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Catalytic Enantioselective Formation of Chiral-Bridged Dienes Which Are Themselves Ligands for Enantioselective Catalysis

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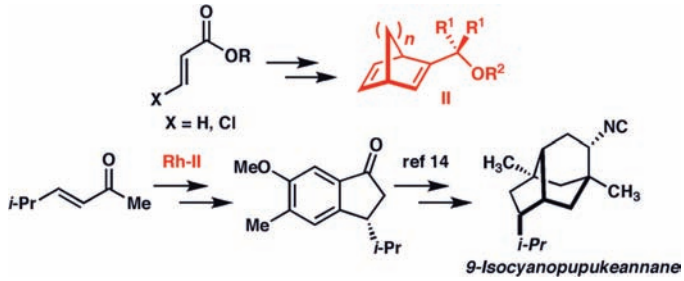
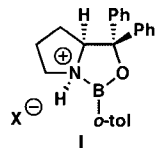
ABSTRACT

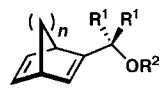


This paper reports a method for highly enantioselective Diels−Alder reaction with an acetylene equivalent to produce chiral-bridged dienes. These dienes, by coordination to Rh(I), can serve as catalysts for the enantioselective addition of vinyl or aryl groups to α,β-unsaturated ketones.

Reaction sequences in which a catalytic enantioselective process produces a catalyst for another enantioselective transformation are synthetically advantageous. In addition, along with template-directed molecular reproduction, such catalytic cascades are fundamental to life.



I



II

The *N*-protonated oxazaborolidine **I** and its N^+-$AlBr_3$ and N^+-CH_3 coordinated analogues represent a new class of chiral and strong Lewis acids that have proved to be remarkably useful for the synthesis of chiral organic molecules from simple, achiral precursors.[1] These catalysts offer numerous advantages in enantioselective Diels−Alder reactions, including: (1) broad applicability, even with less reactive substrates, (2) 20:1 or better enantioselectivity, and (3) predictable absolute configuration of product. Their use has enabled the conversion of some of the most important multistep syntheses of racemic natural products to catalytic enantioselective versions. This letter describes the use of **I** toward two objectives: first, the development of a method for the enantioselective synthesis of Diels−Alder adducts of acetylenic dieneophiles;[2] and second, the development of methodology for the catalytic enantioselective synthesis of catalysts (e.g., [M]-**II**), which can function enantioselectively. The advent of cascades of processes for the generation of enantioselective catalysts would allow significant improvement in the power of chemical synthesis. One can envisage that there will eventually be a large collection of

(1) (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100–2117.

(2) (a) Corey, E. J.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 5755–5758. (b) Ishihara, K.; Kondo, S.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 3026–3027. (c) Evans, D. A.; Miller, S. J.; Lectka, T.; Matt, P. V. *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573. (d) Ishihara, K.; Fushimi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7532–7533. (e) Payette, J. N.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 8060–8062.

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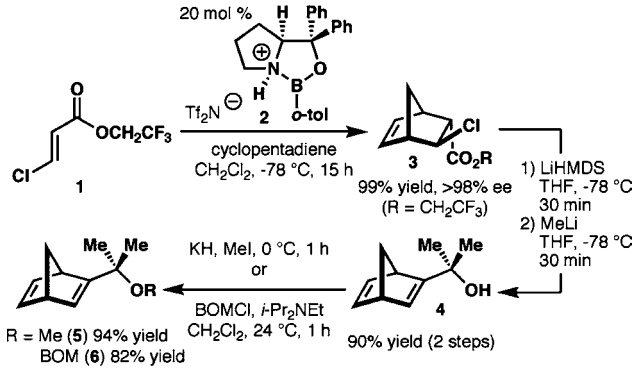
molecules produced by enantioselective catalysts that constitutes a "catalytic pool" analogous to the "chiral pool" of naturally produced organic molecules.

Chiral, nonracemic, bridged dienes have proven to be exceptionally useful ligands for several classes of catalytic enantioselective C−C bond forming reactions.[3] Nearly all of the known bicyclic diene ligands are prepared in enantiomerically pure form from either chiral pool starting materials or by the use of resolution techniques (fractional crystallization or HPLC with a chiral column).

