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Rhodium-Catalyzed Asymmetric Cyclization/Hydroboration of 1,6-Enynes

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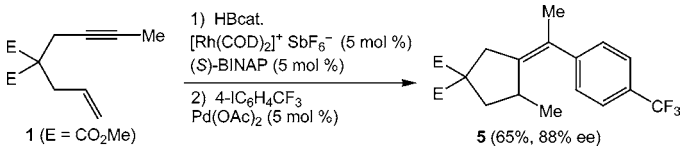
ABSTRACT



Reaction of enyne 1 with catecholborane catalyzed by a 1:1 mixture of $[Rh(COD)_2]^+SbF_6^-$ and (*S*)-BINAP (5 mol %) followed by Pd-catalyzed arylation with *p*-$IC_6H_4CF_3$ gave benzylidenecyclopentane 5 in 65% yield with 88% ee. Rhodium-catalyzed asymmetric cyclization/hydroboration followed either by Pd-catalyzed arylation or by oxidation was applied to the synthesis of a number of chiral, nonracemic carbocycles and heterocycles.

Hydroboration is one of the most important methods utilized for the functionalization of C−C multiple bonds due in large part to the synthetic versatility of the resulting organoboranes.[1] Employment of transition metal catalysts has extended the scope of hydroboration by allowing access to chemo-, regio-, and diastereoselectivity not realized via the noncatalyzed transformation.[2−4] Furthermore, efficient asymmetric hydroboration has been achieved through the employment of chiral, nonracemic transition metal catalysts without the necessity of a stoichiometric amount of a chiral borane.[5] Although a number of the complexes that catalyze hydroboration also catalyze the carbocyclization of enynes and related substrates,[6] efficient catalytic processes that couple catalytic hydroboration with carbocyclization have not been forthcoming.[7,8] This shortcoming is unfortunate, as such a transformation would represent an expedient route to the synthesis of functionalized carbocycles and heterocycles, particularly if effective asymmetric induction were realized.

(1) (a) Brown, H. C. *Hydroboration*; Wiley-Interscience: New York, 1962. (b) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, 1988. (c) Suzuki, A.; Dhillon, R. S. Selective Hydroboration and Synthetic Utility of Organoboranes Thus Obtained. In *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer-Verlag: New York, 1986; Vol. 130, pp 23−88.

(2) (a) Männig, D.; Nöth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878. (b) Brown, J. M. Rhodium-Catalyzed Hydroboration Reactions. In *Modern Rhodium Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 33−51. (c) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679. (d) Zhang, J.; Lou, B.; Guo, G.; Dai, L. *J. Org. Chem.* **1991**, *56*, 1670. (e) Pérez Luna, A.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Am. Chem. Soc.* **2002**, *124*, 12098. (f) Pereira, S.; Srebnik, M. *J. Am. Chem. Soc.* **1996**, *118*, 909. (g) Brinkman, J. A.; Nguyen, T. T.; Sowa, J. R. *Org. Lett.* **2000**, *2*, 981. (h) Evans, D. A.; Muci, A. R.; Stürmer, R. *J. Org. Chem.* **1993**, *58*, 5307. (i) Harrison, K. N.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 9220. (j) Kabalka, G. W.; Narayana, C.; Reddy, N. K. *Synth. Commun.* **1994**, *24*, 1019. (k) Gridnev, I. D.; Miyaura, N.; Suzuki, A. *Organometallics* **1993**, *12*, 589. (l) Gridnev, I. D.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 5351. (m) Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1468. (n) Matsumoto, Y.; Naito, M.; Hayashi, T. *Organometallics* **1992**, *11*, 2732. (o) Burgess, K.; Jaspars, M. *Organometallics* **1993**, *12*, 4197. (p) He, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 1696.

(3) (a) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179. (b) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671.

(4) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917.

(5) (a) Carroll, A. M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609. (b) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, *24*, 4695. (c) Hayashi, T. Hydroboration of Carbon−Carbon Double Bonds. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 1, pp 351−364. (d) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1988**, *53*, 5178. (e) Perez Luna, A.; Ceschi, M. A.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Org. Chem.* **2002**, *67*, 3522. (f) Demay, S.; Volant, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1235. (g) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062. (h) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426.

(6) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. *Chem. Rev.* **1996**, *96*, 635.

