Communication

Cobalt-Catalyzed Asymmetric Hydroboration/ Cyclization of 1,6-Enynes with Pinacolborane

Songjie Yu, Caizhi Wu, and Shaozhong Ge

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 28 Apr 2017

Cobalt-Catalyzed Asymmetric Hydroboration/Cyclization of 1,6-Enynes with Pinacolborane

Songjie Yu, Caizhi Wu, and Shaozhong Ge*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore

Supporting Information Placeholder

ABSTRACT: We report the a cobalt-catalyzed asymmetric hydroboration/cyclization of 1,6-enynes with catalysts generated from $Co(acac)_2$ and chiral bisphosphine ligands and activated in situ by the reaction with pinacolborane (HBpin). A variety of oxygen-, nitrogen-, and carbon-tethered 1,6-enynes underwent this asymmetric transformation, yielding both alkyl- and vinyl-substituted boronate esters containing chiral tetrahydrofuran, cyclopentane, and pyrrolidine moieties with high to excellent enantioselectivities (86%–99% ee).

Chiral five-membered carbocyclic and heterocyclic structural motifs are present in a variety of bioactive natural products (Figure 1).[1] The transition metal-catalyzed enantioselective cycloisomerizaiton of 1,6-enynes[2] and related reductive cyclization[3] represent powerful approaches to such chiral cyclic structural units.[4] However, borylative cyclization[5] is arguably more important for synthetic applications because of the versatile chemistry of the boryl functionality.[6] Several catalysts have been reported for asymmetric borylative cyclization of specific classes of alkene-containing multiply unsaturated substrates with bis(pinacolato)diboron (B_2pin_2).[7]

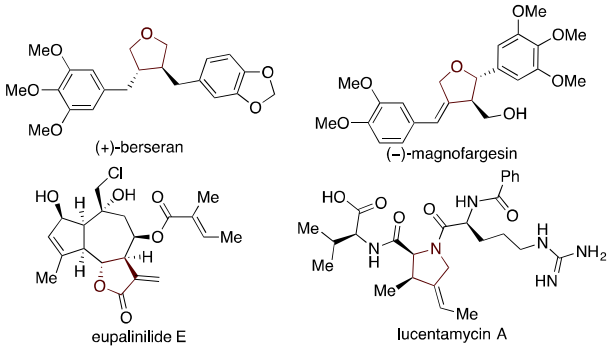
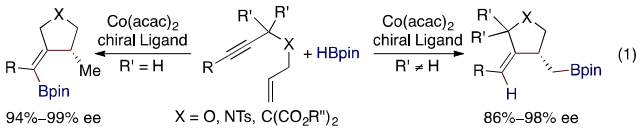


Figure 1. Examples of related nature products

In 2013, Lin, Tian, and coworkers reported a Cu-catalyzed asymmetric borylative cyclization of cyclohexadienone-containing oxygen-tethered enynes with B_2pin_2 in the presence of methanol as a proton source.[7c] Mechanistic studies reveal that the coordination of the oxygen atom in the propargylic ether unit with the copper catalyst is crucial to achieve the borylative cyclization. Carbon- and nitrogen-tethered 1,6-enynes do not undergo this copper-catalyzed asymmetric transformation.

The hydroboration/cyclization of 1,6-enynes with HBpin, a more atom-economical approach than borylative cyclization with B_2Pin_2, could potentially produce both vinyl and alkyl boronate products (eq 1). This reaction has been studied with a chiral rhodium catalyst and affords only vinyl boronate products.[8] This rhodium system requires the use of catecholborane (HBcat) to achieve good yields of vinyl boronate products and generally shows low to modest enantioselectivities. In addition, the use of HBcat limits its applications because of the poor stability of catechol boronate products. In view of broad synthetic applications of pinacol boronate esters[9] and importance of chiral carbocyclic and heterocyclic structural motifs, we are interested in developing a base metal-catalyzed asymmetric hydroboration/cyclization of 1,6-enynes with HBpin to prepare chiral cyclic boronate esters. Here we report the first asymmetric cobalt-catalyzed hydroboration/cyclization of 1,6-enynes that produces both alkyl and vinyl boronate esters (eq 1).[10]