As illustrated in Scheme 1, we have established a catalytic enantioselective route to norbornadiene-based ligands (**4**−**6**).[4,6a]

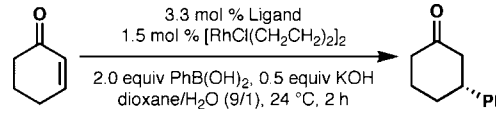
Scheme 1. Preparation of Norbornadiene-Based Ligands



The route hinges on the use of a catalytic enantioselective Diels−Alder cycloaddition of β-chloroacrylate **1** (a relatively unreactive dieneophile) with cyclopentadiene promoted by protonated oxazaborolidine **2**, which proceeds with high enantioselectivity and in good yield. From there, the dienes are prepared in enantiomerically pure form in two to three straightforward, high-yielding transformations (Scheme 1).

The utility of dienes **4**−**6** as chiral ligands was examined in the context of Rh-catalyzed enantioselective conjugate additions of $ArB(OH)_2$ to α,β-unsaturated ketones (Table 1).[3,5,6] Initial studies

Table 1. Initial Survey of Norbornadiene-Based Chiral Ligands



entry	ligand	% convn, ee
1	R = H (**4**)	70, 98
2	R = Me (**5**)	90, 96
3	R = BOM (**6**)	95, 96

established that while use of ligands **4**−**6** all lead to highly enantioselective reactions (96−98% ee), the BOM-ether **6** gives the highest conversion of starting material (Table 1, entry 3).

As illustrated in Table 2, highly enantioselective (86−97% ee) conjugate additions of $PhB(OH)_2$ to various α,β-

Table 2. Rh-Catalyzed Enantioselective Conjugate Addition of $PhB(OH)_2$ to Various Enones Promoted by Rh-**6**[a]

entry	enone	product	mol % Rh	% yield[b], ee[c]
1	n = 1		0.5	95, 97
2	n = 2		0.5	85, 96
3	n = 3		3.0	83, 94
4	C_5H_{11} Me	C_5H_{11} Ph Me	3.0	74, 86

[a] Reactions carried out under N_2, in dioxane/H_2O (5/2) with 1.0 equiv of KOH (aq), 2 h reaction time, 24 °C, 1.1:1 (**6**:Rh). [b] Yield of isolated product after silica gel column chromatography. [c] Determined by HPLC analysis with a chiral column.

unsaturated carbonyls promoted by Rh-**6** can be carried out. With five- and six-membered-ring α,β-unsaturated ketones (Table 2, entries 1 and 2), only 0.5 mol % catalyst is adequate, but somewhat more (3 mol %) is appropriate for less reactive substrates, such as cycloheptenone (Table 2, entry 3) or an acyclic enone (Table 2, entry 4).[7]

During the course of our studies, we discovered that the efficiency of the reaction depends on the order of addition of reagents as outlined in Figure 1. One explanation for this observation is that the ligand (**6**) is transformed into a catalytically incompetent product under the conditions of the conjugate addition. This possibility was tested by allowing the diene **6** to react with stoichiometric amounts of $PhB(OH)_2$ and $[RhCl(CH_2CH_2)_2]_2$ in dioxane−KOH−H_2O for 10 min at 24 °C. Under these standard reaction conditions, rapid phenylation of the

(3) For reviews regarding diene-based ligands, see: (a) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840–871. (b) Defieber, C.; Grutzmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482–4502.

(4) Initial studies on the synthesis of the diene framework by Diels−Alder cycloaddition of dienes to *alkyne*-based dieneophiles were discontinued because only moderate enantioselectivities were observed.

(5) (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (b) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13–21. (c) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279–1300.

(6) For early reports regarding catalytic enantioselective reactions with diene-based ligands, see: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508–11509. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628–1629. (c) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873–3876. For selected recent reports on Rh-catalyzed conjugate addition with diene-based ligands, see: (d) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387–4389. (e) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669–7672. (f) Grendrineay, T.; Genet, J.-P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486–3489. (g) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815–4817. (h) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588–13589. (i) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744–4747. (j) Mahoney, S. J.; Dumas, A. M.; Fillion, E. *Org. Lett.* **2009**, *11*, 5346–5349. (k) Shintani, R.; Ichikawa, Y.; Takatsu, K.; Chen, F.-X.; Hayashi, T. *J. Org. Chem.* **2009**, *74*, 869–873. For mechanistic studies on Rh-catalyzed conjugate addition, see: (l) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052–5058. (m) Kina, A.; Yasuhara, Y.; Nishimura, T.; Iwamura, H.; Hayashi, Y. *Chem. Asian J.* **2006**, *1*, 707–711.