(7) Molander, G. A.; Pfeiffer, D. *Org. Lett.* **2001**, *3*, 361.

(8) For other examples of cyclization/boration, see: (a) Onozawa, S.-y.; Hatanaka, Y.; Tanaka, M. *Chem. Commun.* **1997**, 1229. (b) Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **1998**, *17*, 5233−5235. (c) Onozawa, S.-y.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389.

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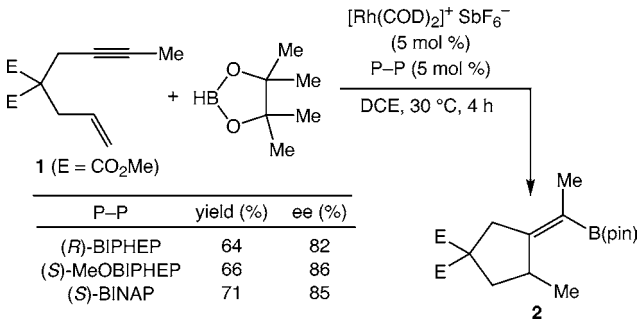
Here we report the rhodium-catalyzed asymmetric cyclization/hydroboration of 1,6-enynes to form functionalized carbocycles and heterocycles.

We recently reported the asymmetric cyclization/hydrosilylation of 1,6-enynes catalyzed by a 1:1 mixture of $[Rh(COD)_2]^+SbF_6^-$ and (*R*)-BIPHEP (5 mol %).[9−11] This catalyst system served as a starting point for the development of an asymmetric cyclization/hydroboration protocol. In an initial experiment, reaction of enyne **1** with pinacolborane catalyzed by a 1:1 mixture of $[Rh(COD)_2]^+SbF_6^-$ and (*R*)-BIPHEP (5 mol %) in 1,2-dichloroethane (DCE) at 30 °C for 4 h led to isolation of borylated alkylidene cyclopentane **2** in 64% yield as a single diastereomer with 82% ee (Scheme 1). Subsequent experimentation indicated that employment

Scheme 1

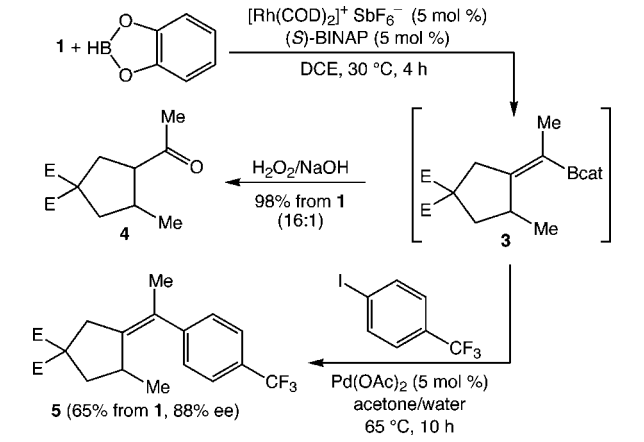


P–P	yield (%)	ee (%)
(*R*)-BIPHEP	64	82
(*S*)-MeOBIPHEP	66	86
(*S*)-BINAP	71	85

of (*S*)-BINAP as the supporting ligand improved both the yield and enantioselectivity of rhodium-catalyzed conversion of **1** to **2** (Scheme 1).

The yield and enantioselectivity of the rhodium-catalyzed asymmetric cyclization/hydroboration of **1** was further improved through employment of catecholborane as the borylating agent. Reaction of **1** with catecholborane catalyzed by a 1:1 mixture of $[Rh(COD)_2]^+SbF_6^-$ and (*S*)-BINAP (5 mol %) in DCE at 30 °C for 4 h led to formation the borylated alkylidene cyclopentane **3** as the exclusive product with ≥20:1 isomeric purity (^{1}H NMR, Scheme 2). Oxidation

