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ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · JUNE 2010

Impact Factor: 12.11 · DOI: 10.1021/ja103812e · Source: PubMed

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A C_2-Symmetric Chiral Bis-Sulfoxide Ligand in a Rhodium-Catalyzed Reaction: Asymmetric 1,4-Addition of Sodium Tetraarylborates to Chromenones

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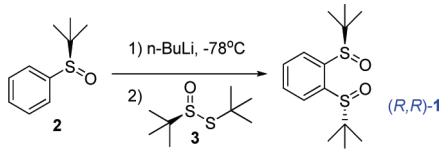
Asymmetric catalysis provides efficient and useful methods for the preparation of enantiopure compounds. In this field, the development of new chiral ligands has been considered one of the most interesting topics.[1] Sulfoxides as moieties with sulfur chirality, whose coordination chemistry is well-known,[2] are ideal candidates. However, over the past three decades, only a few examples of the application of chiral sulfoxide ligands have been described. In fact, such reported methods could not provide particularly effective chiral environments for asymmetric catalysis.[3] A recent breakthrough was achieved by Dorta's group, who developed a class of bis-sulfoxide ligands with an atropisomeric backbone that induced excellent outcomes in rhodium-catalyzed asymmetric reactions.[4] Recently, we reported a new class of chiral hybrid bidentate ligands (P−SO ligands) using a *tert*-butylsulfinyl moiety[5] as the ligating entity and source of chirality in Cu-, Pd-, and Rh-catalyzed reactions.[6] Since C_2-symmetric chiral ligands play an important role in catalytic asymmetric reactions,[7] efficient C_2-symmetric chiral bis-sulfoxides were sincerely considered.[3b,c] Shibasaki has reported a beautiful example of asymmetric catalysis with 1,2-bis(*p*-tolylsulfinyl)benzene as the ligand.[3c] Herein we present a novel and readily prepared C_2-symmetric chiral bis-sulfoxide ligand and its successful use in the Rh-catalyzed asymmetric 1,4-addition reaction, especially for 1,4-addition of sodium tetraarylborates to chromenones.

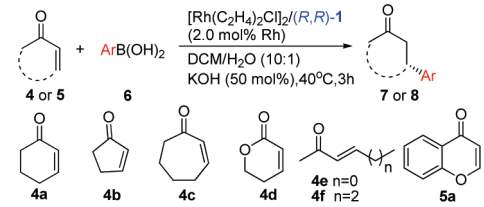
The synthesis of the new C_2-symmetric chiral bis-sulfoxide, (*R*,*R*)-1,2-bis(*tert*-butylsulfinyl)benzene [(*R*,*R*)-**1**], was accomplished in one concise step using (*R*)-benzyl *tert*-butylsulfoxide (**2**)[6a,8] (Scheme 1). After deprotonation of **2** with 1.1 equiv of *n*-BuLi at −78 °C for 1 h followed by addition of 1.1 equiv of (*R*)-thiosulfinate **3**,[9] the mixture was stirred for 0.5 h at −78 °C and then warmed to room temperature. The desired product (*R*,*R*)-**1** was obtained in 45% yield as a white solid by flash chromatography purification.

Scheme 1. Synthesis of (*R*,*R*)-1,2-Bis(*tert*-butylsulfinyl)benzene [(*R*,*R*)-**1**]



We chose the Rh-catalyzed 1,4-addition of arylboronic acids to electron-deficient olefins as the model reaction to evaluate (*R*,*R*)-**1** in asymmetric catalysis; this reaction was pioneered by Hayashi and Miyaura and is considered to be a useful tool for asymmetric C−C bond formation.[10,11] To our satisfaction, the products were formed in good to excellent yields (87−99%) and high enantioselectivities (92−98%) in the presence of 2 mol % Rh complex. The excellent results were achieved when various arylboronic acids **6** were surveyed with various electron-deficient olefins **4**, including cyclic enones, a cyclic ester, and linear enones (Table 1, entries 1−16).

Table 1. Rh-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acid to Olefins **4** and **5**[a]



entry	4/5	Ar	7/8	yield (%)[b]	ee (%)[c]
1	**4a**	Ph (**6p**)	**7ap**	96	98 (*R*)
2	**4a**	4-FC_6H_4 (**6q**)	**7aq**	97	97
3	**4a**	4-ClC_6H_4 (**6r**)	**7ar**	99	97
4	**4a**	4-MeC_6H_4 (**6s**)	**7as**	95	95
5	**4a**	4-*t*-BuC_6H_4 (**6t**)	**7at**	87	97
6	**4a**	3-ClC_6H_4 (**6u**)	**7au**	99	98
7	**4a**	3-MeC_6H_4 (**6v**)	**7av**	97	96
8	**4a**	2-MeC_6H_4 (**6w**)	**7aw**	90	96
9	**4a**	3,5-$Me_2C_6H_3$ (**6x**)	**7ax**	95	97
10	**4a**	1-naphthyl (**6y**)	**7ay**	93	92
11	**4a**	2-naphthyl (**6z**)	**7az**	98	93
12	**4b**	Ph (**6p**)	**7bp**	98	94
13	**4c**	Ph (**6p**)	**7cp**	95	93
14	**4d**	Ph (**6p**)	**7dp**	87	94
15	**4e**	Ph (**6p**)	**7ep**	97	98
16	**4f**	Ph (**6p**)	**7fp**	95	97
17[d]	**5a**	Ph (**6p**)	**8a**	32	99
18[e]	**5a**	Ph (**6p**)	**8a**	31	97

