cyclization, failed. A recent breakthrough was achieved by Scheidt et al.[8] who utilized chiral thioureas as organocatalysts in the asymmetric intramolecular conjugate addition of phenols to unsaturated ketones; the corresponding flavanones were generated in yields and with excellent *ee* values. A similar approach was reported by Hintermann; modest enantioselectivities were observed (up to 64%*ee*) when quinine was used as a catalyst.[9] On the other hand, Feng et al.[10] employed chiral *N*,*N*′-dioxide nickel(II) catalysts in enantioselective intramolecular oxa-Michael (IOM) additions and flavanones were obtained with up to 99%*ee*.

Pioneered by Hayashi and Miyaura,[11] rhodium-catalyzed 1,4-addition of organoboron reagents to electron-deficient olefins is one of the most powerful strategies for enantioselective C–C bond formation. Recently, we described a new method to prepare chiral flavanones, which proceeds through rhodium-catalyzed conjugate addition of sodium tetraarylborates to chromenones when a C_2-symmetric chiral disulfoxide is used as the ligand. Good reactivities (yields up to 75%) and excellent enantioselectivities (up to >99%*ee*) were achieved.[12] Although sodium tetraarylborates can promote the 1,4-addition because of high nucleophilicity, there are still some limitations in their use: lack of readily available functionalized sodium tetraarylborates,[13] and the byproducts are generally toxic.[14] Utilizing commercially available arylboronic acids as the nucleophiles is obviously an attractive and convenient way to make functionalized chiral flavanones.[15]

Achieving rhodium-catalyzed 1,4-addition of arylboronic acids to chromenones is significantly challenging work and few reports describe this strategy for the synthesis of chiral flavanones.[12,16] Undesirable reversibility of the reaction by ring-opening/cyclization under the basic conditions of the 1,4-addition would lead to erosion of the enantiomeric excess and yield of the chiral flavanones [Equation (1)].[16c]



ref.[16c] (1)

Although (*R*)-BINAP gives an excellent *ee* value (97%), a low yield (31%) was observed; our C_2-symmetric disulfoxide ligand, [(*R*,*R*)-1,2-bis(*tert*-butylsulfinyl)benzene], also demonstrated unsatisfactory reactivity (32% yield).[12] Therefore, it was necessary to modify our chiral disulfoxide ligand to improve the reactivity. In this way, good yields and high *ee* values of the chiral flavanones might be achieved.

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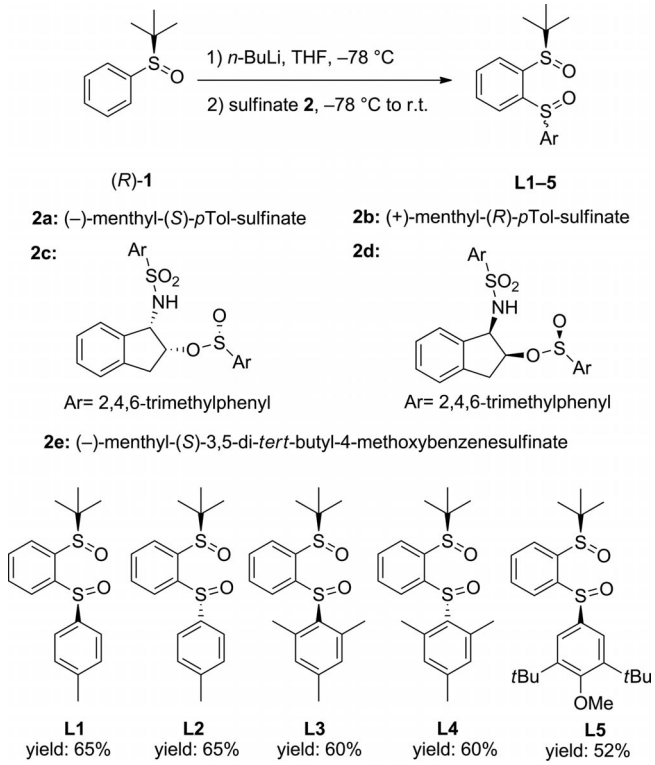
In investigations performed by Dorta,[17] chiral aryl sulfoxides acted as highly efficient ligands in the rhodium-catalyzed 1,4-addition of arylboronic acids to electron-deficient acceptors. In our recent work, *tert*-butyl sulfoxide ligands showed encouraging results in asymmetric reactions.[12,18,19] We thus expected that combination of simple chiral *tert*-butyl and aryl sulfoxides, which would allow the advantages associated with each framework, in one framework would provide a highly efficient ligand. Herein, we would like to report a new class of chiral heterodisulfoxide ligands containing *tert*-butyl and aryl sulfoxides within a rigid benzene scaffold, and we also evaluate these ligands in the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to chromenones.