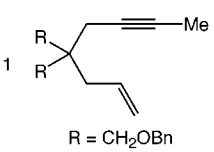
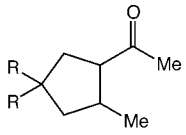
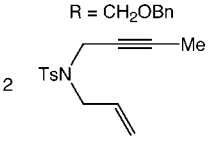
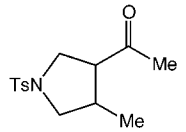
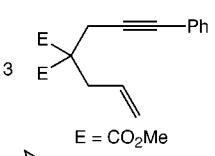
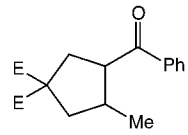
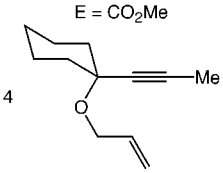
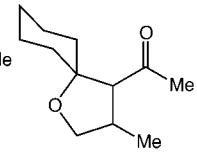
Scheme 2



of crude **3** without isolation gave acetylcyclopentane **4** in 98% yield as a 16:1 mixture of diastereomers (Scheme 2). In a separate experiment, crude **3** was treated with *p*-$IC_6H_4CF_3$ and a catalytic amount of $Pd(OAc)_2$ in acetone/water at 65 °C for 10 h to give benzylidenecyclopentane **5** in 65% yield with >95% isomeric purity and 88% ee (Scheme 2).

Rhodium-catalyzed asymmetric cyclization/hydroboration followed either by oxidation or by arylation was applied to the synthesis of a number of chiral, nonracemic carbocycles and heterocycles (Tables 1 and 2). These protocols tolerated

Table 1. Cyclization/Hydroboration of 1,6-Enynes Catalyzed by a 1:1 Mixture of $[Rh(COD)_2]^+SbF_6^-$ and (*S*)-BINAP (5 mol %) in DCE at 30 °C Followed by Oxidation with H_2O_2/OH^-

entry	enyne	product	yield (%)[a]	dr	ee (%)
1			78	15:1	88
2			81	4.5:1	92
3			84	23:1	75
4			88	1.3:1	83

[a] Isolated material of >95% purity.

alkyl or aryl substitution at the alkyne carbon atom and *gem*-dialkyl substitution at either the propargylic or allylic position (Tables 1 and 2), although substitution at the allylic position led to a significant decrease in enantioselectivity (Table 2, entry 2). Conversely, 1,6-enynes that possessed either a terminal C≡C bond or a substituted C═C bond and 1,7-enynes failed to undergo efficient rhodium-catalyzed asymmetric cyclization/hydroboration.

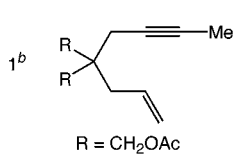
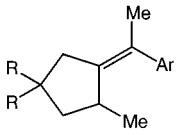
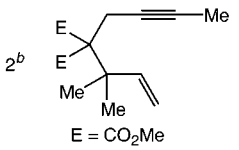
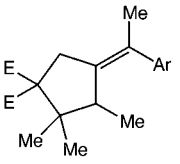
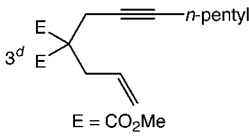
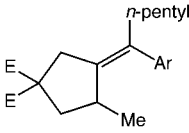
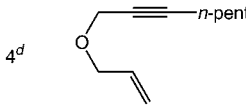
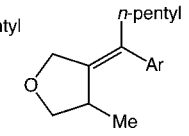
We considered two mechanisms for the Rh-catalyzed conversion of **1** to **3** that account for selective transfer of

(9) Chakrapani, H.; Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2003**, *5*, 157.

(10) For recent examples of Rh-catalyzed asymmetric carbocyclization, see: (a) Jang, H.-Y.; Hughes, F. W.; Gong, H.; Zhang, J.; Brodbelt, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 6174. (b) Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 12466. (c) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, *7*, 4737. (d) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526. (e) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 11472.

(11) For other examples of asymmetric cyclization/hydrometalation, see: (a) Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960. (b) Pei, T.; Widenhoefer, R. A. *J. Org. Chem.* **2001**, *66*, 7639. (c) Muci, A. R.; Bercaw, J. E. *Tetrahedron Lett.* **2000**, *41*, 7609.

