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Simple Chiral Diene Ligands Provide High Enantioselectivities in Transition-Metal-Catalyzed Conjugate Addition Reactions

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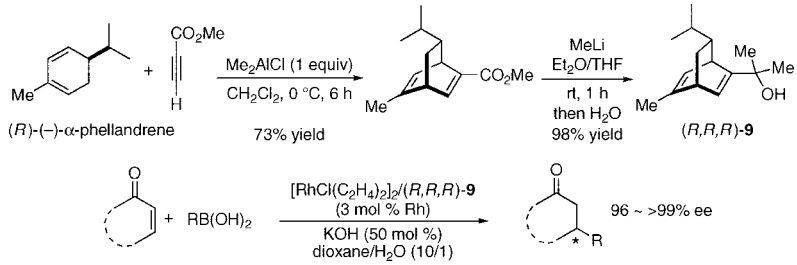
ABSTRACT



Chiral dienes possessing the bicyclo[2.2.2]octadiene framework were prepared readily through the [4 + 2] cycloaddition of (*R*)-α-phellandrene with methyl propiolate as the key step. Diene 9, substituted with a tertiary alcohol on one of the two double bonds, is prepared in just one step from the cycloadduct and is highly effective as a chiral ligand for rhodium-catalyzed asymmetric conjugate addition reactions, giving the corresponding addition products with higher enantioselectivity than other chiral dienes.

The recent development of chiral diene ligands for transition-metal-catalyzed asymmetric reactions has opened up new vistas for ligand design.[1] Chiral dienes have been found to be superior to other types of chiral ligands, such as chiral bisphosphines, in terms of both catalytic activity and enantioselectivity, especially in rhodium-catalyzed asymmetric carbon−carbon bond-forming reactions. The most effective chiral dienes reported to date for catalytic asymmetric reactions are those based on the bicyclic diene frameworks, **1**−**5**,[2−7] as shown in Figure 1. Noteworthy among these is Carreira's diene (**3**), which has the advantage that it is readily available from an inexpensive terpene, (−)-carvone, through a seven-step sequence.[4] The development of even simpler routes to chiral diene ligands is expected to spur further advances in transition-metal-mediated catalytic asymmetric reactions.[1b] We report here an exceedingly simple, two-step synthesis of a chiral diene from the inexpensive terpene, (*R*)-α-phellandrene. The new diene is

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(1) For reviews, see: (a) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840. (b) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.

(2) Diene **1**: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Berthon-Gelloz, G.; Hayashi, T. *J. Org. Chem.* **2006**, *71*, 8957. (c) Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961.

(3) Diene **2**: (a) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (b) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503. (c) Shintani, R.; Kimura, T.; Hayashi, T. *Chem. Commun.* **2005**, 3213. (d) Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3909. (e) Shintani, R.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 4757. (f) Hayashi, T.; Tokunaga, N.; Okamoto, K.; Shintani, R. *Chem. Lett.* **2005**, *34*, 1480. (g) Chen, F.-X.; Kina, A.; Hayashi, T. *Org. Lett.* **2006**, *8*, 341. (h) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Org. Lett.* **2006**, *8*, 979. (i) Shintani, R.; Sannohe, Y.; Tsuji, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 7277. (j) Shintani, R.; Ichikawa, Y.; Hayashi, T.; Chen, J.; Nakao, Y.; Hiyama, T. *Org. Lett.* **2007**, *9*, 4643. (k) Sörgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589.

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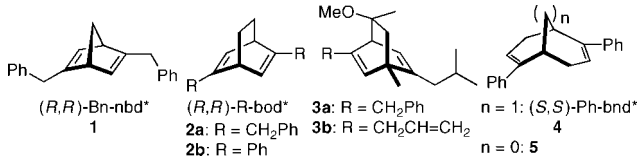
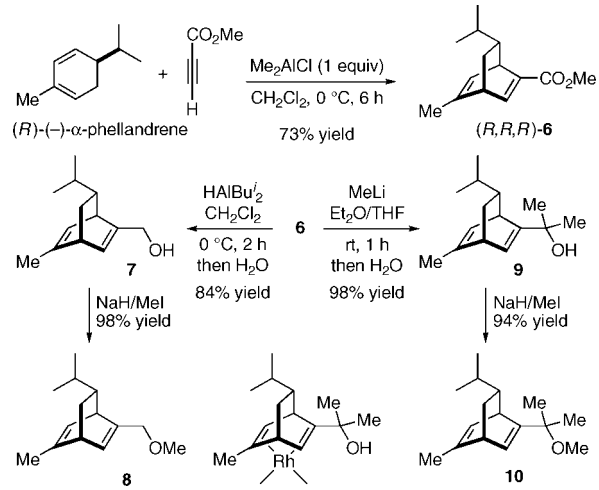


Figure 1. Chiral diene ligands for catalytic asymmetric reactions.