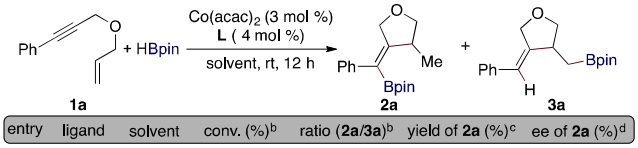


Recently, cobalt complexes have been emerging as active catalysts for hydrogenation,[11] hydroboration,[12] and hydrosilylation[13] of alkenes and alkynes.[14] During our effort in developing cobalt catalysis, we have found that cobalt complexes with bisphosphine ligands are effective for alkene hydrosilylation.[15] In this study, we targeted cobalt complexes with chiral bisphosphine ligands for asymmetric hydroboration/cyclization of 1,6-enynes because the accessibility of a wide range of chiral bisphosphine ligands provides a possibility to control both regio- and enantioselectivity of this transformation.

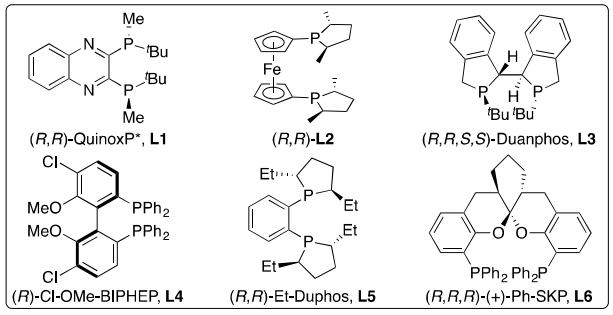
We initiated our studies of Co-catalyzed hydroboration/cyclization by evaluating the reaction between (3-(allyloxy)prop-1-yn-1-yl)benzene (**1a**) and HBpin. We tested various cobalt precursors, bisphosphine ligands and solvents for this reaction (see SI for the detailed evaluation)

and the selected examples are summarized in Table 1. The reaction conducted with $Co(acac)_2$ and (*R*,*R*)-QuinoxP* (**L1**) in THF afforded the vinyl boronate product **2a** as major product with high enantioselectivity (98% ee) (entry 1). Next, we tested this reaction in various solvents (entries 2–4) and we found that the reaction conducted in toluene gave **2a** in 85% isolated yield with excellent enantioselectivity (99% ee) (entry 4). Other chiral bisphosphine ligands **L2**–**L6** were tested and these reactions showed lower selectivity for **2a** over **3a** (entries 5–9). In addition, these reactions afforded **2a** with lower enantioselectivities.

Table 1. Evaluation of Conditions for Co-Catalyzed Hydroboration/Cyclization of Enyne 1a[a]



entry	ligand	solvent	conv. (%)[b]	ratio (**2a**/**3a**)[b]	yield of **2a** (%)[c]	ee of **2a** (%)[d]
1	**L1**	THF	97	9.2:1	54	98
2	**L1**	hexane	>99	19:1	77	99
3	**L1**	Et_2O	93	13:1	63	97
4	**L1**	toluene	>99	49:1	85	99
5	**L2**	toluene	96	4.7:1	69	84
6	**L3**	toluene	94	8:1	56	25
7	**L4**	toluene	67	8:1	38	81
8	**L5**	toluene	<5	-:-	-	-
9	**L6**	toluene	<5	-:-	-	-



