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Chiral [2.2.2] Dienes as Ligands for Rh(I) in Conjugate Additions of Boronic Acids to a Wide Range of Acceptors

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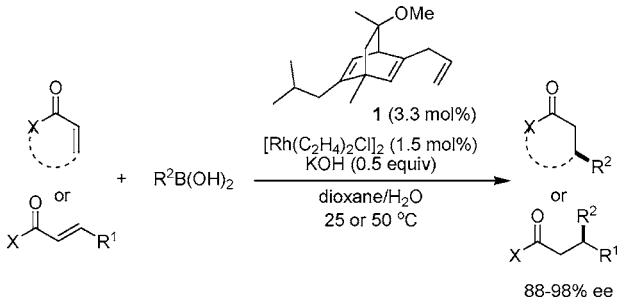
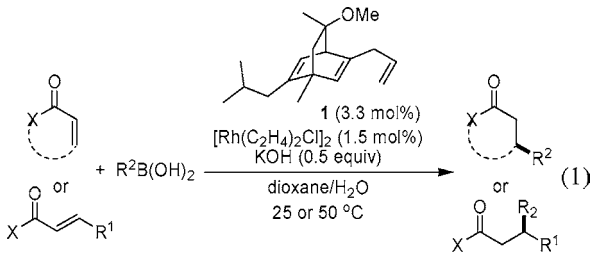
ABSTRACT

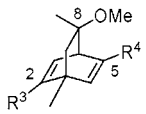


We document a series of investigations that led to new substituted [2.2.2]-diene ligands which display high selectivity in Rh(I)-catalyzed conjugate addition reactions to substrates not previously examined with diene ligands. Moreover, we disclose an unexpected, interesting effect that results from the introduction of a third C═C onto the ligand scaffold (cf. 1).

The recent reports by Hayashi and ourselves on the use of chiral dienes derived from [2.2.1]bicycloheptadiene and [2.2.2]bicyclooctadiene, respectively, as ligands for transition metals open new avenues for the development of asymmetric processes.[1−3] The initial experiments indicated an interesting complementarity between the two diene ligands, namely, that the [2.2.1] diene was superior in the Rh(I)-catalyzed conjugate addition reaction of boronic acids, while the [2.2.2] ligands proved beneficial in Ir(I)-catalyzed allylic displacement reactions. A key advantage of the latter ligands is their ease of synthesis (four steps) from readily available (*R*)- or (*S*)-carvone, permitting diversity-oriented synthesis of the [2.2.2] scaffold. Herein, we document new substituted [2.2.2] diene ligands which display high selectivity in Rh(I)-catalyzed conjugate addition reactions of boronic acids to the standard set of substrates as well as some not previously examined with diene ligands.[4,5] Moreover, we disclose an unexpected, interesting enhancement of selectivity that results from the introduction of a third C═C onto the ligand scaffold (cf. **1**, eq 1).



(1)



2 R_3 = Ph, R_4 = Bn
3 R_3 = Ph, R_4 = allyl
4 R_3 = Ph, R_4 = *n*-Pr
5 R_3 = Ph, R_4 = 3-butenyl

(1) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508.
(2) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.
(3) For a mini review, see: Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364; *Angew. Chem.* **2004**, *116*, 3444.

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In the study by Hayashi of norbornadiene-derived ligand **6** (Figure 1), only cycloalkenones as well as an unsaturated

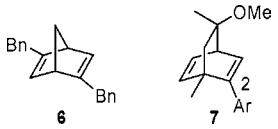


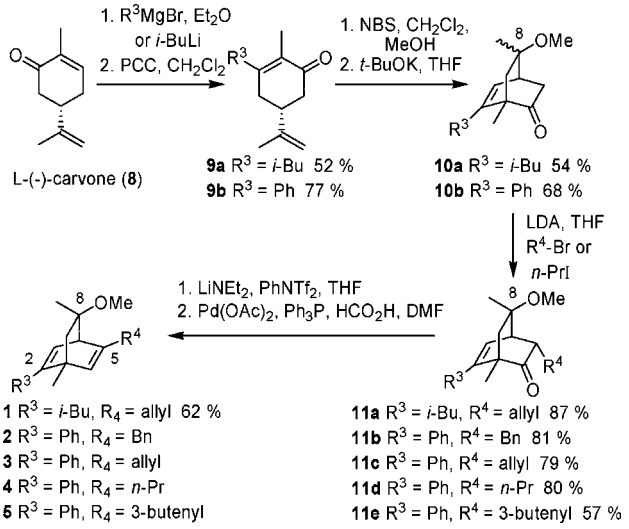
Figure 1.

