Published in final edited form as:

Org Lett. 2008 October 2; 10(19): 4387–4389. doi:10.1021/ol801931v.

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

Kazuhiro Okamoto[†], Tamio Hayashi^{†,*}, and Viresh H. Rawal^{‡,*}

[†]Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

[‡]Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

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 Chart 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 7 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.^{1a} We report here an exceedingly simple, two-step synthesis of a chiral diene from the inexpensive terpene, *(R)*- α -phellandrene. The new diene is 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 $98.8 \pm 0.2\%$ 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

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^t_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.

(1)

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, 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 1). 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

Support has been provided in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan (the Global COE Program "Integrated Materials Science" on Kyoto University). K. O. thanks the Japan Society for the Promotion of Science for the award of a fellowship for graduate students. VHR thanks the NIH for partial support of this work.

References

1. For reviews: (a) Johnson JB, Rovis T. *Angew. Chem., Int. Ed* 2008;47:840. (b) Defieber C, Grützmacher H, Carreira EM. *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. [PubMed: 13129348] (b) Berthon-Gelloz G, Hayashi T. J. Org. Chem 2006;71:8957. [PubMed: 17081029] (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. [PubMed: 15493893] (b) Otomaru Y, Okamoto K, Shintani R, Hayashi T. J. Org. Chem 2005;70:2503. [PubMed: 15787536] (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. [PubMed: 16209528] (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. [PubMed: 16408910] (h) Nishimura T, Yasuhara Y, Hayashi T. Org. Lett 2006;8:979. [PubMed: 16494489] (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. [PubMed: 17914835] (k) Sörgel S, Tokunaga N, Sasaki K, Okamoto K, Hayashi T. Org. Lett 2008;10:589. [PubMed: 18217766]
4. Diene **3**: (a) Fischer C, Defieber C, Suzuki T, Carreira EM. J. Am. Chem. Soc 2004;126:1628. [PubMed: 14871082] (b) Defieber C, Paquin J-F, Serna S, Carreira EM. Org. Lett 2004;6:3873. [PubMed: 15469371] (c) Paquin J-F, Defieber C, Stephenson CRJ, Carreira EM. J. Am. Chem. Soc 2005;127:10850. [PubMed: 16076189] (d) Paquin J-F, Stephenson CRJ, Defieber C, Carreira EM. Org. Lett 2005;7:3821. [PubMed: 16092884] (e) Fessard TC, Andrews SP, Motoyoshi H, Carreira EM. Angew. Chem., Int. Ed 2007;46:9331. (f) Miura T, Murakami M. Org. Lett 2005;7:3339. [PubMed: 16018655] (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. [PubMed: 15646984] (b) Otomaru Y, Kina A, Shintani R, Hayashi T. Tetrahedron: Asymmetry 2005;16:1673.
6. Diene **4**: (a) Otomaru Y, Tokunaga N, Shintani R, Hayashi T. Org. Lett 2005;7:307. [PubMed: 15646984] (b) Otomaru Y, Kina A, Shintani R, Hayashi T. Tetrahedron: Asymmetry 2005;16:1673.
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. [PubMed: 16354092]
8. Examples of the [4 + 2] cycloaddition of α -phellandrene: (a) Trost BM, Lunn G. J. Am. Chem. Soc 1977;99:7079. (b) Lauer M, Samuel O, Kagan HB. J. Organomet. Chem 1979;177:309. (c) Escher S, Keller U, Willhalm B. Helv. Chim. Acta 1979;62:2061. (d) Paquette LA, Doehner RF 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 $98.9 \pm 0.2\%$ ee.
10. (*S*)- α -Phellandrene is readily prepared, in 3 steps, from (*R*)(-)-carvone: Sen A, Grosch W. Flavour Fragrance J 1990;5:233. Also see: Dauben WG, Lorber ME, Vietmeyer ND, Shapiro RH, Duncan JH, 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, Evans P. Chapter 3. Modern Rhodium-Catalyzed Organic Reactions Germany Wiley-VCH Weinheim (b) Hayashi T, Yamasaki K. Chem. Rev 2003;103:2829. [PubMed: 12914482] (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. [PubMed: 12517183] First report: (g) Takaya Y, Ogasawara M, Hayashi T, Sakai M, Miyaura N. J. Am. Chem. Soc 1998;120:5579.
13. For the mechanism of rhodium-catalyzed 1,4-addition: Hayashi T, Takahashi M, Takaya Y, Ogasawara M. J. Am. Chem. Soc 2002;124:5052. [PubMed: 11982369]
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)

Figure 1.
Chiral Diene Ligands for Catalytic Asymmetric Reactions

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

Scheme 1.
Synthesis of Chiral Dienes

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 (<i>R</i>)	
2	6	11a	20 °C, 3 h	89	87 (<i>R</i>)	
3	7	11a	30 °C, 1 h	96	95 (<i>R</i>)	
4	8	11a	30 °C, 1 h	88	94 (<i>R</i>)	
5	9	11a	30 °C, 1 h	90	99.3 (<i>R</i>)	
6	10	11a	30 °C, 1 h	90	99.1 (<i>R</i>)	
7	1	11a	30 °C, 1 h	94	96 (<i>R</i>)	2a
8	2a	11a	30 °C, 1 h	97	95 (<i>R</i>)	3b
9	2b	11a	30 °C, 1 h	97	96 (<i>R</i>)	3b
10	3b	11a	25 °C, —	87	95 (<i>S</i>)	4b
11	9	11b	30 °C, 3 h	95	98.8 (<i>S</i>)	
12	10	11b	30 °C, 3 h	90	99.0 (<i>S</i>)	
13	2a	11b	30 °C, 3 h	94	98 (<i>S</i>)	3b

^aThe reaction was carried out with enone **10** (0.30 mmol), PhB(OH)₂ (0.45 mmol), [RhCl(C₂H₄)₂]₂ (3 mol % Rh), diene (3.3 mol %), and 1.5 M aq KOH (0.1 mL) in dioxane (1.0 mL).

^bDienes **6–10** had >99.8% ee

^cIsolated yield.

^dDetermined by HPLC analysis with chiral stationary phase columns.

^eee = 98.8%.

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

entry	enone	boronic acid: R	conditions	yield (%) ^b	% ee ^c
1	11a	12n : 4-MeOC ₆ H ₄	30 °C, 1 h	98	>99.5 (<i>R</i>)
2	11a	12o : 4-CF ₃ C ₆ H ₄	30 °C, 1 h	97	99.1 (<i>R</i>)
3	11a	12p : 2-MeC ₆ H ₄	30 °C, 1 h	95	99.4 (<i>R</i>)
4	11a	12q : (<i>E</i>)-PhCH=CH	30 °C, 3 h	97	99.3 (<i>R</i>)
5	11a	12r : (<i>E</i>)-C ₃ H ₁₁ CH=CH	30 °C, 3 h	81	98.7 (<i>R</i>)
6	11c	12m : Ph	50 °C, 1 h	94	98 (<i>R</i>)
7	11d	12m : Ph	30 °C, 3 h	84	96 (<i>R</i>)
8	11e	12m : Ph	50 °C, 3 h	97	99.4 (<i>S</i>)

^aThe reaction was carried out with enone **10** (0.30 mmol), PhB(OH)₂ (0.45 mmol), [RhCl(C₂H₄)₂]₂ (3 mol % Rh), diene (3.3 mol %), and 1.5 M aq KOH (0.1 mL) in dioxane (1.0 mL).

^bDienes **6–10** had >99% ee

^cIsolated yield.

^dDetermined by HPLC analysis with chiral stationary phase columns.

^eee = 98.8%.