Communication

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Cobalt-Catalyzed Asymmetric Sequential Hydroboration/Hydrogenation of Internal Alkynes

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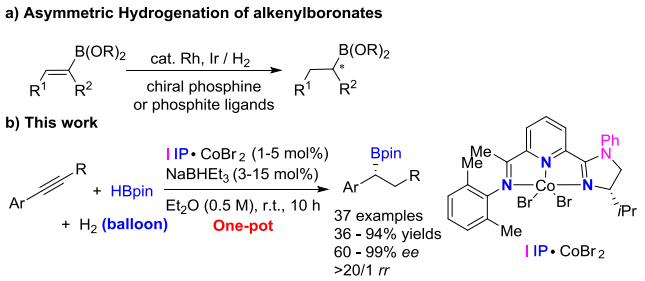
Supporting Information Placeholder

ABSTRACT: A highly regio- and enantioselective cobalt-catalyzed hydroboration/hydrogenation of internal alkynes with HBpin and a hydrogen balloon in one pot was developed. A new type of chiral imidazoline iminopyridine (IIP) ligand was introduced for the first time in this novel and efficient strategy. This protocol used relatively simple and available starting materials with good functional group tolerance to construct more valuable chiral secondary organoboronates. The primary mechanistic studies illustrated that the cobalt-catalyzed regioselective hydroboration of alkynes did initially occur followed by HBpin-promoted and cobalt-catalyzed enantioselective hydrogenation of alkenylboronates.

Chiral organoboronates are very useful building blocks for the synthesis of complicated chiral molecules through efficient C-Y (Y = C, N, O etc.) bonds formation from carbon-boron bonds.[1] To date, several strategies, such as stoichiometric stereospecific organoboronate homologation reaction[2] and catalytic asymmetric alkene hydroboration[3], have been widely used for the enantioselective construction of carbon-boron bond. Compared to the above two methodologies, asymmetric hydrogenation of alkenylboronic esters provides an attractive alternative strategy (Scheme 1). Although asymmetric hydrogenation of alkenylboronic esters[4] have been reported to afford chiral organoboronates by Miyaura, Morken, Andersson, Pfaltz, and other groups, the catalysts are still limited to noble transition metals rhodium[5] and iridium[6] with chiral phosphine containing ligands. It will be ideal to realize asymmetric hydrogenation of alkenylboronates using earth-abundant transition metal catalyst not only for fundmental studies but also for potentially broader utility. Additionally, the functional group tolerance of this transformation has not been described. Furthermore, the preparation and purification of some unstable alkenylboronates increase difficulties for this type of transformation. Thus, the development of novel strategies for asymmetric hydrogenation of alkenylboronates is still highly desirable.

Although asymmetric sequential hydroboration/hydrogenation of alkynes in one pot is an ideal and step-economic strategy, it has not been previously reported. There are several challenges: 1) hydroboration and hydrogenation are competitors in a same catalytic system; 2) The regio- and enantioselectivities have to be

Scheme 1 The asymmetric hydrogenation strategies for the construction of chiral secondary organoboronates.

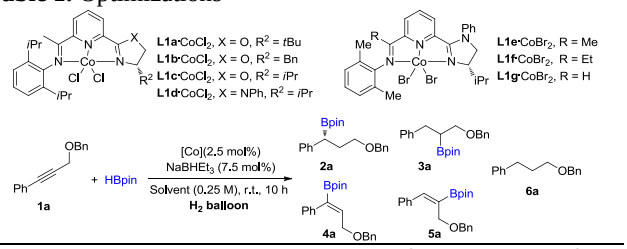


controlled carefully for making this transformation synthetically useful. Very recently, our group reported a cobalt-catalyzed regio- and enantioselective sequential hydrosilylation/hydrogenation of terminal alkynes.[7] Although the internal alkynes were not suitable for the previously reported reaction, it still strongly encourages us to explore new asymmetric transformation of internal alkynes. Here, we developed a highly regio- and enantioselective cobalt-catalyzed hydroboration/hydrogenation of internal alkynes in one pot to afford the chiral secondary organoboronates.