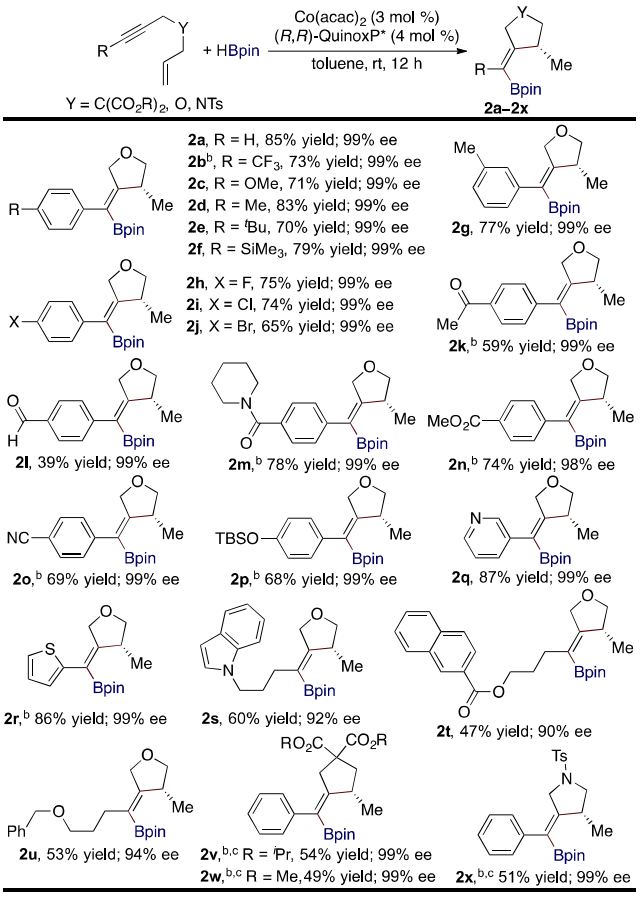
[a]Conditions: **1a** (0.200 mmol), HBpin (0.300 mmol), $Co(acac)_2$ (6.0 μmol), ligand (8.0 μmol), solvent (1 mL), rt, 12 h, [b]conversions of **1a** and ratios of **2a**:**3a** were determined by GC analysis on the crude reaction mixture; [c]isolated yields; [d]ee was determined by chiral HPLC analysis using the isolated compound **2a**.

The scope of 1,6-enynes for this cobalt-catalyzed asymmetric hydroboration/cyclization to produce vinyl boronate esters is summarized in Table 2. In general, a wide range of oxygen-, nitrogen-, or carbon-tethered 1,6-enynes reacted in the presence of 3 mol % of $Co(acac)_2$ and 4 mol % of (*R*,*R*)-quinoxP* to provide vinyl boronate esters (**2a**–**2x**) with modest to high isolated yields (59%–87%) and high enantioselectivities (94%–99%).

The 1,6-enynes containing a series of electronically varied aryl groups (**2a**–**2c**) reacted smoothly with high yields and excellent enantioselectivities. Aliphatic 1,6-enynes also reacted to give the corresponding vinyl boronate esters (**2s**–**2u**) with high enantioselectivities. Nitrogen- and carbon-tethered 1,6-enynes underwent hydroboration/cyclization at 60 °C to afford the corresponding vinyl boronate esters (**2v**–**2x**) with modest yields and excellent enantioselectivities (99%).[16]

This asymmetric transformation shows high functional group tolerance and a wide range of reactive groups, such as trifluoromethyl (**2b**), silyl (**2f**), ether (**2c** and **2u**), fluoro (**2h**), chloro (**2i**), bromo (**2j**), ketone (**2k**), aldehyde (**2l**), amide (**2m**), ester (**2n** and **2t**), cyano (**2o**), and silylether (**2p**) moieties, are compatible with the reaction conditions. In addition, enynes containing pyridine, thiophene, or indole moieties also reacted, affording the corresponding vinyl boronate esters (**2q**–**2s**) with high yields and excellent enantioselectivities. However, the reactions of enynes containing internal alkenes, terminal alkynes, nitro, and unprotected hydroxyl and amino groups did not occur. The absolute configuration of **2b** and **2n** was determined to be (*R*) by single-crystal X-ray diffraction.

Table 2. Scope of 1,6-Enynes for Vinyl Boronate Esters[a]



