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Simple Chiral Chain Dienes as Ligands for Rh(I)-Catalyzed Conjugated Additions

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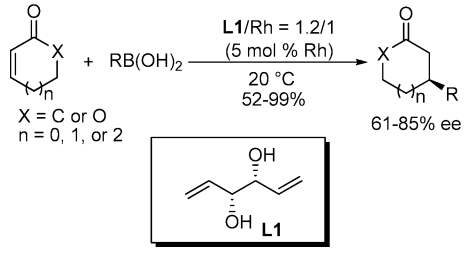
ABSTRACT



This paper describes that a simple and readily available chain diene (3*R*,4*R*)-hexa-1,5-diene-3,4-diol (L1) was successfully utilized as a novel steering ligand for Rh(I)-catalyzed asymmetric conjugated additions. Encouraging yields and ee's have been achieved, which may provide a new and practical direction for designing chiral diene ligands in the future.

The development of structurally new, effective, and accessible chiral ligands represents one of the most important subjects in asymmetric catalysis.[1] Recently, since the seminal contributions by Hayashi and Carreira,[2] several chiral chelating dienes have been successfully exploited as novel and highly efficient steering ligands for metal-catalyzed asymmetric reactions. Especially, in some cases, chiral dienes exhibit an obvious advantage over other types of ligands.[3] Some representatives (**1**−**5**) are listed in Figure 1, and it can be found that these types of ligands all bear rigidly bicyclic frameworks, which partially account for both high reactivity and enantioselectivity.[4−7] However, bicyclic structures also lead to synthetic problems to some extent. As stated by Carreira: "To ensure wide acceptance of these ligand systems, an easy and straightforward synthetic access to chiral dienes is of prime importance".[3b] Compared with bicyclic ones, chain dienes are more easily obtained. Although some chiral chain dienes are well-known compounds, to the best of our

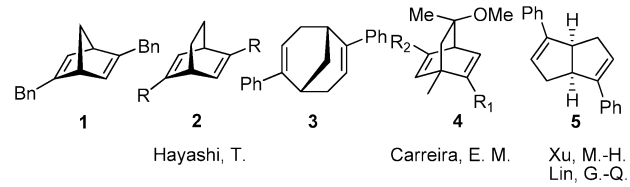


Figure 1. Representative diene ligands for asymmetric catalysis.

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vols. 1−3. (c) Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley-VSH: New York, 2000.

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

(3) For reviews on chiral diene ligands, see: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364. (b) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.

(4) For leading references on ligands **1**−**3**, see: (a) Ref 2a. (b) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425. (c) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (d) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (e) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307. (f) Shintani, R.; Sannohe, Y.; Tsuji, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 7277. (g) Shintani, R.; Ichikawa, Y.; Takatsu, K.; Chen, F.-X.; Hayashi, T. *J. Org. Chem.* **2009**, *74*, 869.

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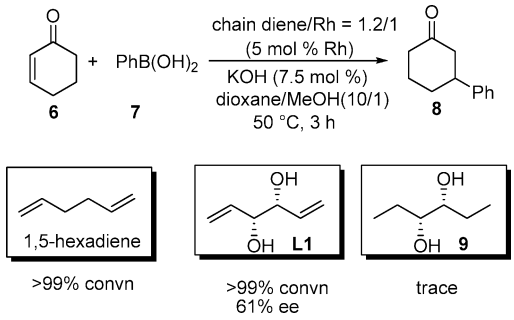
knowledge, successfully utilizing them as ligands for asymmetric reactions has never been reported.[8] The challenge may consist in the flexibility character of chain dienes. Herein, we wish to report our efforts on the development of chiral chain dienes as effective ligands for Rh(I)-catalyzed conjugated additions.[9]

To test the feasibility of using chain dienes as ligands, an initial study was conducted with Rh(I)-catalyzed conjugated addition as a model reaction. As shown in Scheme 1, the

Scheme 1. Initial Studies Using Chain Dienes As Ligands



reaction between 2-cyclohexenone (**6**) and phenylboronic acid (**7**) employing $[RhCl(C_2H_4)_2]_2$ (5 mol % Rh) as a catalyst precursor and 1,5-hexadiene (6 mol %) as a chain diene ligand in dioxane/MeOH (v/v = 10:1) at 50 °C proceeded smoothly to give the corresponding product **8** in quantitative conversion in 3 h,[10] while a control experiment without addition of 1,5-hexadiene gave no desired product. These results suggested that chain dienes could no doubt be utilized as efficient ligands and encouraged us to investigate the possibility of using chiral chain dienes as ligands. Hence, (3*R*,4*R*)-hexa-1,5-diene-3,4-diol (**L1**) was prepared and subjected as a chiral ligand to this reaction (Scheme 1).[11] To our surprise, with such a simple chiral diene bearing two terminal double bonds, the reaction went efficiently to afford the desired product **8** in >99% conversion and an encouraging 61% ee (Scheme 1). To prove that **L1** was not a diol but a diene ligand, (3*R*,4*R*)-hexane-3,4-diol (**9**) was subjected to this conjugated addition. Only a trace amount of product was observed, which strongly supports that olefin moieties of **L1** played the key role for this asymmetric process. As a flexible diene, the coordination mode and asymmetric induction pathway remain unknown and need further investigation. Although the enantioselectivity is still not satisfactory, it represents a successful example for application of a chiral chain diene as a novel type of diene ligand for metal-catalyzed asymmetric reactions.