Results and Discussion

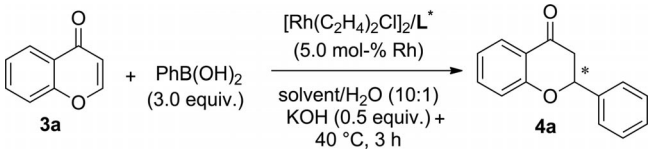
The sequence of ligand synthesis is outlined in Scheme 1. The preparation of new heterodisufoxide ligands **L1**–**L5** was accomplished efficiently in one step from (*R*)-phenyl *tert*-butyl sulfoxide (**1**).[17a,20] Sulfoxide **1** was submitted to *ortho*-lithiation by using *n*BuLi (1.1 equiv.) in THF at –78 °C for 1 h. Subsequent trapping of electrophilic sulfinate ester **2a**–**e**[21,22] at –78 °C followed by slow warming to room temperature gave disulfoxide ligands **L1**–**L5** in 52–65% yield.



Scheme 1. Synthesis of chiral heterodisulfoxide ligands **L1**–**L5**.

With chiral heterodisufoxide ligands **L1**–**L5** in hand, our initial efforts were focused on ligand screening and establishing optimal conditions. Using rhodium catalysts generated in situ from $[Rh(C_2H_4)_2Cl]_2$ (2.5 mol-%) and ligand **L1**–**L5** (6.0 mol-%), aqueous KOH (50 mol-%) was added to a solution of chromenone **3a** and phenylboronic acid (3.0 equiv. with respect to **3a**) in CH_2Cl_2, and the mixture was heated at 40 °C for 3 h (Table 1). For ligand **L1**, the enantioselectivity was poor (72%*ee*) but a moderate yield (45%) of flavanone **4a** was obtained (Table 1, Entry 1). On the contrary, diastereomer **L2** gave a low yield (20%), though the enantioselectivity was high (95%*ee*; Table 1, Entry 2). Interestingly, ligand **L3**, which is similar to **L1** except for two *ortho*-methyl substituents, provided the best result (56% yield and 91%*ee*; Table 1, Entry 3). However, bulky ligands **L4** and **L5** were not effective and low yields and low enantioselectivities were observed (Table 1, Entries 4 and 5). Moreover, diene catalyst $[Rh(cod)Cl]_2$ was also tested, and a poor yield (10%) was observed;[23] moreover, the 1,2-adduct of the carbonyl group was not observed in the heterodisufoxide/Rh^I catalytic system.

Table 1. Rh-catalyzed enantioselective 1,4-addition of phenylboronic acid to chromenone **3a**. Screening of ligands and solvents.[a]



Entry	Ligand	Solvent	Yield [%][b]	*ee* [%][c]
1	**L1**	CH_2Cl_2	45	72 (*R*)[d]
2	**L2**	CH_2Cl_2	20	95
3	**L3**	CH_2Cl_2	55	91
4	**L4**	CH_2Cl_2	20	71
5	**L5**	CH_2Cl_2	trace	n.d.
6	**L3**	toluene	70	91
7	**L3**	cyclohexane	60	86
8	**L3**	1,4-dioxane	trace	n.d.
9	**L3**	EtOH	trace	n.d.

