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Readily Accessible Chiral Diene Ligands for Rh-Catalyzed Enantioselective Conjugate Additions of Boronic Acids

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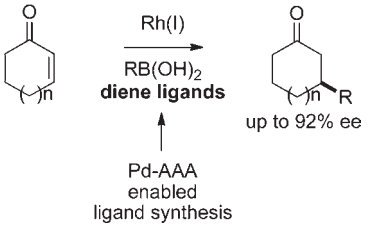
ABSTRACT



Enabled by the broad scope of the Pd-catalyzed asymmetric alkylation of *meso*- and *d,l*-divinylethylene carbonate, several chiral diene ligands were prepared in two steps from commercial materials. Subsequently, these ligands were evaluated in the Rh-catalyzed asymmetric conjugate addition of boronic acids to enones.

There has been recent interest in the use of chiral dienes as ligands in transition metal catalysis.[1] The Hayashi and Carreira groups have pioneered this area, demonstrating that bicyclic dienes (Figure 1, **L1** and **L2**) promote rhodium-catalyzed conjugate additions of boronic acids to α,β-unsaturated electrophiles.[2,3] Despite offering an excellent substrate scope and effecting high enantioselectivities in conjugate addition reactions, ligand availability remains a concern. Toward this end, Du has reported "simple chiral dienes" as ligands for rhodium-catalyzed conjugate additions of aryl and vinyl boronic acids to cyclic enones.[4] In preliminary studies, (3*R*,4*R*)-hexa-1,5-diene-3,4-diol, synthesized in three steps from D-mannitol, provided conjugate addition adducts in up to 85% ee, although the absolute stereochemistry of ligands built on this platform is limited by the lack of access to the enantiomeric diene diol (i.e., L-mannitol is not readily available). Similar results were obtained in a subsequent study using imidazolidinone ligands (prepared in three

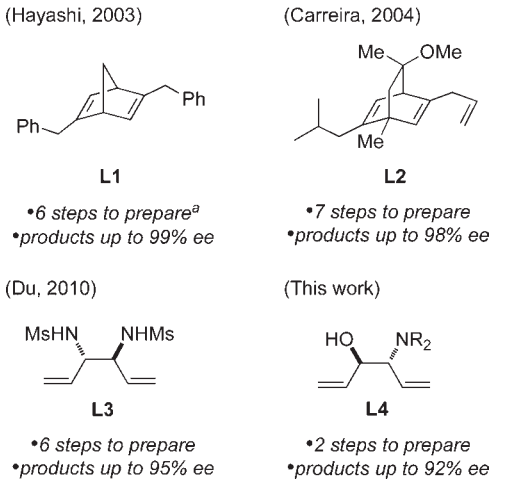


Figure 1. Representative chiral diene ligands used in Rh-catalyzed enantioselective conjugate additions. [a]Due to the lability/volatility of **L1**, this ligand is typically complexed with Rh^I in a subsequent step. For details, see ref 2b.

(1) For reviews on chiral olefin 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. (c) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31.

(2) (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.

(3) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873.

(4) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744.

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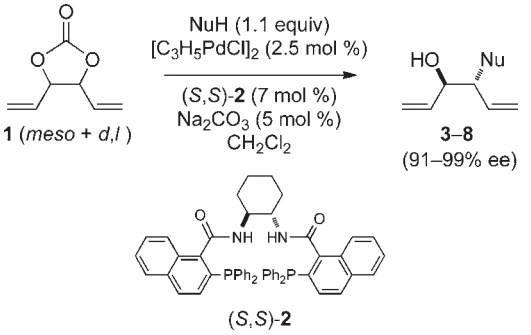
steps from commercial materials).[5] Recently, Du has reported the use of diene disulfonamide ligand **L3**, which provides products in up to 95% ee. However, this ligand requires six steps to prepare from 1,5-hexadiene.[6] In a similar effort, Yu has reported the successful use of a *bis*-terminal diene ligand (five steps from commercial materials) in rhodium-catalyzed conjugate additions.[7] With this in mind, a more convenient synthetic approach toward chiral dienes for use in transition metal catalysis became the primary objective of this work. Moreover, it is desirable to do so by implementation of a robust chemical method on a common intermediate. In this sense, one can rapidly produce a structurally diverse library of potential ligands.