[a] Reaction conditions: **4** (0.5 mmol), **6** (1.0 mmol), $[Rh(C_2H_4)_2Cl]_2$ (2.0 mol % Rh), (*R*,*R*)-**1** (2.4 mol %), and KOH (2.5 M, 0.1 mL) in CH_2Cl_2 (1.0 mL) at 40 °C for 3 h. [b] Isolated yield. [c] Determined by HPLC analysis with chiral columns; the absolute configuration was determined by comparison to literature data.[10] [d] Using 5 mol % Rh and 3.0 equiv of **6p** for 5 h. [e] Using 5 mol % Rh, 6 mol % (*R*)-BINAP, 3.0 equiv of **6p**, and KOH (2.5M, 0.1 mL) in dioxane (1.0 mL) at 70 °C for 12 h.

It is important to note that our catalyst system also worked in the addition of phenylboronic acid to chromenone **5a**, which has generally been considered to be a challenging substrate for Rh-catalyzed 1,4-addition arising from the induction of an electron-donating group at the γ-position. In fact, such an adduct was shown to be a key scaffold in a large family of natural products, flavanones, which possess many biological activities, such as antitumor and anti-inflammatory properties.[12] Notably, to date, relatively few

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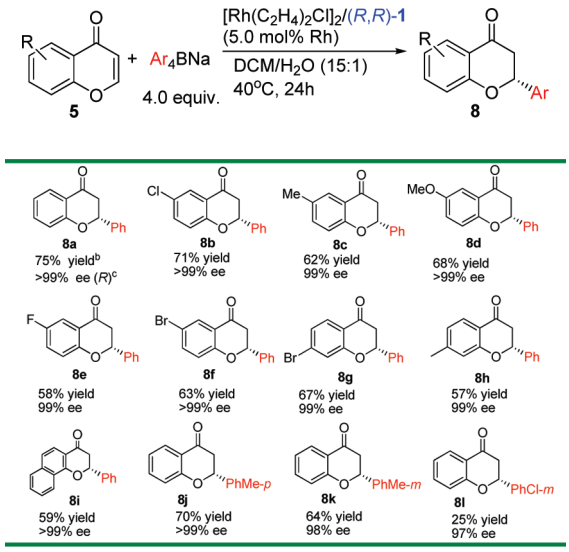
methods have been reported for the asymmetric catalytic synthesis of this class of skeletons,[13] and the strategy of the addition of arylboronic reagents to chromenones remains elusive.[14] In comparison with the previously reported system with Rh−BINAP (31% yield and 97% ee), the method developed here showed similar yield and 99% ee under mild conditions (Table 1, entries 17 and 18).

To our delight, such a transformation was highly promoted when sodium tetraarylborates[15] were utilized in place of $PhB(OH)_2$. Under optimal conditions, the desired products **8** were obtained in moderate to good yields (58−75%; Table 2, **8a**−**k**) and up to >99% ee.

Table 2. Rh-Catalyzed Asymmetric 1,4-Addition of Sodium Tetraarylborates to Chromenones **5**[a]



[a] Reaction conditions: **5** (0.2 mmol), sodium tetraarylborate (0.8 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.0 mol % Rh), and (*R*,*R*)-**1** (6.0 mol %) in CH_2Cl_2 (1.5 mL) at 40 °C for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis with chiral columns; the absolute configuration was determined by comparison to literature data.[13b]

Figure 1 shows the X-ray crystal structure of [{(*R*,*R*)-**1**}RhCl]$_2$. The bis-sulfoxide ligand (*R*,*R*)-**1** acts as a rigid pincer, with the rhodium atom clamped into a five-membered ring via the sulfur atoms; the two *tert*-butyl groups provide an excellent stereoenvironment that may generate the high enantioselectivity in the 1,4-addition.

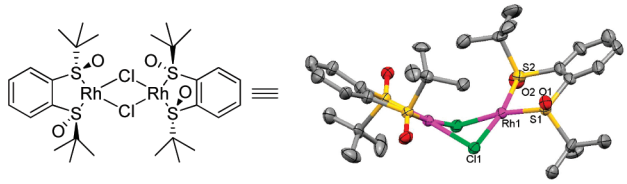


Figure 1. Structure and ORTEP illustration of [{(*R*,*R*)-**1**}RhCl]$_2$ with thermal ellipsoids drawn at the 50% probability level (hydrogen atoms have been omitted for clarity).

In conclusion, a novel and effective C_2-symmetric chiral bis-sulfoxide ligand has been developed for the rhodium-catalyzed asymmetric 1,4-addition of arylboronic reagents to α,β-unsaturated substrates, which afforded the corresponding adducts in good yields and excellent enantioselectivities. The present work is the first to offer a sufficient method for accessing optically pure flavanones through 1,4-addition of arylboronic reagents to chromenones.

Acknowledgment. We are grateful for support from the NSFC (20872139), the West Light Foundation of the Chinese Academy of Sciences, and the National Basic Research Program of China (973 Program, 2010CB833300).

Supporting Information Available: Experimental procedures, spectral data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA1005477