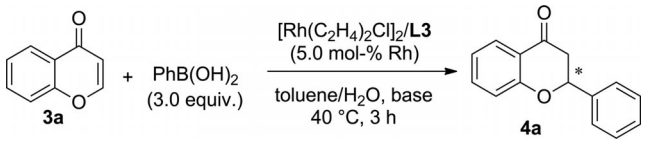
[a] The reaction was performed with **3a** (0.2 mmol), phenylboronic acid (0.6 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.0 mol-% Rh), and **L** (6.0 mol-%) in solvent (1 mL) at 40 °C for 3 h. [b] Isolated yield. [c] The *ee* values were determined by HPLC with a chiral column. [d] The absolute configuration was determined by comparison to literature data.[8]

To improve the reactivity and enantioselectivity of ligand **L3** further, a variety of solvents were examined. The reaction proceeded well in nonpolar solvents (toluene and cyclohexane; Table 1, Entries 6 and 7), and a low activity of ligand **L3** was observed in polar solvents (dioxane and ethanol; Table 1, Entries 8 and 9). Toluene was found to be the best solvent for this reaction (70% yield, 91%*ee*; Table 1, Entry 6).

Encouraged by these results, the effect of the added base, which plays an important role in the reactivity and enantioselectivity of rhodium-catalyzed 1,4-additions, was studied. The rhodium-catalyzed asymmetric 1,4-addition to **3a** was optimized by using 0.5 equiv. of base in the presence of Rh/**L3** (5.0 mol-% Rh) in toluene/H_2O (10:1) at 40 °C for 3 h (Table 2). When KOH and K_2CO_3 were used, about 70% yield and 90%*ee* were obtained (Table 2, Entries 1 and 2). Cs_2CO_3 and Et_3N did not give better results (Table 2, En-

tries 3 and 4). It is interesting to note that increased enantioselectivity of **4a** was observed (*ee* >95%) when weak bases ($KHCO_3$ and KF) were used, but the yields were lower (Table 2, Entries 5 and 6).

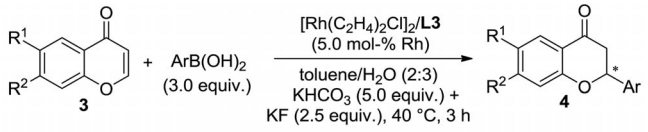
Table 2. Rh-catalyzed enantioselective 1,4-addition of phenylboronic acid to chromenone **3a**. Screening of bases.[a]

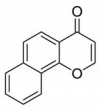


Entry	Toluene/H_2O	Base (equiv.)	Yield [%][b]	*ee* [%][c]
1	10:1	KOH (0.5)	70	91
2	10:1	K_2CO_3 (0.5)	75	89
3	10:1	Cs_2CO_3 (0.5)	55	91
4	10:1	Et_3N (0.5)	45	93
5	10:1	$KHCO_3$ (0.5)	40	95
6	10:1	KF (0.5)	40	96
7	1:1	$KHCO_3$ (5.0)	60	95
8	2:1	KF (2.5)	57	94
9	2:1	KF (12.0)	80	87
10	2:3	$KHCO_3$ (5.0) + KF (2.5)	67	94

[a] The reaction was performed with **3a** (0.2 mmol), phenylboronic acid (0.6 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.0 mol-% Rh), and **L3** (6.0 mol-%) in toluene (1 mL) at 40 °C for 3 h. [b] Isolated yield. [c] The *ee* values were determined by HPLC with a chiral column.

Table 3. Rh-catalyzed enantioselective 1,4-addition of arylboronic acids to chromenones **3**.[a]



Entry	Substrate	R^1	R^2	Ar	Yield [%][b]	*ee* [%][c]
1	**3a**	H	H	Ph	67 (**4a**)	94
2	**3b**	CH_3	H	Ph	53 (**4b**)	94
3	**3c**			Ph	60 (**4c**)	92
4	**3d**	Br	H	Ph	70 (**4d**)	92
5	**3e**	Cl	H	Ph	65 (**4e**)	93
6	**3f**	H	Br	Ph	60 (**4f**)	93
7	**3g**	H	CH_3	Ph	53 (**4g**)	95
8	**3h**	F	H	Ph	56 (**4h**)	93
9	**3i**	H	H	4-MeC_6H_4	64 (**4i**)	95
10	**3j**	H	H	3-MeC_6H_4	60 (**4j**)	92
11	**3k**	H	H	2-MeC_6H_4	35 (**4k**)	95
12	**3l**	H	H	3-$MeOC_6H_4$	63 (**4l**)	95
13	**3m**	H	H	2-naphthyl	67 (**4m**)	95

[a] The reaction was performed with **3** (0.2 mmol), arylboronic acid (0.6 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.0 mol-% Rh), and **L3** (6.0 mol-%) in toluene (1 mL) at 40 °C for 3 h. [b] Isolated yield. [c] The *ee* values were determined by HPLC with a chiral column.