Initially, we chose the internal alkyne **1a** as a simple model substrate and oxazoline iminopyridine (OIP) cobalt complex as a precatalyst. The reaction of **1a** with HBpin in the presence of 2.5 mol% of cobalt precatalyst **L1a** $CoCl_2$ and 7.5 mol% of $NaBHEt_3$ in a solution of Et_2O (0.5 M) at room temperature with a hydrogen balloon for 10 h was carried out to afford a mixture of alkyne hydroboration products **4a** and **5a** in 64% and 16% yield, respectively, however with only few desired sequential products **2a** and **3a** (< 5% yield) (entry 1, table 1). Using L-phenylalanine-derivated ligand **L1b**, the reaction did afford **2a** in 13% yield with 49% ee (entry 2). Encouragingly, using L-valine-derivated ligand **L1c**, alkyl boronic ester **2a** was obtained with 93% ee, however, in a rather poor yield (entry 3). To our delight, using more electron-rich *N*-phenyl protected chiral imidazoline iminopyridine (IIP) ligand **L1d**, the yield of **2a** was promisingly increased to 58% yield with 91% ee (entry 4). A significant raise in both yield (81%) and the enantioselectivity (97% ee) was observed by using less sterically bulky 2,6-dimethyl imine ligand (**L1e**) (entry 5).[8]

Additionally, the change of the substituent on the shoulder of imine (**L1f** and **L1g**) showed similar reactivities with a slightly lower ee (entries 6 and 7). When dioxane and toluene were used, enantioselectivity of **2a** was decreased slightly (entries 8 and 9). Unexpectedly, only hydrogenation product **6a** was afforded in 80%

Table 1. Optimizations[a]



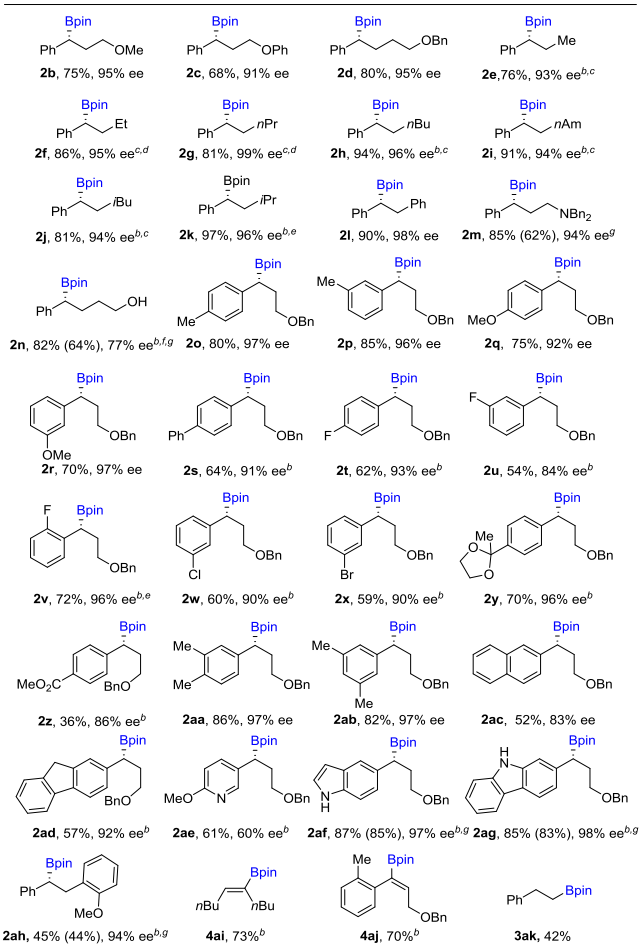
entry	[Co]	solvent	yield of **2a**/**3a**/**4a**/**5a** (%)	ee of **2a** (%)
1	**L1a** $CoCl_2$	Et_2O	<5/<1/64/16	~
2	**L1b** $CoCl_2$	Et_2O	13/<1/50/19	49
3	**L1c** $CoCl_2$	Et_2O	8/<1/50/17	93
4	**L1d** $CoCl_2$	Et_2O	58/<1/18/<1	91
5	**L1e** $CoBr_2$	Et_2O	81/<1/<1<1	97
6	**L1f** $CoBr_2$	Et_2O	82/<1/<1<1	93
7	**L1g** $CoBr_2$	Et_2O	78/<1/<1<1	79
8	**L1e** $CoBr_2$	dioxane	68/<1/<1<1	93
9	**L1e** $CoBr_2$	toluene	74/<1/<1<1	93
10	**L1e** $CoBr_2$	THF	<1/(80)[b]	~
11[c]	**L1e** $CoBr_2$	Et_2O	82/<1/<1<1	90
12[d]	**L1e** $CoBr_2$	Et_2O	82/<1/<1<1	96