Encouraged by this promising result, a variety of chiral chain dienes[12,13] were prepared and subjected to the Rh(I)-catalyzed asymmetric conjugated additions between 2-cyclohexenone (**6**) and phenylboronic acid (**7**) to search for more effective ligands. Some selected results are summarized in Figure 2. It was found that most of the ligand modified

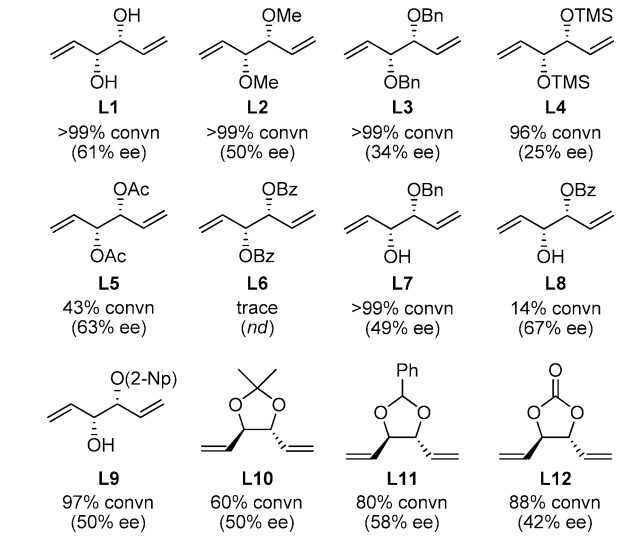


Figure 2. Selected diene ligands for asymmetric 1,4-additions.[14]

Rh(I) catalysts can promote this reaction efficiently to afford the desired product **8** in 43−>99% conversions and 25−67% ee's. Studies showed that the steric bulkiness of oxygen substituents for ligands (**L1**−**L4**) has a large impact on enantioselectivity. Monobenzoyl ester **L8** gave 67% ee but

(5) For leading references on ligand **4**, see: (a) Ref 2b. (b) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873. (c) Paquin, J.-F.; Steptenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821.

(6) For leading references on ligand **5**, 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.; Shao, C.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 4101. (c) Feng, C.-G.; Wang, Z.-Q.; Tian, P.; Xu, M.-H.; Lin, G.-Q. *Chem. Asian J.* **2008**, *3*, 1511.

(7) For other selected examples of chiral diene ligands, see: (a) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331. (b) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (c) Gendrineau, T.; Genet, J.-P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486.

(8) For references on formation of metal complexes with natural chiral dienes (one terminal double bond involved), see: (a) Johnson, B. D. G.; Lewis, J.; Yarrow, D. J. *J. Chem. Soc., Dalton Trans.* **1974**, 1054. (b) Winter, W.; Koppenhöfer, B.; Schurig, V. *J. Organomet. Chem.* **1978**, *150*, 145. (c) Oro, L. A. *J. Less-Common Met.* **1977**, *53*, 289.

(9) For leading reviews on Rh-catalyzed asymmetric conjugated additions, see: (a) Hayashi, T.; Yamashaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Gennari, C.; Monti, C.; Piarulli, U. *Pure Appl. Chem.* **2006**, *78*, 303. (c) Christoffers, J.; Koripelly, G.; Rosoak, A.; Rössle, M. *Synthesis* **2007**, 1279.

(10) Complex $[RhCl(1,5\text{-hexadiene})]_2$ is commercially available.

(11) For leading references on the preparation and application of **L1** in organic synthesis, see: (a) Ramo Rao, A. V.; Mysorekar, S. V.; Gurjar, M. K.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *28*, 2183. (b) Yadav, J. S.; Mysoreka, S. V.; Pawar, S. M.; Gurjar, M. K. *J. Carbohydr. Chem.* **1990**, *9*, 307. (c) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 71. (d) Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513. (e) Marvin, C. C.; Clemens, A. J. L.; Burke, S. D. *Org. Lett.* **2007**, *9*, 5353. (f) Purser, S.; Timothy, T. D. W.; Odell, B.; Moore, P. R.; Gouverneur, V. *Org. Lett.* **2008**, *10*, 4263.