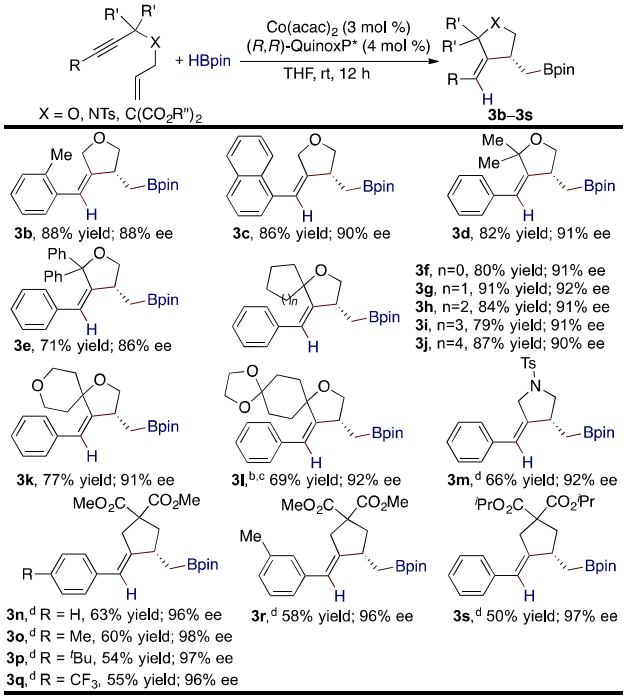
[a]Conditions: enyne (0.200 mmol), HBpin (0.300 mmol), $Co(acac)_2$ (6.0 μmol), (*R*,*R*)-quinoxP* (8.0 μmol), toluene (1 mL), rt, 12 h, isolated yields, and ee was determined by chiral HPLC analysis; [b]60 °C; [c]THF (1 ml).

The data in Table 2 show that the enynes containing *para*- (**2b**–**2f**) or the *meta*-substituted (**2g**) arenes reacted to afford vinyl boronate esters as major products. However, the enynes containing *ortho*-substituted aryl groups reacted to provide alkyl boronate esters (**3b** and **3c** in Table 3) with good isolated yields and high enantioselectivities. Subsequently, we tested the reactions of oxygen-tethered 1,6-enynes with two substituents at the propargalic position in the presence of $Co(acac)_2$ and (*R*,*R*)-QuinoxP*. These reactions occurred smoothly at room temperature and afforded

alkyl boronate esters (**3d**–**3l** in Table 3) with high isolated yields (69%–91%) and high ee (86%–92%).

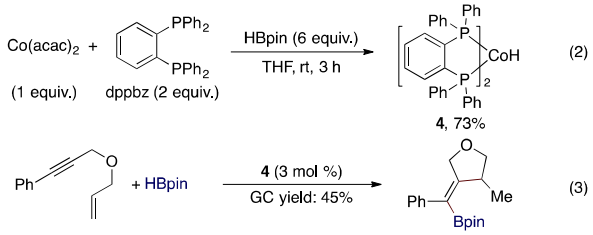
When catalyzed by $Co(acac)_2$ and (*R*,*R*)-quinoxP* at room temperature, nitrogen- and carbon-tethered 1,6-enynes reacted to give the products from *anti*-Markovnikov hydroboration of the alkene without cyclization (see SI for the details). However, under modified conditions with (*R*,*R*)-**L2** (see Table 1 for its structure), nitrogen- and carbon-tethered enynes underwent hydroboration/cyclization smoothly at room temperature, affording the corresponding alkyl boronate esters (**3m**–**3s** in Table 3) with high enantioselectivities, albeit with modest isolated yields.

Table 3. Scope of 1,6-Enynes for Alkyl Boronate Esters[a]

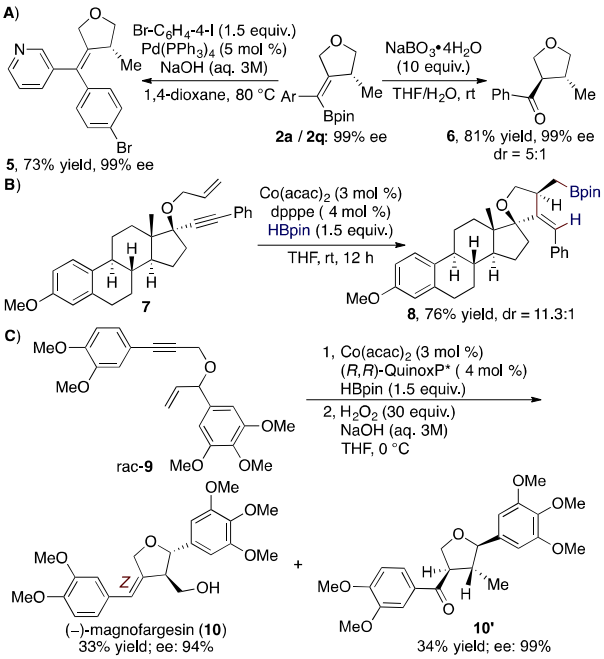


[a]Conditions: enyne (0.200 mmol), HBpin (0.300 mmol), $Co(acac)_2$ (6.0 μmol), (*R*,*R*)-quinoxP* (8.0 μmol), THF (1 mL), rt, 12 h, isolated yields, and ee was determined by chiral HPLC analysis; [b]toluene (1 mL); [c]The absolute configuration of **3l** was determined by single-crystal X-ray analysis on the corresponding alcohol obtained by the oxidation of **3l**. [d](*R*,*R*)-**L2** (8.0 μmol).