[a] Yields were determined by ^{1}HNMR using TMSPh as an internal standard. [b] Yield of **6a**. [c] Commercially available Et_2O was directly used without any drying process. [d] 1 mol% of catalyst was used in a solution of Et_2O (0.5 M).

yield when THF was used as a solvent (entry 10). The reaction underwent smoothly using non-predried diethyl ether as a solvent to afford **2a** in a similar yield with a slightly lower ee (entry 11), which demonstrated that this protocol was not moisture-sensitive. When decreasing the catalyst loading to 1 mol%, the reaction could undergo smoothly to afford **2a** in 82% yield with 96% ee (entry 12). The standard conditions are identified as 1 mmol of alkyne, 2 mmol of HBpin, 1 mol% of **L1e** $CoBr_2$ and 3 mol% of $NaBHEt_3$ in 2 mL of Et_2O with a hydrogen balloon.

With the optimized reaction conditions, the substrate scope was illustrated in Table 2. Unless otherwise noted, the *rr* values of all the substrates were greater than 20/1 (**2**/**3**). The methyl propargyl ether **1b** could be converted to **2b** in 75% yield and 95% ee. The phenyl (**1c**) or benzyl (**1d**) homopropargyl ether could also be delivered to **2c** and **2d** in 68 - 80% yield and 91 - 95% ee. The phenyl alkyl (Me, Et, *n*-Pr, *n*-Bu, *n*-Am, *i*-Bu) alkynes could be smoothly transformed to the corresponding products in 76 - 94% yield with greater than 93% ee (**2e** ~ **2j**). The use of $NaBHEt_3$ could efficiently promote these transformations. Here, a more mild reagent LiOtBu was also found to be suitable as an activator which has been reported by Thomas group.[9] Due to the steric effect, the hydroboration reaction of more sterically bulky **1k** did occur slowly. It was worthy of noting that the asymmetric hydrogenation of alkenylboronic ester **4k** did undergo smoothly to afford **2k** in 97% yield and 96% ee. The diaryl alkyne could participate to give **2l** in 90% yield with 98% ee. The dibenzyl-protected propargyl amine **1m** could also be transformed smoothly into chiral amino alcohol derivate **2m** in 62% yield with 94% ee after direct oxidation. Due to the low activity in the hydrogenation step, the **1n** containing a free alcohol could be delivered to chiral 1,4-diol **2n** in 64% yield with a slightly lower ee when 4.0 equivalent of HBpin was used as a hydrogen source instead of H_2 to accelerate the hydrogenation step. The electron-donating and withdrawing substituents on phenyl ring, such as alkyl, ether, halide, acetyl, and ester, could be tolerated to afford **2o** – **2u** and **2w** - **2ab** in 36 - 86% yields and 84 - 97% ee. Due to the steric effect, the more sterically bulky *ortho*- substituted product **2v** could be obtained in 72% yield with 96% ee through asymmetric hydrogenation of the corresponding alkenylboronic ester. The polycycles and heterocycles, such as 2-naphthyl (**1ac**),