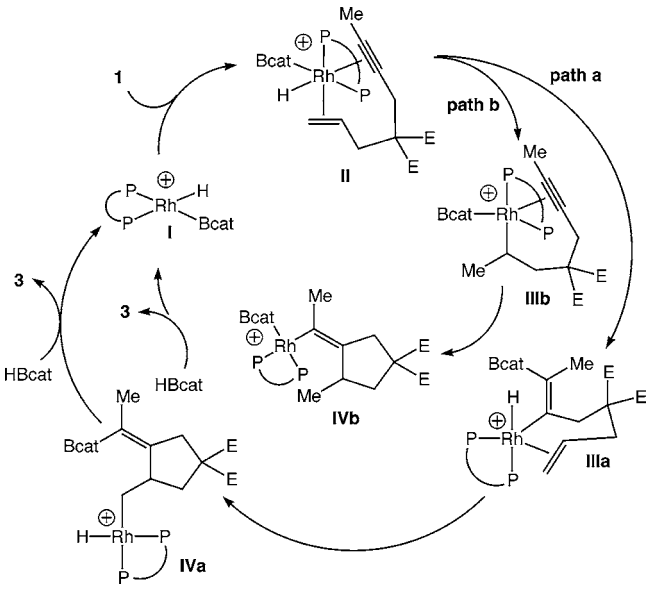
Table 2. Cyclization/Hydroboration of 1,6-Enynes Catalyzed by a 1:1 Mixture of $[Rh(COD)_2]^+SbF_6^-$ and (*S*)-BINAP (5 mol %) in DCE at 30 °C Followed by Pd-Catalyzed Cross-Coupling with Aryl Iodide

entry	enyne	product	yield (%)[a]	ee (%)
1[b]	 R = CH_2OAc		61[c]	87
2[b]	 E = CO_2Me		70	45
3[d]	 E = CO_2Me		68	82
4[d]			40	98

[a] Isolated material of >95% purity. [b] Ar = 4-$C_6H_4CF_3$. [c] 20:2:1 mixture of isomers. [d] Ar = 4-$C_6H_4NO_2$.

the boryl group to the C≡C bond of the enyne. Oxidative addition of catecholborane to a Rh(I) bis(phosphine) species could form the Rh(III) boryl hydride species **I**,[12] which could react with enyne **1** to form the η^4-rhodium enyne complex **II**. Borylmetalation of the C≡C bond of **II** followed by intramolecular carbometalation of the resulting rhodium alkenyl olefin complex **IIIa** could form the rhodium alkyl hydride species **IVa** (Scheme 3, path a). C−H reductive elimination from **IVa** coupled with B−H oxidative addition would release **3** with regeneration of **I**. Alternatively, hydrometalation of the C=C bond of **II** followed by intramolecular carbometalation of the resulting rhodium alkyl alkyne complex **IIIb** could form the rhodium alkenyl boryl species **IVb** (Scheme 3, path b). C−B reductive elimination from **IVb** coupled with B−H oxidative addition would release **3** with regeneration of **I**.[13,14] Although we cannot

Scheme 3



distinguish between these two pathways, η^4-coordination of the enyne to rhodium (**II**) appears necessary to achieve selective transfer of rhodium to the more sterically hindered atom of the C−C multiple bond in the initial insertion step (**II** → **III**). The regioselectivity of rhodium-catalyzed hydroboration has been shown to be strongly affected by the presence of a suitable directing group.[4] Furthermore, C−C multiple bonds have been shown to function as directing groups for both the Rh-catalyzed cyclization/arylation of enynes with arylboronic acids[15] and for the Ni-catalyzed addition of aldehydes to enynes.[16]

In summary, we have developed an effective rhodium-catalyzed protocol for the asymmetric cyclization/hydroboration of 1,6-enynes terminated either via Pd-catalyzed arylation or by oxidation. We have applied these protocols to the synthesis of a number of chiral, nonracemic heterocycles and carbocycles.

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Supporting Information Available: Experimental procedures and spectroscopic data for products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Daura-Oller, E.; Segarra, A. M.; Poblet, J. M.; Claver, C.; Fernandez, E.; Bo, C. *J. Org. Chem.* **2004**, *69*, 2669.

(13) Both of the proposed pathways possess some unusual features. Pathway a invokes initial insertion into the Rh−B bond in preference to the Rh−H bond. Although insertion into a Rh−B bond has been demonstrated,[14] it is generally accepted that Rh-catalyzed hydroboration occurs via initial insertion into the Rh−H bond of the rhodium boryl hydride intermediate.[3] Conversely, pathway b invokes initial metalation of the C=C bond in preference to the typically more reactive C≡C bond.

(14) Baker, R. T.; Calabrese, J. C.; Westcott, S. A.; Nguyen, P.; Marder, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 4367.

(15) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094.

(16) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342.