We recognized that our palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) of *meso*- and *d*,*l*-divinylethylene carbonate (**1**)[8] with suitable nucleophiles would provide rapid access (i.e., two steps from commercial materials) to chiral diene ligands (Scheme 1). In addition to providing an efficient modular approach[9] toward an initial chiral diene ligand screen, it should also be noted that either enantiomer of a respective ligand is equally accessible using this method. This is not the case for the previously mentioned diene diol ligand described by Du[4] or the bicyclo[2.2.2]octadiene ligands synthesized in two steps from (*R*)-α-phellandrene reported by Hayashi and Rawal.[10]

Scheme 1. Synthesis of Chiral Diene Ligands via Pd-AAA of *meso*- and *d*,*l*-1,2-Divinylethylene Carbonate



Several diene ligands (Figure 2, **3**–**9**) were prepared and evaluated with respect to conversion and enantiomeric excess in the rhodium-catalyzed conjugate addition of phenylboronic acid to 2-cyclopentenone (**10**).

At the outset we chose to evaluate 2-cyclopentenone, a substrate which has consistently proved challenging in previous studies with chiral terminal olefin ligands.[4–6] To our delight, use of ligand **3** gave the corresponding product (**11**) in 74% ee. Saturated imides **4** and **5** led to significantly reduced yields and, in the case of **4**, lowered enantioselectivity. Incorporation of other heterocycles, such as the isatin-derived ligand **6** or the benzoxazolidinone-derived ligand **7** did not provide improvement. Known diene **8**[8] was tested to observe the effect of heteroatom substitution (i.e., oxygen vs nitrogen) and led to a reduction of yield and enantioselectivity. Compound **9**,[11] which is prepared from the Pd-AAA of butadiene monoepoxide with phthalimide, and which is structurally analogous to **3** with exclusion of the second olefin, provided very little conversion or enantioselectivity.[12] This result highlights the requirement of a bidentate ligand (e.g., diene) and suggests that the hydroxyl moiety is not involved in binding with rhodium.

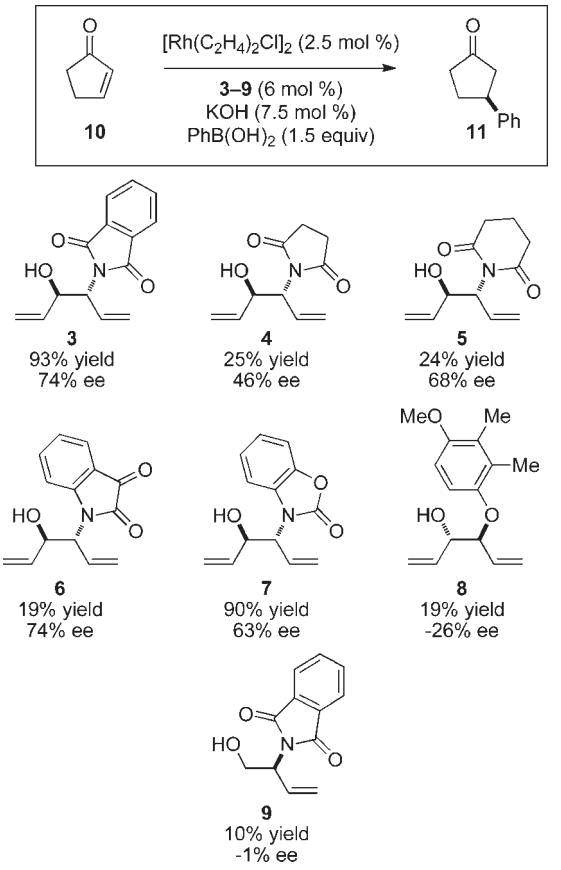


Figure 2. Ligand screen in Rh-catalyzed conjugate addition of phenylboronic acid to **10**.

Next, we examined the effect of solvent on the conjugate addition of phenylboronic acid to **10** (Table 1). It was found that a 2:1 ratio of dioxane and water at room

(5) Hu, X.; Cao, Z.; Liu, Z.; Wang, Y.; Du, H. *Adv. Synth. Catal.* **2010**, *352*, 651.
(6) Wang, Y.; Hu, X.; Du, H. *Org. Lett.* **2010**, *12*, 5482.
(7) Li, Q.; Dong, Z.; Yu, Z.-X. *Org. Lett.* **2011**, *13*, 1122.
(8) Trost, B. M.; Aponick, A. *J. Am. Chem. Soc.* **2006**, *128*, 3931.
(9) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
(10) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387.