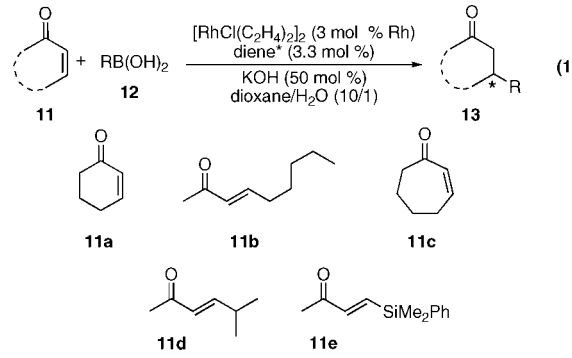
highly effective as a ligand for rhodium-catalyzed asymmetric addition reactions, providing among the highest enantioselectivities reported for these reactions.

One of the most efficient methods of constructing a bicyclo[2.2.2]octadiene framework involves the [4 + 2] cycloaddition of a 1,3-cyclohexadiene derivative with an acetylene. We chose (*R*)-α-phellandrene, which is one of the most inexpensive terpenes, as the chiral diene for construction of enantiomerically enriched bicyclo[2.2.2]octadiene.[8] Thus, technical grade (*R*)-α-phellandrene (~70% chemical purity,[9,10] 1.05 equiv) was allowed to react with methyl propiolate in the presence of chlorodimethylaluminum (1.0 equiv) in dichloromethane at 0 °C for 6 h. The reaction mixture was subjected to silica gel column chromatography to give 73% isolated yield of the cycloaddition product **6**, together with an ene-type reaction product.[11] The cycloaddition took place with high regio- and diastereoselectivity to produce bicyclo[2.2.2]octadiene (*R*,*R*,*R*)-**6** as a single diastereoisomer (Scheme 1). The enantiomeric purity of **6**, determined using a chiral stationary column (Chiralpak AD-H), was found to be 98.8 ± 0.2% ee, coincident with the purity of the commercial sample of (*R*)-α-phellandrene. An enantiomerically pure sample of **6** was readily obtained using preparative chiral HPLC. Alternatively, the cycloaddition can be performed with α-phellandrene of higher enantiomeric purity.[10]

Scheme 1. Synthesis of Chiral Dienes



While cycloadduct **6** can itself be used as a chiral diene ligand, the ester functionality can be easily modified to generate derivatives. Thus, reduction of **6** with $HAlBu^i_2$ gave alcohol **7**, subsequent methylation of which gave methyl ether **8**. A quantitative yield of tertiary alcohol **9** was obtained by treatment of **6** with methyllithium. The corresponding ether (**10**) was also prepared.



Chiral dienes **6**−**10**, prepared in just one to three steps from (*R*)-α-phellandrene, were examined as chiral ligands for the rhodium-catalyzed asymmetric 1,4-additions (eq 1).[12] Some of the results of this study are summarized in Table 1, which also contains the data reported with other dienes for comparison. In the addition of phenylboronic acid (**12m**) to 2-cyclohexen-1-one (**11a**), the (*R*,*R*,*R*)-dienes substituted with an ester **6**, alcohol **7**, and its methyl ether **8** gave the phenylation product **13am** with 87%, 95%, and 94% ee,

(4) Diene **3**: (a) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (b) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873. (c) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (d) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821. (e) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331. (f) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339. (g) Miura, T.; Murakami, M. *Chem. Commun.* **2005**, 5676. (h) Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 595.

(5) Diene **4**: (a) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307. (b) Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673.

(6) Diene **5**: (a) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (b) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331.