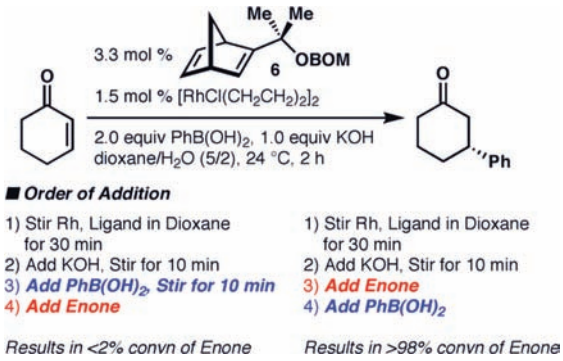
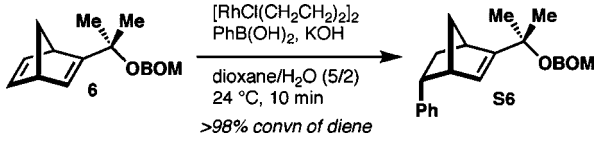


Figure 1. Investigations into order of addition.

disubstituted olefinic linkage of **6** occurred to form the product shown in Scheme 2 (stereochemistry assumed).

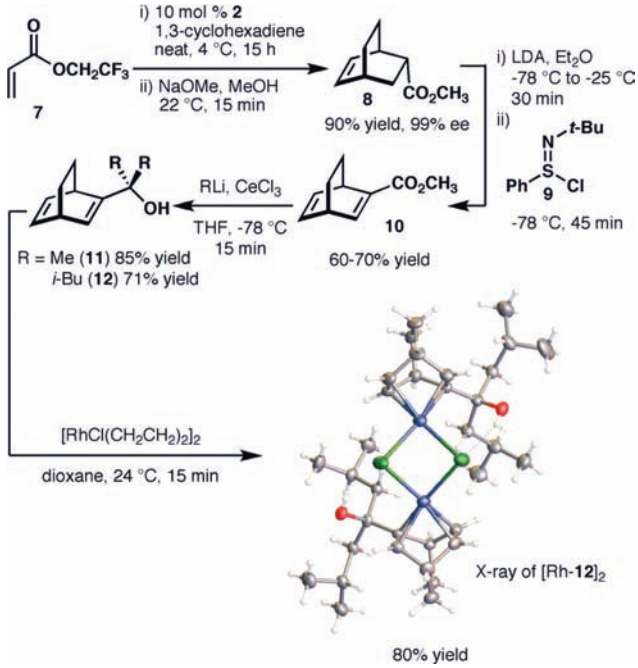
Scheme 2. Arylation of Diene **6**



Catalytic arylation of norbornenes has been observed previously.[8]

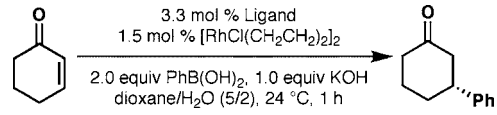
To overcome the issues associated with such strained ligands, we turned to the less strained bicyclooctadiene systems. As illustrated in Scheme 3, bicyclooctadienes **11** and **12** are prepared efficiently in three steps. Diels−Alder reaction of trifluoroethylacrylate (**7**) and 1,3-cyclohexadiene gives **8** in 90% yield and 99% ee with **2** as catalyst.[9] Oxidation of **8** with the Mukaiyama reagent **9**[10] followed by reaction with an alkyllithium reagent provides the diene ligands **11** and **12**.[11] Although it is not necessary to prepare and isolate Rh-**12** for efficient conjugate addition, we have established its structure by X-ray crystallography (Scheme 3).