To improve the reactivity and maintain the high enantioselectivity of ligand **L3**, the amount of $KHCO_3$ and KF was increased, respectively. When 5.0 equiv. of $KHCO_3$ was added, the yield was increased (60%) and the enantioselectivity was still high (95%*ee*; Table 2, Entry 7). Similar results were achieved by using 2.5 equiv. KF (Table 2, Entry 8). Nevertheless, a higher loading of KF gave a yield of 80%, but the selectivity was lower (Table 2, Entry 9). The latter was slightly improved by a combination of $KHCO_3$ (5 equiv.) and KF (2.5 equiv.; Table 2, Entry 10), which served as the best conditions for further studies. A prolonged reaction time (12 h) also did not improve the yield.

Under the optimal reaction conditions, the substrate scope was evaluated. A variety of chromenones **3** and arylboronic acids were well suited for this catalyst system. Desired 1,4-adducts **4** were well obtained in moderate to good yield (53–70%) with excellent enantioselectivities (92–95%*ee*, Table 3).

Conclusions

In conclusion, we have developed a novel class of chiral hetero-disulfoxide ligands **L1**–**L5**, which are effective ligands for asymmetric rhodium-catalyzed 1,4-addition of arylboronic acids to chromenones. The enantioselective addition process affords flavanones **4** in excellent enantioselectivities (92–95% *ee*) and up to 70% yield under mild conditions. This paper represents a practical strategy to prepare a series of chiral flavanones through rhodium-catalyzed 1,4-addition.

Experimental Section

General Procedure for the Preparation of Chiral Heterodisufoxide Ligands L1–L5: At –78 °C, *n*BuLi (2.5 M in hexane, 1.8 mL, 4.4 mmol) was added dropwise to a solution of (*R*)-*tert*-Butylsulfinylbenzene (**1**; 0.73 g, 4.0 mmol) in tetrahydrofuran (15 mL). The resulting mixture was stirred for 1 h at –78 °C and optically pure sulfinate ester **2**[21,22] (4.4 mmol) was added to the mixture. After 0.5 h at –78 °C the reaction was warmed to room temperature. The resulting mixture was quenched with water (10 mL), the organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried with Na_2SO_4 and concentrated to a small volume. Flash chromatography (petroleum/EtOAc, 2:1) of the crude material afforded ligands **L1**–**L5**.

General Procedure for the Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Chromenones: Under an argon atmosphere and at room temperature, to a 10-mL Schlenk tube with a Teflon cap was added ligand **L** (6.0 mol-%), $[RhCl(C_2H_4)_2]_2$ (1.94 mg, 5.0 mol-% Rh), and CH_2Cl_2 (1.0 mL), and the mixture was stirred at 25 °C. After 30 min, CH_2Cl_2 was evaporated. Then, $ArB(OH)_2$ (0.6 mmol, 3.0 equiv.), chromene **3** (0.2 mmol), toluene (1.0 mL), and $KHCO_3$ (1.0 mmol, 5.0 equiv.) + KF (5.0 mmol, 2.5 equiv.) in degassed H_2O (1.5 mL) was added sequentially. The mixture was stirred for 3 h at 40 °C and directly charged onto a column (silica gel) and purified by flash chromatography (petroleum/EtOAc) to afford product **4**.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization of the prepared compounds, copies of the NMR spectra, and chiral HPLC spectra of the Michael addition products.

Acknowledgments

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[23] Reaction conditions: **3a** (0.2 mmol) and phenylboronic acid (0.6 mmol) in 1,4-dioxane/H_2O (10:1) at 60 °C for 12 h in the presence of $[Rh(cod)Cl]_2$ (5.0 mol-% Rh) and KOH (50 mol-%).

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