ester and a methyl ketone, both substituted at C-β with *i*-Pr, were examined. Notably absent from this study were additional substrates of interest such as coumarins along with unsaturated amides and lactones.[6−9]

In our initial study, the carvone-derived [2.2.2] ligand **7** (Ar = 4-*t*-Bu-Ph, Figure 1) effected the addition of $PhB(OH)_2$ to 2-cyclohexenone to afford product in only 52% yield and 71% ee. We have become interested in investigating whether the diminished selectivity with this ligand results from an inherent structural disadvantage of the [2.2.2] scaffold and whether the use of other substituted systems, such as **1**−**5**, could lead to improvements.

The initially disclosed synthesis for **7** provided access to only C-2-substituted dienes, incorporating disubstituted and trisubstituted C=C donors. Therefore, to generate a larger class of [2.2.2] ligands, the development of a different synthesis was necessary. In this respect, the modified sequence shown in Scheme 1 permitted ready variation of

Scheme 1



the substituents at C-2 and C-5. There are two key differences with respect to our earlier route: an initial addition/transposition sequence with carvone (**8** → **9**) and subsequent alkylation of the [2.2.2] ketone (**10** → **11**).[10] Although a separable mixture of C-8 diastereomers is obtained for **10**, the derived Rh(I) complexes for both lead to identical results.

With access to a family of ligands, we screened these in the test reaction of $PhB(OH)_2$ and 2-cyclohexenone under conditions previously reported (Table 1).[1] In general, the C-2/C-5 disubstituted systems (**1** and **2**−**5**) afford adducts in higher selectivity (up to 95% ee) when compared to the original ligand **7** (71% ee). For [2.2.2] bicyclic cyclooctadienes substituted at C-2 with a phenyl group, variation at C-5 was examined. In this series, the presence of a C=C in the substituents at C-5 leads to improvement in selectivity (compare **4** at 82% ee with **3** at 91% ee). This effect is not present if the olefin is absent (cf. **4** at 82% ee and **2** at 88% ee) or is attenuated with a more flexible spacer (cf. **5** at 93% ee). Interestingly, a study of the Rh·**1** complex by ^{1}H NMR spectroscopy indicates coordination by all three double bonds, with potential implications for the enantiodetermining step. When the phenyl group was replaced by an isobutyl group (cf. **1**), improvement in the product enantioselectivity was observed.

Table 1. Effect of Ligand Substitution on Selectivity (eq 2)

ligand	yield[a] (%)	ee[b] (%)
1	87	95 (*S*)
2	91	88 (*S*)
3	91	91 (*S*)
4	85	82 (*S*)
5	63	93 (*S*)

[a] Isolated yields of pure material. [b] Determined by chiral HPLC.

(4) For reviews involving the addition of boronic acids to acceptors using complexes derived from chiral phosphines, see: (a) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13. (b) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(5) Mechanistic study: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(6) For additions of boronic acids to unsaturated ketones employing phosphine ligands, see: (a) Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871; *Angew. Chem.* **2003**, *115*, 6051. (b) Amengual, R.; Michelet, V.; Genêt, J.-P. *Synlett* **2002**, *11*, 1791. (c) Iguchi, Y.; Itooka, R.; Miyaura, N. *Synlett* **2003**, *7*, 1040. (d) Pucheault, M.; Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2002**, 3552. (e) Reetz, M.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083. (f) Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 685. (f) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 3111. (g) Kuriyama, M.; Nagai, K.; Yamada, K.-i.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932. (i) Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(7) Meyer, O.; Becht, J.-M.; Helmchen, G. *Synlett* **2003**, *10*, 1539.

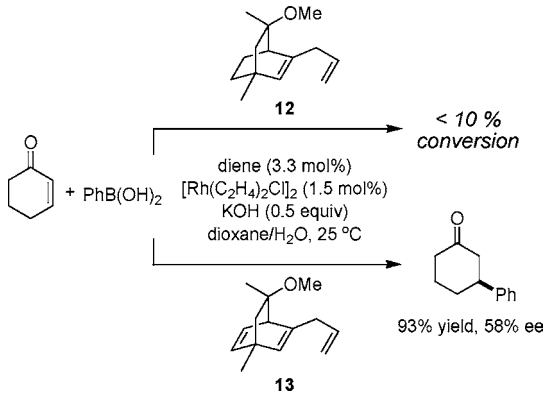
(8) For additions of boronic acids to unsaturated esters employing phosphine ligands with control at both α and β carbons, see: (a) Navarre, L.; Darses, S.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719; *Angew. Chem.* **2004**, *116*, 737. (b) Navarre, L.; Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2004**, 69. (c) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. (d) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047.