Scheme 3. Preparation of Bicyclooctadiene-Based Ligands



The hydroxy bicyclooctadienes **11** and **12** are excellent ligands for the Rh-catalyzed enantioselective conjugate addition of $PhB(OH)_2$ to cyclohexenone (Table 3) and Rh-**12** is especially effective with only 0.25 mol % catalyst (Table 4, entry 2).[12]

Table 3. Initial Survey of Bicyclooctadiene-Based Chiral Ligands

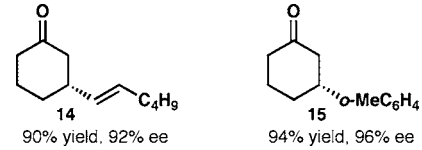


entry	ligand	% convn, ee
1	R^1 = Me, R^2 = H (**11**)	>98, 95
2	R^1 = Me, R^2 = BOM (**13**)	>98, 88
3	R^1 = *i*-Bu, R^2 = H (**12**)	>98, 96

Table 4. Rh-Catalyzed Enantioselective Conjugate Addition of $PhB(OH)_2$ to Various Enones Promoted by Rh-**12**[a]

entry	enone	product	temp (°C)	mol % Rh	% yield[c] ee[d]
1	n = 1		24	0.5	96, 89
2[b]	n = 2		24	0.25	88, 96
3	n = 3		50	0.5	90, 87
4	C_5H_{11}, Me	C_5H_{11}, Ph, Me	50	0.5	91, 90

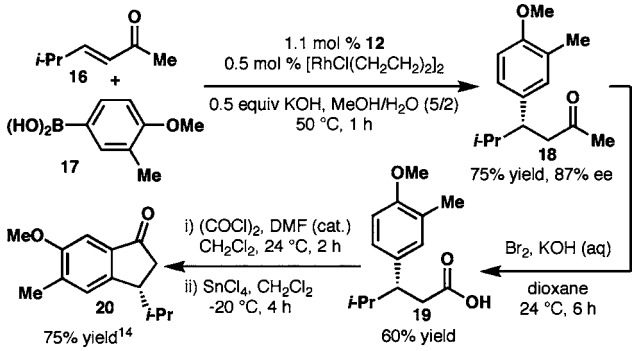
[a] Reactions carried out under N_2, in MeOH/H_2O (5/2) with 0.5 equiv of KOH (aq), 1 h reaction time, 1.1:1 (**12**:Rh). [b] Reaction carried out in dioxane/H_2O (5/2). [c] Yield of isolated product after silica gel column chromatography. [d] Determined by HPLC analysis with a chiral column.



Several points regarding reactions promoted by Rh-**12** merit mention:[13] (1) Lower catalyst loading of Rh-**12** can be employed as compared to Rh-**6** (0.5 mol % vs. 3.0 mol %, Table 4). (2) Addition of a vinylboronic acid or a

sterically hindered arylboronic acid to cyclohexenone (1 mol % Rh-**12**, dioxane, 50 °C, 2 h) provides **14** or **15** (respectively) in high yield and enantiomeric excess. (3) Rhodium-catalyzed conjugate addition of boronic acid **17** to α,β-unsaturated ketone **16** provides **18**, a key intermediate for the enantioselective synthesis of 9-isocyanopupukeanane via the bicyclic ketone **20** (Scheme 4).[14]

Scheme 4. Enantioselective Synthesis of 9-Isocyanopupukeanane Intermediate **20**



The results above effectively address the longstanding problem of catalytic enantioselective synthesis of adducts of 1,3-dienes and acetylenic dieneophiles. The application of this advance leads to a useful catalytic cascade in which a catalyst is used for the enantioselective synthesis of another chiral catalyst.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Use of 1.0 equiv of KOH is optimal for reactions promoted by Rh-**6**.

(8) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464–10465.

(9) Diels−Alder cycloaddition promoted by **2** between β-chloroacrylate **1** and 1,3-cyclohexadiene (24 °C) results in <2% conversion.

(10) Mukaiyama, T.; Matsuo, J.-I.; Kitagawa, H. *Chem. Lett.* **2000**, 1250–1251.

(11) **13** was prepared from **11** in 87% yield (BOMCl, *i*-Pr_2NEt, CH_2Cl_2, 24 °C).

(12) In select cases, Rh-**12** is significantly more selective than Rh-**11**. For example, the reaction presented in Table 4, entry 4 promoted by Rh-**11** furnishes the product with 75% ee.

(13) For reactions promoted by Rh-**12**, in general, use of MeOH leads to slightly higher levels of enantioselectivity versus dioxane. For reactions presented in Table 2, MeOH was found to provide similar results as dioxane.

(14) Corey, E. J.; Behforouz, M.; Ishiguro, M. *J. Am. Chem. Soc.* **1979**, *101*, 1608–1609.