(12) For leading references on **L2**−**L4**, see: (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (b) Gurjar, M. K.; Pawar, S. M. *Indian J. Chem., Sect. B* **1987**, *26B*, 55. (c) Abdelhedi, R.; Bouguerra, M. L.; Pommelet, J. C.; Chuche, J. *J. Soc. Chim. Tunis* **1986**, *2*, 7.

(13) For leading references on **L5**−**L7**, **L10**, and **L12**, see: (a) Ref 11c. Ref 11b. (c) Ref 11a. (d) Kang, S. H.; Ryu, D. H. *Chem. Commun.* **1996**, 355. (e) Trost, B. M.; Aponick, A.; Stanzl, B. N. *Chem.*−*Eur. J.* **2007**, *13*, 9547.

with a low conversion. Ligands bearing cyclic backbones (**L10**−**L12**) were also effective for catalyzing this reaction to give good conversions and moderate ee's. Overall, **L1** proved to be the best ligand to give both the highest conversion and enantioselectivity.

With the best ligand **L1** in hand, to further improve the enantioselectivity, the reaction conditions, including base, solvent, and temperature, were investigated. It was found that base has a significant effect on both reactivity and enantioselectivity (Table 1, entries 1−4), and KOH proved to be the best one. Water was found to play a crucial role in this reaction which awaits further studies: up to 80% ee was obtained when changing MeOH with H_2O (Table 1, entry 1 vs 5), but the conversion only reached 59%. Studies showed that the reaction using water as a solvent was very fast but only gave a quite low enantioselectivity (Table 1, entry 8). By tuning the ratio of dioxane and water to 2:1, >99% conversion and 72% ee were obtained (Table 1, entry 7). Other organic solvents were also studied (Table 1, entries 9−12), and CH_2Cl_2 could give 75% ee with 82% conversion. When the temperature was lowered to 20 °C, up to 82% ee was afforded without losing any activity (Table 1, entry 13). Further reduction of the temperature to 10 °C could improve the enantioselectivity to 85%, but the reaction needs longer time (Table 1, entry 14). Overall, the best reaction conditions (Table 1, entry 13) involved 5 mol % of Rh(I) and 6 mol % of **L1** in dioxane/H_2O (v/v 2:1) at 20 °C for 3 h.

Table 1. Optimizing Reaction Conditions for Rh(I)/**L1**-Catalyzed Conjugated Addition of Phenylboronic Acid (**7**) to 2-Cyclohexenone (**6**)[a]

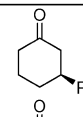
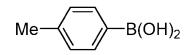
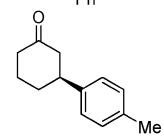
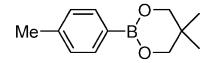
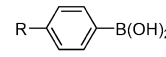
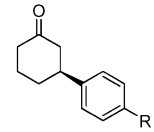
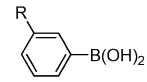
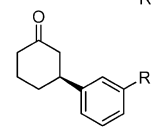
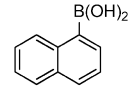
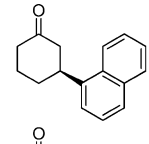
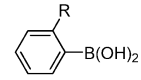
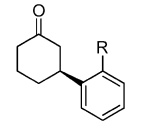
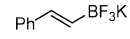
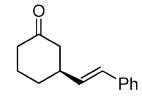
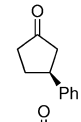
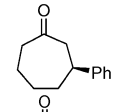
entry	solvent[c]	base	temp (°C)	convn (%)[d]	ee (%)[e]
1	dioxane/MeOH (10/1)	KOH	50	>99	61
2	dioxane/MeOH (10/1)	K_2CO_3	50	96	50
3	dioxane/MeOH (10/1)	KOAc	50	14	64
4	dioxane/MeOH (10/1)	Et_3N	50	65	55
5	dioxane/H_2O (10/1)	KOH	50	59	80
6	dioxane/H_2O (5/1)	KOH	50	81	73
7	dioxane/H_2O (2/1)	KOH	50	>99	72
8	H_2O	KOH	50	>99	49
9	toluene/H_2O (2/1)	KOH	50	98	58
10	DCE/H_2O (2/1)	KOH	50	78	68
11	THF/H_2O (2/1)	KOH	50	>99	68
12	CH_2Cl_2/H_2O (2/1)	KOH	50	82	75
13	**dioxane/H_2O (2/1)**	**KOH**	**20**	**>99**	**82**
14[b]	dioxane/H_2O (2/1)	KOH	10	91	85
15	dioxane/H_2O (2/1)	KOH	0	43	85

[a] All the reactions were carried out with 2-cyclohexenone (**6**) (0.20 mmol), phenylboronic acid (**7**) (0.30 mmol), base (0.015 mmol), $[RhCl(C_2H_4)_2]_2$ (0.005 mmol), and **L1** (0.012 mmol) in solvent (0.60 mL) under argon for 3 h unless otherwise stated. [b] The reaction was carried out for 12 h. [c] The ratio was in volume. [d] The conversion was determined by crude ^1H NMR. [e] The ee was determined by chiral HPLC (Chiralpak AD-H column).