Table 2. Scope of chiral organoboronic esters.[a]



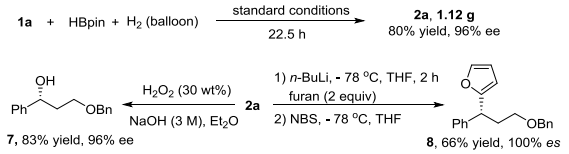
[a] 1 mmol of alkyne, 2 mmol of HBpin, 1 mol% of **L1e** $CoBr_2$ and 3 mol% of $NaBHEt_3$ in 2 mL of Et_2O with a hydrogen balloon. [b] 0.5 mmol scale with 5 mol% of cobalt complex. [c] LiO^{t}Bu instead of $NaBHEt_3$. [d] 0.5 mmol scale with 2.5 mol% of cobalt complex. [e] from vinyl boronic ester. [f] 4.0 equivalent HBpin was used instead of H_2 and run for 24 h. [g] Isolated yield for corresponding alcohol in parenthesis and NMR yield for boronic ester outside the parenthesis.

9-*H*-fluoren-2-yl (**1ad**), 3-pyridyl (**1ae**), 5-indyl (**1af**) and 3-carbazolyl (**1ag**), could be tolerated to deliver chiral boronic esters or the corresponding alcohols after oxidation in 52 - 85% yields and 60 - 98% ee. Asymmetric diaryl acetylene **1ah** could participate to give **2ah** in 44% yield with 94% ee and the other hydroboration isomer **5ah** in 56% yield. When symmetric dec-5-yne **1ai** and *ortho*-methyl substituted aromatic substrate **1aj** were used, only alkyne hydroboration products **4ai** and **4aj** were obtained in 80% and 70% yield, respectively. When phenylacetylene was used, the terminal hydroboration product and terminal hydroboration/hydrogenation product were obtained in 33% yield and in 43% yield, respectively. [10] The absolute configuration was verified by comparison of optical rotation of **2a** with previously reported data and the other products were then assigned by analogy to **2a**.[11]

The gram scale reaction could be carried out smoothly for 22.5 h to afford **2a** in 80% yield and 96% ee. The chiral carbon-boron bond could be easily converted to C-O bond through oxidation and C-C bond through cross-coupling in a stereospecific manner[12] (Scheme 2).

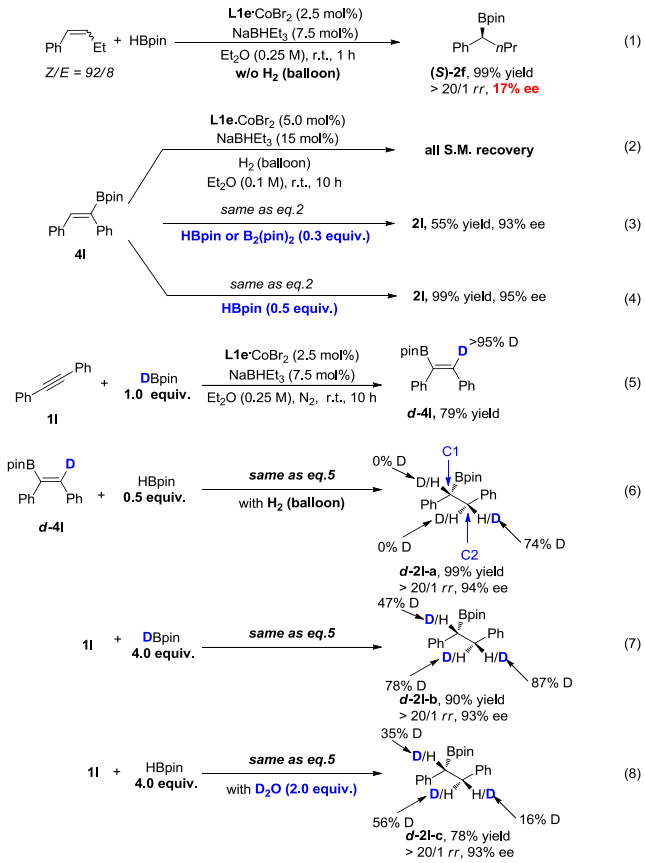
Several control experiments were conducted to elucidate the possible reaction pathway. The hydroboration of (*Z*)-but-1-en-1-ylbenzene gave **(*S*)-2f** in 99% yield and >20/1 *rr*, however, with