(7) Other chiral diene ligands used for asymmetric reactions: (a) Läng, F.; Breher, F.; Stein, D.; Grützmacher, H. *Organometallics* **2005**, *24*, 2997. (b) Kina, A.; Ueyama, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5889.

(8) Examples of the [4 + 2] cycloaddition of α-phellandrene: (a) Trost, B. M.; Lunn, G. *J. Am. Chem. Soc.* **1977**, *99*, 7079. (b) Lauer, M.; Samuel, O.; Kagan, H. B. *J. Organomet. Chem.* **1979**, *177*, 309. (c) Escher, S.; Keller, U.; Willhalm, B. *Helv. Chim. Acta* **1979**, *62*, 2061. (d) Paquette, L. A.; Doehner, R. F., Jr. *J. Org. Chem.* **1980**, *45*, 5105.

(9) Kanto Chemicals Ltd. *p*-Cymene is a major component of the impurity. The enantiomeric purity measured by a chiral GC column (CP-Chiralsil-Dex CB) is 98.9 ± 0.2% ee.

(10) (*S*)-α-Phellandrene is readily prepared, in three steps, from (*R*)-(−)-carvone Sen, A.; Grosch, W. *Flavour Fragrance J.* **1990**, *5*, 233. Also see: Daubin, W. G.; Lorber, M. E.; Vietmeyer, N. D.; Shapiro, R. H.; Duncan, J. H.; Tomer, K. *J. Am. Chem. Soc.* **1968**, *90*, 4762.

(11) (*E*)-Methyl 3-(5-isopropyl-2-methylenecyclohex-3-enyl)propenoate: See: Supporting Information.

(12) For reviews: (a) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 3. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13. (d) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465. (e) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (f) Fagnou, K.; Lautens, M *Chem. Rev.* **2003**, *103*, 169. First report: (g) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

Table 1. Asymmetric 1,4-Addition of $PhB(OH)_2$ (**12m**) to **11a** and **11b** Catalyzed by Rhodium−Diene Complexes[a]

entry	diene ligand[b]	enone	conditions	yield[c] (%)	% ee[d]	ref
1	**6**[e]	**11a**	20 °C, 3 h	93	86 (*R*)	
2	**6**	**11a**	20 °C, 3 h	89	87 (*R*)	
3	**7**	**11a**	30 °C, 1 h	96	95 (*R*)	
4	**8**	**11a**	30 °C, 1 h	88	94 (*R*)	
5	**9**	**11a**	30 °C, 1 h	90	99.3 (*R*)	
6	**10**	**11a**	30 °C, 1 h	90	99.1 (*R*)	
7	**1**	**11a**	30 °C, 1 h	94	96 (*R*)	2a
8	**2a**	**11a**	30 °C, 1 h	97	95 (*R*)	3b
9	**2b**	**11a**	30 °C, 1 h	97	96 (*R*)	3b
10	**3b**	**11a**	25 °C, −	87	95 (*S*)	4b
11	**9**	**11b**	30 °C, 3 h	95	98.8 (*S*)	
12	**10**	**11b**	30 °C, 3 h	90	99.0 (*S*)	
13	**2a**	**11b**	30 °C, 1 h	94	98 (*S*)	3b

[a] The reaction was carried out with enone **11** (0.30 mmol), $PhB(OH)_2$ (0.45 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol % Rh), diene (3.3 mol %), and 1.5 M aq KOH (0.1 mL) in dioxane (1.0 mL). [b] Dienes **6**−**10** had >99.8% ee. [c] Isolated yield. [d] Determined by HPLC analysis with chiral stationary-phase columns. [e] ee = 98.8%.

respectively (entries 1−4). The enantioselectivity observed here with **7** and **8** is comparable to that with the dienes **1**−**3** which had been the best diene ligands for this asymmetric transformation (entries 7−10). To our delight, the dienes **9** and **10**, which bear the tertiary alcohol and its methyl ether, respectively, as a substituent on one of the two olefins, gave **13am** with 99% ee (entries 5 and 6). The very high enantioselectivity (99% ee) with dienes **9** and **10** was also observed in the addition to linear enone, 3-nonen-2-one (**11b**) (entries 11 and 12).