(9) For the addition of boronic acids to amides and vinylogous amides employing phosphine ligands, see: (a) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240. (b) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852. (c) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944.

(10) As shown in Scheme 1, the final step in the synthesis of **1** furnishes the diene ligand in good yields. The conversions of **11b**−**e** to **2**−**5** proceeded in considerably poorer yields (18−42%); however, these yields were unoptimized, as the ligands were shown to be inferior (Table 1).

We conducted further preliminary investigations of the unexpected effect of an additional C═C with ligands **12** and **13** (Scheme 2). Interestingly, the use of **12** fails to give any

Scheme 2

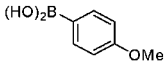
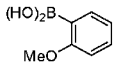
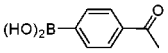
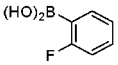
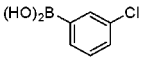
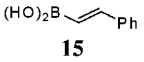
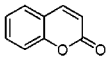
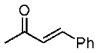
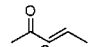
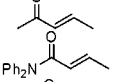
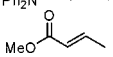


significant amount of product; by contrast, **13** furnishes adduct in 93% yield and 58% ee. Although the latter result is inferior to those described above, it does open up new potential avenues of investigation involving the synthesis and screening of ligands with varied exocyclic olefin substituents.

We then proceeded to examine the addition reaction for a range of acceptors utilizing the optimal ligand **1** (Table 2). Additions to cyclohexenone afforded products in high selectivity (94−97% ee) and 83−96% yield, employing 4-, 3-, and 2-substituted phenylboronic acids. The use of 2-substituted phenylboronic acids has not been peviously examined in these reactions with diene ligands. When cyclopentenones were subjected to additions with both substituted phenyl as well as 2-styrylboronic acids, adducts were isolated in 90−97% ee and 91−98% yield. Conjugate additions to cyclopentenone have historically proven difficult to effect in high selectivities under a variety of conditions. It is important to note that the selectivities we obtained for 3-phenylcyclopentanone (97% ee with **1**; when the addition is carried out with **3** the same adduct is obtained in 98% ee) represent to the best of our knowledge the highest observed to date using any of the available methods.[11] In previous reports involving chiral dienes as ligands, acceptors such as coumarin, 2-(5*H*)-furanone, unsaturated amides, and the simple 3-penten-2-one were not examined. Using Rh(I)·**1**, these additions are all executed successfully (88−98% ee).

In summary, we have documented for the first time the successful use of a [2.2.2]bicyclooctadiene ligand in the Rh-(I)-catalyzed addition of aryl and styryl boronic acids to a variety of acceptors. Included in the set of substrates that were investigated are unsaturated lactones, an acyclic amide, and a simple ketone, none of which had been previously examined with diene ligands. Within this ligand family, we have observed interesting and unexpected observations that result from the introduction of a third C═C, underscoring the dramatic effects that can ensue with relatively minor structural modifications of the scaffold. In particular, this study establishes the versatility of the [2.2.2] ligands derived from (*R*)- or (*S*)-carvone using a new synthetic sequence, which may lead to the potential wider study and use of diene−metal complexes in asymmetric catalysis.

Table 2. Reactions of Acceptors and Boronic Acids Catalyzed by Rh(I)·**1**

none	boronic acid	yield[a] [%]	ee [%]
		83	96 (*S*)
	 **14**	85[c]	96[b] (*R*)
		93[c]	94 (*S*)
		96[c]	97 (*S*)
		94[c]	97 (*S*)
	$PhB(OH)_2$	91	94[b] (*R*)
	$(PhBO)_3$	95	97 (*S*)
		98[c]	95[b] (*R*)
	 **15**	97	90[b] (*R*)
	$PhB(OH)_2$	81	95[b] (*R*)
	$PhB(OH)_2$	80	90 (*S*)
	$PhB(OH)_2$	43[c]	98 (*S*)
	**14**	68	90 (*S*)
	**15**	78	89 (*R*)
	$PhB(OH)_2$	98[c]	93 (*R*)
	$PhB(OH)_2$	93	88 (*R*)

[a] See eq 2 for conditions; reaction times 1−18 h. [b] Reaction carried out with *ent*-**1** to facilitate analysis by chiral HPLC. [c] Conducted at 50 °C.

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(11) (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 17. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.

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Supporting Information Available: General experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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