Scheme 2 Gram scale reaction and transformations of chiral organoboronic ester **2a**

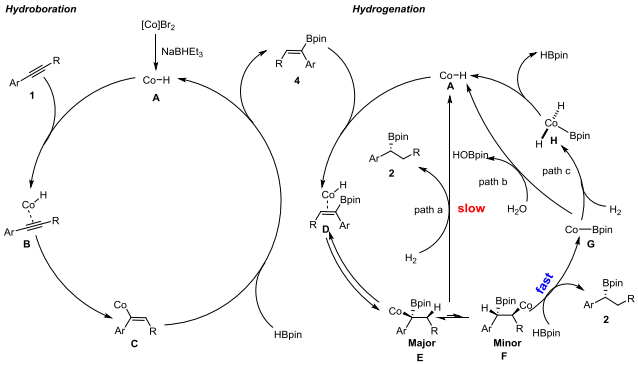


17% ee (eq. 1), which ruled out the hydrogenation of alkynes followed by alkenes hydroboration pathway to achieve high enantioselectivity. It also demonstrated that alkyne hydrogenation followed by alkene hydroboration could be a side reaction to decrease the enantioselectivity in some cases. The alkenylboronic ester **4l** could be obtained through alkyne hydroboration. It should be noted that **4l** could not be hydrogenated under the standard conditions without HBpin (eq. 2). When 0.3 equivalent of HBpin or $B_2(pin)_2$ was added, the hydrogenation reaction underwent smoothly to afford **2l** with similar results (55% yield and 93% ee) (eq. 3). The use of 0.5 equivalent of HBpin could perfectly promote the hydrogenation reaction (eq. 4). These results indicated that the HBpin or boronic group might promote the trisubstituted alkenylboronates hydrogenation process[13]. These control reactions suggested that the reaction should undergo alkyne hydroboration followed by HBpin-promoted alkene hydrogenation pathway.

The reaction of **1l** with DBpin without hydrogen gas afforded *d*-**4l** in 79% yield with >95% D-incoporation (eq. 5). The *d*-**4l** could also be hydrogenated to afford *d*-**2l-a** in 99% yield with >20/1 *rr* and 94% ee with around 20% of D-atom loss at C2 position (eq. 6). This demonstrated that alkene insertion to cobalt hydride bond was reversible. The reaction of **1l** with 4.0 equivalent of DBpin without hydrogen gas afforded *d*-**2l-b** in 90%



Scheme 3 The proposed mechanisms of sequential hydroboration/hydrogenation of internal alkynes.



yield with >20/1 *rr* and 93% ee (eq. 7). Unexpectedly, the D-incoporation was not 100% and the amount of added hydrogen was more than the reductant used. We proposed that the hydrogen might come from adventitious water. When 2.0 equivalent D_2O was added to the system using 4.0 equivalent HBpin as the hydrogen source, the significant D-incoporation was appeared at both C1 and C2 positions in *d*-**2l-c** (eq. 8). This demonstrated that the trace water in the reaction system did not affect the yield and ee, however, could paly a role of hydrogen source[14] in the presence of HBpin to participate the hydrogenation proccess.