The high enantioselectivity of dienes **9** and **10** can be ascribed to the steric bulkiness of the 1-hydroxy- or 1-methoxy-1-methylethyl group attached to the double bond. The comparable results obtained with **9** and **10** precludes hydrogen bonding as playing a role in organizing the transition state complex. The absolute configuration of the products, (*R*) for cyclic enone **13am** and (*S*) for acyclic enone **13bm**, is consistent with the stereochemical pathway proposed for the reactions using C_2-symmetric diene ligands.[2,3,13] In the case of (*R*,*R*,*R*)-**9**, which is unsymmetrically substituted with methyl and the tertiary alcohol, phenyl−rhodium bond may be formed on the open methyl side leaving the other, sterically congested, side for coordination of an enone (Figure 2). The sterically bulky tertiary alcohol appears to better distinguish the enantiofaces of enones than the primary alkyl groups or aryl groups which are the substituents on the chiral dienes reported to date.[2−6,14]

Chiral diene ligand **9** also induced high enantioselectivity in the conjugate addition of other substrates, as shown in Table 2. Thus, the addition of arylboronic acids **12n**−**p** substituted with 4-methoxy, 4-trifluoromethyl, and 2-methyl

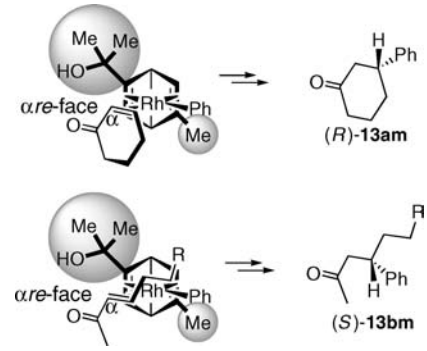


Figure 2. Stereochemical pathway with Rh/(*R*,*R*,*R*)-**9**.

Table 2. Asymmetric 1,4-Addition of Boronic Acids **12** to Enones **11** Catalyzed by Rhodium/(*R*,*R*,*R*)-**9** Complex[a]

entry	enone	boronic acid: R	conditions	yield (%)[b]	% ee[c]
1	**11a**	**12n**: 4-$MeOC_6H_4$	30 °C, 1 h	98	>99.5 (*R*)
2	**11a**	**12o**: 4-$CF_3C_6H_4$	30 °C, 1 h	97	99.1 (*R*)
3	**11a**	**12p**: 2-MeC_6H_4	30 °C, 1 h	95	99.4 (*R*)
4	**11a**	**12q**: (*E*)-PhCH=CH	30 °C, 3 h	97	99.3 (*R*)
5	**11a**	**12r**: (*E*)-C_5H_{11}CH=CH	30 °C, 3 h	81	98.7 (*R*)
6	**11c**	**12m**: Ph	50 °C, 1 h	94	98 (*R*)
7	**11d**	**12m**: Ph	30 °C, 3 h	84	96 (*R*)
8	**11e**	**12m**: Ph	50 °C, 3 h	97	99.4 (*S*)

[a] The reaction was carried out with enone (0.30 mmol), $RB(OH)_2$ (0.45 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol % Rh), (*R*,*R*,*R*)-**9** (3.3 mol %), and 1.5 M aq KOH (0.1 mL) in dioxane (1.0 mL). [b] Isolated yield. [c] Determined by HPLC analysis with chiral stationary phase columns.

all proceeded with over 99% enantioselectivity (entries 1−3). Ligand **9** is also very effective for alkenylboronic acids (entries 4−5). 2-Cyclohepten-1-one (**11c**) and linear enones, **11d** and **11e**, undergo the 1,4-phenylation with high enantioselectivities (entries 6−8).

In summary, chiral dienes possessing the bicyclo[2.2.2]-octadiene framework can be easily prepared through the [4 + 2] cycloaddition of the inexpensive chiral terpene (*R*)-α-phellandrene with an alkynyl dienophile. Simple further elaboration of the cycloadduct, requiring just one or two steps, provides dienes that are the most effective ligands reported so far for the rhodium-catalyzed asymmetric addition reactions.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For the mechanism of rhodium-catalyzed 1,4-addition, see: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(14) For the asymmetric addition of $PhB(OH)_2$ to 2-cyclopenten-1-one, diene **9** is less enantioselective than Ph-bod* (**2b**), the latter giving the corresponding phenylation products with 99% ee (ref 3b).