(11) (a) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968. (b) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem.—Eur. J.* **2006**, *12*, 6607.
(12) It should be noted that the absolute configurations of **8** and **9** are opposite to that of the other ligands studied and were used arbitrarily due to availability.

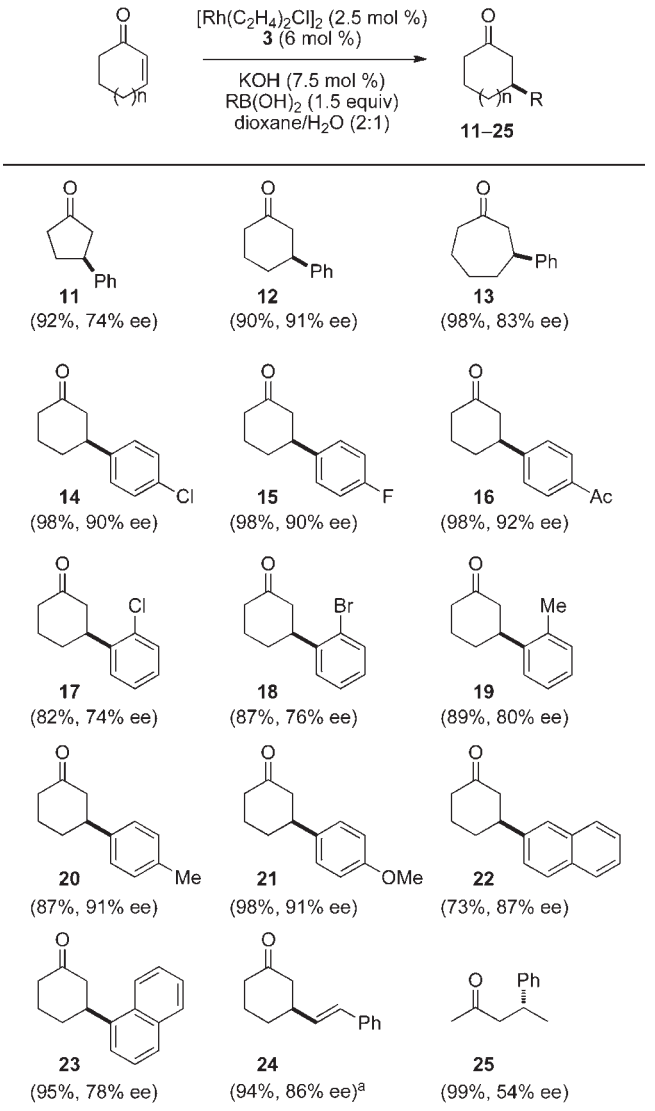
temperature was optimal with respect to conversion and ee (entry 2). This finding is consistent with Du's studies of diene diol ligands.[4] Either reducing or increasing the ratio of dioxane to water (entries 1 and 4) led to decreased ee and/or isolated yield of **11**, but this effect was minimal in the latter case. Water, the ligand, and base were each necessary to effect the desired transformation (entries 3, 5, and 6). Additional solvents/cosolvents were evaluated (entries 7–17), but none proved superior. Interestingly, the reaction is relatively insensitive to the solvent identity with respect to enantioselectivity. Neither alternative bases (entries 18–20) nor additives improved upon the results of entry 2 (e.g., $In(OTf)_3$, $BF_3 \cdot OEt_2$, TBAT, or DMAP).