According to the control experiments and deuterium experiments, the primary mechanisms were proposed in Scheme 3. The cobalt precatalyst enters the catalytic cycle by reaction with $NaBHEt_3$ to form cobalt hydride species **A**. The alkyne coordination with species **A** followed by alkyne insertion to the cobalt hydrogen bond delivers cobalt vinyl species **C**. The intermediate **C** goes through σ-bond metathesis with HBpin to afford alkenyl boronic esters **4** and regenerate cobalt hydrides **A**.[15] The **4** is employed to the next hydrogenation cycle by alkene insertion into the cobalt hydrogen bond to form chiral interconvertible alkyl cobalt species **E** or **F**. Species **E** or **F** may slowly react with H_2 to afford **2** and regenerate species **A** (path a). The mostly possible pathway may be that species **E** or **F** undergoes σ-bond metathesis with HBpin to form cobalt (I) boryl species **G** and **2**. The active cobalt hydride species **A** could be regenerated from species **G** through two possible pathways. For path b: cobalt hydride species **A** can be regenerated by sigma-bond metathesis of species **G** with water which was analogous to the previous reports on palladium catalyzed diboron-mediated transfer hydrogenation using water[14]. For path c: the species **G** undergoes through oxdative addition of H_2 to form cobalt (III) boryl dihydrides species **H** which undergoes reductive elimination to regenerate species **A**. More mechanistic studies should be further executed to demonstrate the details for regio- and enatioselectivities.

In summary, we have developed a highly regio- and enantioselective cobalt-catalyzed hydroboration/hydrogenation of alkynes with HBpin and a hydrogen balloon. A new type of chiral imidazoline iminopyridine (IIP) cobalt complex has been proven to be an efficient catalyst precursor. This novel protocol used relatively simple and available starting materials to construct more valuable chiral organoboronates. Compared to traditional asymmetric hydrogenation of alkenylboronates, this one-pot strategy does avoid making alkenylboronates and emerge the advantage of atom and step-economy. The primary mechanistic studies illustrated that regioselectivity was originated from hydroboration of alkynes and enantioselectivity from hydrogenation of alkenylboronates. HBpin or boronic group

might promote the trisubstituted alkenylboronates hydrogenation process. The further mechanistic studies are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data for all compounds (PDF). X-ray diffraction of **L1d** $CoCl_2$ (CIF) and **L1e** $CoBr_2$ (CIF).

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) Hall, D. G. in *Boronic Acids* (Ed.: Hall, D. G.), Wiley-VCH, Weinheim, **2006**, pp. 1 – 99. For some selected reviews: a) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287-293. b) Brown, H. C.; Ramachandran, V. P. *Pure Appl. Chem*. **1991**, *63*, 307-316. c) Brown, H. C.; Ramachandran, V. P. *J. Organomet. Chem*. **1995**, *500*, 1-19. d) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704-6716. e) Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481-5494. f) Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Ind. Ed.* **2017**, *56*, 11700-11733.

(2) For some selected reviews, see: a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535-1551. b) Thomas, S. P.; French, R. M.; Aggarwal, V. K. *Chem. Rec.* **2009**, *9*, 24-39. For some recent examples, see: c) Sun, X.; Blakemore, P. R. *Org. Lett.* **2013**, *15*, 4500-4503. d) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature*, **2014**, *513*, 183-188. e) Balieu, S.; Hallett, G. E.; Burns, M.; Bootwicha, T.; Studley, J.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 4398-4403. f) Bootwicha, T.; Feilner, J. M.; Myers, E. L.; Aggarwal, V. K. *Nature Chem.* **2017**, *9*, 896-902.