(14) All the reactions were carried out with 2-cyclohexenone (**6**) (0.20 mmol), phenylboronic acid (**7**) (0.30 mmol), KOH (0.015 mmol), $[RhCl(C_2H_4)_2]_2$ (0.005 mmol), diene ligand (0.012 mmol) in dioxane/MeOH (10/1, v/v, 0.60 mL) at 50 °C under argon for 3 h.

Under the optimized conditions, the substrate scope was investigated, and some of the results are summarized in Table 2. It was found that the chiral chain diene **L1** modified Rh-catalyst can promote these reactions with moderate to excellent reactivities (50−99% yields) and moderate to good enantioselectivities (61−83% ee's). Addition of *meta*- or *para*-substituted arylboronic acids to 2-cyclohexenone (**6**)

Table 2. Rh(I)/**L1**-Catalyzed Asymmetric Conjugated Additions[a]

entry	organoboron reagent	product[d]	yield (%)[e]	ee (%)[f]
1	$PhB(OH)_2$		98	82
2	$(PhBO)_3$		99	83
3[b]	$PhBF_3K$		65	81
4			99	82
5			98	81
6	 R = OMe		98	82
7	R = F		91	80
8[b]	R = CF_3		73	78
9	 R = Me		98	82
10	R = Cl		91	79
11			94	67
12	 R = OMe		96	66
13	R = Cl		95	64
14[c]			52	64
15	$PhB(OH)_2$		87	61
16	$PhB(OH)_2$		56	73
17	$PhB(OH)_2$		84	62

[a] All the reactions were carried out with an organoboron reagent (0.30 mmol), unsaturated carbonyl compound (0.20 mmol), KOH (0.015 mmol), $[RhCl(C_2H_4)_2]_2$ (0.005 mmol), and **L1** (0.012 mmol) in dioxane/H_2O (2/1, v/v, 0.60 mL) under argon for 3 h unless otherwise noted. For entry 2, the reaction was carried out with organoboron reagent (0.10 mmol), and for entries 9 and 14−17, the reaction scale was doubled. [b] The reaction was carried out for 12 h. [c] The reaction was carried out at 50 °C for 5 h. [d] The absolute configuration was deterimined by comparing the optical rotation with the reported one. [e] Isolated yield. [f] The ee was determined by chiral HPLC (Chiralpak AD-H column) unless otherwise stated, Chiralcel OD-H column for entries 8 and 14, Chiralcel OJ-H column for entries 11 and 16, Chiralcel OB-H column for entry 15, and Chiralcel AS-H column for entry 17.

under the catalysis of Rh(I)/**L1** gave excellent yields and good ee's, and boronic acids with electron-donating groups displayed higher activities (Table 2, entries 4, 6, and 9). *Ortho*-substituted arylboronic acids are also effective substrates for this reaction but only resulted in relatively lower ee's (Table 2, entries 11−13). The reactions between other types of organoboron reagents, such as boronate ester and potassium trifluoroborates, and 2-cyclohexenone (**6**) went smoothly to afford desired products in good yields and ee's (Table 2, entries 3, 5, and 14). Rh(I)/**L1** can also promote the asymmetric conjugated addition of phenylboronic acid (**7**) to other unsaturated carbonyl compounds, giving the corresponding adducts in 56−87% yields with 61−73% ee's (Table 2, entries 15−17).

In summary, a simple chiral chain diene **L1** bearing two terminal double bonds was successfully employed as a novel type and effective chelating ligand for Rh(I)-catalyzed asymmetric conjugated additions, and encouraging results (up to 85% ee) have been achieved. Although the efficiency, enantioselectivity, and substrate scope still await further improvement, it demonstrates that flexible chiral chain dienes are able to be used as steering ligands for metal-catalyzed asymmetric reactions, which will probably provide a practical approach to design novel chiral diene ligands in the future. Searching for more effective chiral chain dienes, understanding the detailed coordination mode and asymmetric induction pathway, and expanding the applications of chiral chain diene ligands in other types of metal-catalyzed asymmetric reactions are currently underway in our laboratory.

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Supporting Information Available: The procedure for Rh(I)-catalyzed conjugated addition and the characterization and data for the determination of enantiomeric excess of addition products along with the NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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