Table 1. Optimization Study of Conjugate Addition of Phenylboronic Acid to 2-Cyclopentenone[a]

entry	solvent (v/v)	% yield	% ee
1	dioxane/H_2O (1:2)	40	61
2	**dioxane/H_2O (2:1)**	**92**	**74**
3[b]	dioxane/H_2O (2:1)	<5	nd
4	dioxane (10:1)	90	72
5[c]	dioxane (10:1)	<5	nd
6	dioxane	<5	nd
7[d]	dioxane/MeOH (10:1)	90	59
8	dioxane/trifluoroethanol (10:1)	60	62
9	dioxane/ethylene glycol (10:1)	59	60
10	dioxane/*neo*-pentanol (10:1)	<5	nd
11	THF/H_2O (10:1)	36	70
12	DME/H_2O (10:1)	50	49
13	MTBE/H_2O (2:1)	39	56
14	toluene/H_2O (2:1)	43	74
15	CH_2Cl_2/H_2O (2:1)	17	74
16	acetone/H_2O (2:1)	12	70
17	DMF/H_2O (2:1)	18	32
18[e]	dioxane/H_2O (2:1)	38	38
19[f]	dioxane/H_2O (2:1)	31	26
20[g]	dioxane/H_2O (2:1)	19	30

[a] All reactions were carried out with 2-cyclopentenone (0.25 mmol), phenylboronic acid (0.38 mmol), $[Rh(CH_2CH_2)Cl]_2$ (6.25 μmol), **3** (15 μmol), and KOH (18.7 μmol) in 750 μL of solvent for 6 h. [b] Reaction conducted without ligand. [c] Reaction conducted without KOH. [d] Reaction conducted at 50 °C for 6 h. [e] K_3PO_4 (18.7 μmol) used as the base. [f] K_2CO_3 (18.7 μmol) used as the base. [g] Et_3N (19 μmol) used as the base.

Using these optimized conditions, the scope of the conjugate addition was examined with respect to the boronic acid and enone (Figure 3). 2-Cyclohexenone and 2-cycloheptenone reacted with phenylboronic acid to provide **12** and **13** in good yields and enantioselectivities. Electronic variation of the boronic acid had little effect on yield or ee of the corresponding product. *para*-Substituted boronic acids provided slightly higher yields and enantioselectivities relative to the *ortho*-substituted coupling partners (cf. **14** and **17**). Interestingly, *o*-chloroboronic acid failed as a substrate in the studies of Yu et al., whereas, with ligand **3**, a good yield and enantioselectivity were observed.[7] In addition to phenylboronic acids,



[a] Reaction was conducted with the potassium trifluoroborate salt in place of the boronic acid.

Figure 3. Scope of Rh-catalyzed conjugate addition.

2-naphthylboronic acid is an excellent substrate in the addition to 2-cyclohexenone, affording **22** in good yield and in high enantiomeric excess; 1-naphthylboronic acid provided **23** with a slightly decreased ee. The vinyl boronic acid, *trans*-β-styrylboronic acid, provided **24** in poor yield but with good enantioselectivity (result not shown). During the course of this reaction, consumption of the boronic acid was observed without concomitant product formation. We hypothesized that this was a result of a competitive protiodeborylation, and we reasoned that use of the corresponding potassium trifluoroborate salt[13] would provide a stable reservoir from which the boronic acid would be slowly liberated. Gratifyingly, the use of potassium *trans*-β-styryltrifluoroborate provided **24** in good yield

(13) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.

and ee. Currently, this methodology works best with cyclic acceptors, as an acyclic substrate provided the addition product **25** in excellent yield but with moderate enantioselectivity. To the best of our knowledge, this is the first example of a successful conjugate addition to an acyclic acceptor using a terminal diene ligand.[4−7]

In summary, we have developed a new ligand design platform based on the Pd-AAA of *meso*- and *d*,*l*-divinylethylene carbonate (**1**), and have identified a simple chiral diene that is useful in Rh-catalyzed conjugate additions of boronic acids to enones. Ligand **3** can be prepared in two steps from commercial materials,[14] and provides products in good yields and ee's (up to 92% ee). With respect to product yield and enantioselectivity, **3** is comparable to the best of the previously reported terminal diene ligands, which require more steps to prepare.[6,7] Importantly, either enantiomer of **3** is equally accessible using our Pd-AAA methodology. This strategy toward diene ligand discovery is amenable to providing rapid access to libraries of ligands with substantial structural variation (i.e., altering the nucleophile in the Pd-AAA reaction). Ongoing efforts are underway to identify additional applications of this technology in transition metal ligand development.

(14) For a large-scale preparation of **3** (15 mmol), see: Trost, B. M.; Aponick, A.; Stanzl, B. N. *Chem.—Eur. J.* **2007**, *13*, 9547.

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