(3) For a review on catalytic enantioselective hydroboration of alkenes, see: a) Carroll, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609–631. For some selective examples on enantioselective hydroboration of alkenes, see: b) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426-3428. c) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198-7199. d) Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *J. Am. Chem. Soc.* **2004**, *126*, 9200-9201. e) Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3734-3735. f) Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem. Ind. Ed.* **2009**, *48*, 6062-6064. g) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160-3161. h) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740-1741. i) Zhang, L.; Zuo, Z.; Wan, X.; Huang, Z. *J. Am. Chem. Soc.* **2014**, *136*, 15501-15504. j) Chen, J.; Xi, T.; Ren, X.; Cheng, B.; Guo, J.; Lu, Z. *Org. Chem. Front.* **2014**, *I*, 1306-1309. k) Hu, N.; Zhao, G.; Zhang, Y.; Liu, X.; Li, G.; Tang, W. *J. Am. Chem. Soc.* **2015**, *137*, 6746-6749. l) Shoba, V. M.; Thacker, N. C.; Bochat, A. J.; Takacs, J. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 1465-1469. m) Xi, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 6703-6706. n) Peng, J.; Docherty, J. H.; Dominey, A. P.; Thomas, S. P. *Chem. Commun.* **2017**, *53*, 4726-4729. o) Chakrabarty, S.; Takacs, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 6066-6069. p) Smith, J. R.; Collins, B. S. L.; Hesse, M. J.; Graham, M. A.; Myers, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2017**, *139*, 9148-9151.

(4) For some recent reviews, see: a) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402-1411. b) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, *47*, 7912-7916. c) Woodmansee, D. H.; Pfaltz, A. *Top. Organomet. Chem.* **2011**, *34*, 31-76. d) Källström, K.; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194-3200. e) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 14232-14240. f) Margarita, C.; Andersson, P. G. *J. Am. Chem. Soc.* **2017**, *139*, 1346-1356.

(5) For some selected examples, see: a) Ueda, M.; Saitoh, A.; Miyaura, N. *J. Organomet. Chem.* **2002**, *642*, 145-147. b) Morgan, J. B.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15338-15339. c) Moran, W. J.; Morken, J. P. *Org. Lett.* **2006**, *8*, 2413-2415.

(6) For some selected examples, see: a) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Chem. Commun.* **2009**, 5996-5998. b) Mazuela, J.; Norrby, P. - O.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634-13645. c) Ganić, A.; Pfaltz, A. *Chem. Eur. J.* **2012**, *18*, 6724-6728. d) Biosca, M.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2015**, *21*, 3455-3464.

(7) a) Guo, J.; Lu, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 10835-10838. b) Guo, J.; Shen, X.; Lu, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 615-618.

(8) CCDC number of **L1d** $CoCl_2$: 1525168; CCDC number of **L1e** $CoBr_2$: 1559196.

(9) Docherty, J. H.; Peng, J.; Dominey, A. P.; Thomas, S. P. *Nature chem.* **2017**, *9*, 595-600.

(10) Obligacion, J. V.; Neely, J. M.; Yazdani, A. N.; Pappas, N; Chirik, P.G. *J. Am. Chem. Soc.* **2015**, *137*, 5855-5858.

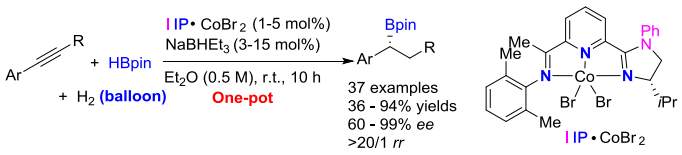
(11) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534-6537.

(12) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nature Chem.* **2014**, *6*, 584-589.

(13) Shoba, V. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 5740-5743.

(14) a) Xuan, Q.; Song, Q. *Org. Lett.* **2016**, *18*, 4250-4253. b) Cummings, S. P.; Le, T. - N.; Fernandez, G. E.; Quiambao, L. G.; Stokes, B. J. *J. Am. Chem. Soc.* **2016**, *138*, 6107-6110. c) Ojha, D. P.; Gadde, K.; Prabhu, K. R. *Org. Lett.* **2016**, *18*, 5062-5065. d) Kong, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 3987-3991.

(15) Semba, K.; Fujihara, T.; Terao, J.; and Tsuji, Y. *Chem. Eur. J.* **2012**, *18*, 4179-4184.



- *earth-abundant transition metal catalyst*
- *new chiral ligand*
- *readily available starting materials*

- *one-pot reaction*
- *good functional group tolerance*
- *highly valuable chiral boronic esters*