To provide insight into the nature of the cobalt intermediate for this cobalt-catalyzed transformation, stoichiometric reactions with $Co(acac)_2$, bisphosphine ligand, and HBpin were conducted. As the hydroboration/cyclization of enyne **1a** catalyzed by the combination of $Co(acac)_2$ and dppbz occurred in a yield and a regioselectivity similar to the corresponding reaction conducted with $Co(acac)_2$ and (*R*,*R*)-QuinoxP, we chose to study the activation of $Co(acac)_2$ with HBpin in the presence of non-chiral dppbz ligand due to its accessibility. An NMR-scale reaction of $Co(acac)_2$ with 6 equivalents of HBpin in the presence of 1 equivalent of dppbz in THF-d_8 revealed the formation of a cobalt complex with a characteristic Co-H resonance (^{1}H NMR) at -14.4 ppm. The same cobalt species was formed for the reaction conducted with 2 equivalent of dppbz (eq 2), and the X-ray analysis on the isolated material (Figure S1) confirmed the identity of a Co^I hydride complex $(dppbz)_2CoH$ (**4**).[17] Importantly, this Co-H complex was active for the hydroboration/cylcization of enyne **1a** (eq 3). The results of these experiments suggest that $Co(acac)_2$ can be reduced by HBpin to generate a catalytically active Co^I-H species (see SI for the proposed mechanism involving migratory insertion of 1,6-enyne into a Co^I-H bond for this hydroboration/cyclization of 1,6-enynes).



Scheme 1. Transformations of Hydroboration/Cyclization Products and Total Synthesis of (-)-Magnofargesin



The synthetic utility of this cobalt-catalyzed transformation is shown in Scheme 1. The vinyl boronate ester **2q** reacted with 1-bromo-4-iodobenzene in the presence of $Pd(PPh_3)_4$ to produce a tetra-substituted alkene **5** in high yield (Scheme 1A). Vinyl boronate ester **2a** underwent a diastereoselective oxidative hydrolysis with $NaBO_3$, affording the ketone **6** in 81% isolated yield with dr of 5:1 (Scheme 1A). Furthermore, we showed that an enantiometrically pure 1,6-enyne **7** underwent a diastereoselective hydroboration/cyclization, yielding an alkyl boronate ester **8**, isolated as a single diastereomer in 76% yield (Scheme 1B). Finally, the synthesis of (-)-magnofargesin (**10**) (Scheme 1C) was achieved in 33% yield with 94% ee *via* the reaction sequence of the diastereo-divergent hydroboration/cyclization of enyne rac-**9** and oxidation of the resulting alkyl boronate ester with H_2O_2 in the presence of aqueous NaOH solution.[18]

In summary, we have developed the first cobalt-catalyzed asymmetric hydroboration/cyclization of 1,6-enynes. The cobalt catalysts were generated in situ from

$Co(acac)_2$ and chiral bisphosphine ligands and activated by the reaction with HBpin in the absence of additional activators. A range of oxygen-, nitrogen-, and carbon-tethered 1,6-enynes reacted to give both alkyl and vinyl boronate esters containing chiral tetrahydrofuran, pyrrolidine, and cyclopentane rings in modest to high yields and excellent enantioselectivities. Further studies to reveal the detailed mechanism of this transformation and to develop cobalt-catalyzed asymmetric hydrofuncationalization/cyclization of other multiply unsaturated substrates will be the subjects of further work.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Experimental procedures, characterization of products, and spectroscopic data (PDF)
Crystallographic data (CIF)

AUTHOR INFORMATION

Corresponding Author

chmgsh@nus.edu.sg

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the National University of Singapore (No. R-143-000-614-133) and the Ministry of Education (MOE) of Singapore (No. R-143-000-635-112). The authors thank Dr. Yanxia Zhao at Northwest University for solving the structure of the Co^{I}-H complex **4**.

REFERENCES

(1) (a) Bianchi, E.; Caldwell, M. E.; Cole, J. R. *J. Pharm. Sci.* **1968**, *57*, 696. (b) Miyazawa, M.; Hiroyuki, K.; Kameoka, H. *Phytochemistry* **1996**, *42*, 531. (c) Huo, J.; Yang, S.-P.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2004**, *67*, 1470. (d) Cho, J. Y.; Williams, P. G.; Kwon, H. C.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 1321.

(2) For recent examples of enantioselective cycloisomerization reactions of enynes, see: (a) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3457. (b) Furstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc*. **2005**, *127*, 12236. (c) Nicolaou, K. C.; Li, A.; Ellery, S. P.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6293. (d) Nishimura, T.; Kawamoto, T.; Nagaosa, M.; Kumamoto, H.; Hayashi, T. *Angew. Chem., Int. Ed*. **2010**, *49*, 1638. (e) Teller, H.; Furstner, A. *Chem. Eur. J*. **2011**, *17*, 7764. (f) Trost, B. M.; Ryan, M. C.; Rao, M.; Markovic, T. Z. *J. Am. Chem. Soc.* **2014**, *136*, 17422. (g) Masutomi, K.; Noguchi, K.; Tanaka, K. *J. Am. Chem. Soc.* **2014**, *136*, 7627. (h) Dieckmann, M.; Jang, Y.-S.; Cramer, N. *Angew. Chem., Int. Ed.* **2015**, *54*, 12149. (i) Deng, X.; Ni, S.-F.; Han, Z.-Y.; Guan, Y.-Q.; Lv, H.; Dang, L.; Zhang, X.-M. *Angew. Chem., Int. Ed.* **2016**, *55*, 6295.

(3) For recent examples of enantioselective reductive cyclization reactions of enynes, see: (a) Chakrapani, H.; Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2003**, *5*, 157. (b) Jang, H.-Y.; Hughes, F. W.; Gong, H.; Zhang, J.; Brodbelt, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 6174. (c) Fan, B.-M.; Xie, J.-H.; Li, S.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 1275. (d) Park, J. H.; Kim, S. M.; Chung, Y. K. *Chem. –Eur. J.* **2011**, *17*, 10852. (e) Ham, Y. J.; Yu, H.; Kim, N. D.; Hah, J.-M.; Selim, K. B.; Choi, H. G.; Sim, T. *Tetrahedron* **2012**, *68*, 1918.

(4) For reviews on reductive cyclization and cycloisomerization of enynes, see: (a) Trost, B. M.; Krische, M. J. *Synlett*. **1998**, *1998*, 1. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (d) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55. (e) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899. (e) Chen, W.-W.; Xu, M.-H. *Org. Biomol. Chem.* **2017**, *15*, 1029.

(5) Buñuel, E.; Cárdenas, D. J. *Eur. J. Org. Chem.* **2016**, *2016*, 5446.

(6) For recent examples, see: (a) Iwai, Y.; Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed*. **2008**, *47*, 3219. (b) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc*. **2011**, *133*, 15362. (c) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449. (d) Wang, C.; Wu, C.; Ge, S. *ACS Catal.* **2016**, *6*, 7585.

(7) (a) Burns, A. R.; González, J. S.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10827. (b) Jiang, T.; Bartholomeyzik, T.; Mazuela, J.; Willersinn, J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2015**, *54*, 6024. (c) Liu, P.; Fukui, Y.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.-Y.; Lin, G.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 11700.

(8) Kinder, R. E.; Widenhoefer, R. A. *Org. Lett*. **2006**, *8*, 1967.

(9) For recent examples, see: (a) Iwai, Y.; Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed*. **2008**, *47*, 3219. (b) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 1202. (c) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362. (d) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449. (e) Wang, C.; Wu, C.; Ge, S. *ACS Catal.* **2016**, *6*, 7585.

(10) During the review process, Lu reported a Co-catalyzed non-asymmetric hydroboration/cyclization of enynes and enantioselective reactions were not achieved when chiral oxazoline iminopyridine ligands were used. See: Xi, T.; Lu, Z. *ACS Catal*. **2017**, *7*, 1181.

(11) For recent examples, see: (a) Monfette, S.; Turner, Z. R.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 4561. (b) Friedfeld, M. R.; Margulieux, G. W.; Schaefer, B. A.; Chirik, P. J. *J. Am. Chem. Soc*. **2014**, *136*, 13178. (c) Fu, S.; Chen, N. Y.; Liu, X.; Shao, Z.; Luo, S. P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588. (d) Tokmic, K.; Fout, A. R. *J. Am. Chem. Soc.* **2016,** *138*, 13700. (e) Tokmic, K.; Markus, C. R.; Zhu, L.; Fout, A. R. *J. Am. Chem. Soc.* **2016**, *138*, 11907. (f) Raya, B.; Biswas, S.; RajanBabu, T. V. *ACS Catal.* **2016**, *6*, 6318.

(12) For recent examples, see: (a) Obligacion, J. V.; Chirik, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 19107. (b) Zhang, L.; Zuo, Z.; Wan, X.; Huang, Z. *J. Am. Chem. Soc.* **2014**, *136*, 15501. (c) Zhang, L.; Zuo, Z.; Leng, X.; Huang, Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 2696. (d) Obligacion, J. V.; Neely, J. M.; Yazdani, A. N.; Pappas, I.; Chirik, P. J. *J. Am. Chem. Soc.* **2015**, *137*, 5855. (e) Palmer, W. N.; Diao, T.; Pappas, I.; Chirik, P. J. *ACS Catal.* **2015**, *5*, 622. (f) Scheuermann, M. L.; Johnson, E. J.; Chirik, P. J. *Org Lett* **2015**, *17*, 2716. (g) Zhang, H.; Lu, Z. *ACS Catal.* **2016**, *6*, 6596.

(13) For recent examples, see: (a) Mo, Z.; Xiao, J.; Gao, Y.; Deng, L. *J. Am. Chem. Soc.* **2014**, *136*, 17414. (b) Chen, C.; Hecht, M. B.; Kavara, A.; Brennessel, W. W.; Mercado, B. Q.; Weix, D. J.; Holland, P. L. *J. Am. Chem. Soc.* **2015**, *137*, 13244. (c) Du, X.; Zhang, Y; Peng, D.; Huang, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 6671. (d) Guo, J.; Lu, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 10835. (e) Teo, W. J.; Wang, C.; Tan, Y. W.; Ge, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 4328.

(14) For reviews, see: (a) Pellissier, H.; Clavier, H. *Chem. Rev*. **2014**, *114*, 2775. (b) Chirik, P. J. *Acc. Chem. Res*. **2015**, *48*, 1687. (c) Gandeepan, P.; Cheng, C. H. *Acc. Chem. Res*. **2015**, *48*, 1194. (d) Sun, J.; Deng, L. *ACS Catal*. **2016**, *6*, 290.

(15) Wang, C.; Teo, W.; Ge, S. *ACS Catal*. **2017**, 7, 855.

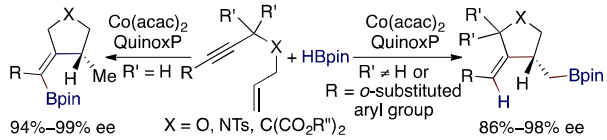
(16) Reactions of these substrates at room temperature afforded the products from *anti*-Markovnikov hydroboration of the terminal alkene in these enynes and no cyclization was observed. See SI for the details.

(17) For a related Co(I)-H species $(dppe)_2CoH$, see: Ciancanelli, R.; Noll, B. C.; DuBois, D. L.; DuBois, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 2984.

(18) For examples of synthesis of magnofargesin, see: (a) Wardrop, D. J.; Fritz, J. *Org. Lett.* **2006**, *8*, 3659. (b) Chakraborty, P.; Jana, S.;

Saha, S.; Roy, S. C. *Tetrahedron Lett.* **2012**, *53*, 6584. (c) Chakraborty, P.; Mandal, S. K.; Roy, S. C. *J. Chem. Sci.* **2016**, *128*, 1067.

Table of Contents



- ♦ Cheap and Readily Available Cobalt Precursor
- ♦ Free of External Activators
- ♦ Dual Selectivity to both Vinyl and Alkyl Boronate Esters
- ♦ 42 examples in total and 39 examples over 90% ee