Communication

A Practical and Asymmetric Reductive Coupling of Isoquinolines Templated by Chiral Diborons

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A Practical and Asymmetric Reductive Coupling of Isoquinolines Templated by Chiral Diborons

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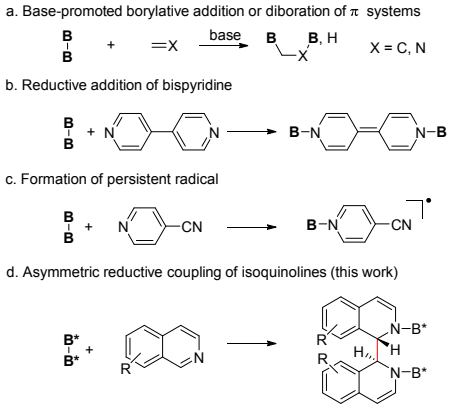
ABSTRACT: We herein describe a chiral diboron-templated highly diastereoselective and enantioselective reductive coupling of isoquinolines which have provided an expedite access to a series of chiral substituted bisisoquinolines in good yields and excellent ee's under mild conditions. The method enjoys a broad substrate scope and good functional group compatibility. Mechanistic investigation suggests that the reaction proceeds through a concerted [3,3]-sigmatropic rearrangement.

Diboron compounds[1] have become increasingly important feed stocks in organic synthesis thanks to the rapid development of the Suzuki-Miyaura cross-coupling[2] and various transition-metal catalyzed borylations.[3] In addition, the transition-metal-free borylation[4] with diboron reagents has built a new dimension of their synthetic utilities. With the addition of a Lewis base, the diboron compound can proceed a borylative addition or a diboration on various π systems (Scheme 1a).[4,5] When a pyridine derivative is employed, a reductive addition[6] of bispyridine (Scheme 1b) or the formation of a persistent radical[7] (Scheme 1c) can result which can proceed further transformations.[8] Herein we describe a transition-metal-free carbon-carbon bond-forming transformation templated by a chiral diboron compound that have led to a highly diastereoselective and enantioselective reductive coupling of isoquinolines, providing the access to a variety of chiral bisisoquinoline diacetamides in good yields and excellent enantioselectivities.

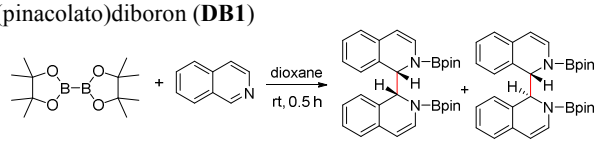
Scheme 1. Transition-metal-free borylation with diboron



Despite the significance of chiral 1,2-diamines[9] and derivatives in organic synthesis, their efficient preparations remain challenges. Chiral bisisoquinolines are used as chiral phase transfer agents or ligand backbones.[10] However, the lack of efficient synthetic methods has hampered their applications. Low *dl*/*meso* selectivities were often observed in reductive coupling of isoquinolines or derivatives.[10b-e] Search for a practical and efficient asymmetric reductive coupling for the synthesis of chiral bisisoquinolines remains an important goal.

During our studies on diboron compounds and related transformations,[11] we were interested in exploring new transformations of diboron compounds in the presence of a heterocyclic compound. Instead of employing a substituted pyridine for activation of diboron compounds, we chose isoquinoline as the base for study (Table 1). When isoquinoline (**2a**) was treated with 0.5 equiv. of bis(pinacolato)diboron (**DB1**) in dioxane at rt for 0.5 h, the reductive coupling product **4** was isolated in an almost perfect yield (entry 1). The facile and exclusive formation of *dl*-*N*,*N*-diborate **4** instead of the *meso* diastereomer **3** was in sharp contrast to the reported reductive coupling methods of isoquinolines with zinc or low-valent niobium as the reducing reagents, where significant amounts of *meso* compounds were formed.[10c-e] No other side-products were observed even when only 0.25 equiv. of **DB1** was employed (entry 2). The reductive coupling can proceed even at -40 °C without compromising the yield of **4** (entry 3). However, when the mixture was stirred at rt for 12 h, a diminished yield (75%) of **4** was isolated, suggesting partial decomposition of **4** with a prolonged reaction time (entry 4).

Table 1. Reductive coupling of isoquinoline mediated by bis(pinacolato)diboron (**DB1**)



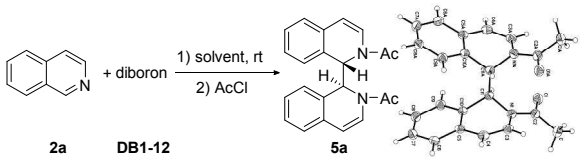
DB1 (0.5 equiv)	**2a** (1.0 equiv)	**3** 0% yield	**4** 99% yield

Entries[a]	Other conditions	Yield of **4** (%)[b]
1	/	99
2	**DB1** (0.25 equiv)	49
3	-40 °C, 2 h	98
4	12 h	75

[a]Unless otherwise specified, the mixture was stirred in dioxane at rt for 0.5 h. [b]Isolated yield.

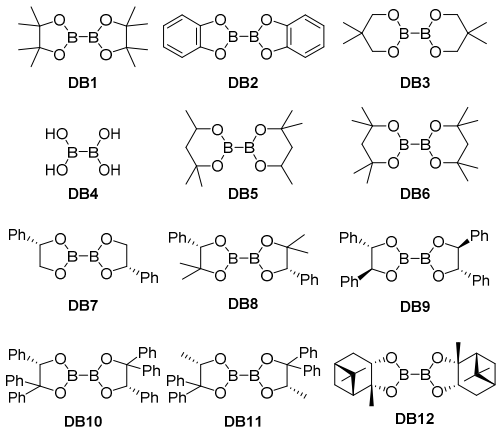
The labile nature of **4** encouraged us to form a stable derivative of **4** during the reaction. Treatment of **4** with acetyl chloride led to the successful formation of diacetamide **5a** in 90% yield. To our delight, the derivatization can be done in one pot with the reductive coupling reaction (Table 2). With this protocol, a variety of diboron compounds **DB1-6** can be applied to form the same product **5a** in various yields (entries 1-6). Bis(pinacolato)diboron (**DB1**) proved to be most effective in terms of yield. In order to form enantiomerically enriched diacetamide **5a**, a series of chiral diborons **DB7-11** were prepared[12] and applied to the reaction. (4*S*,4'*S*)-4,4'-Diphenyl-2,2'-bi(1,3,2-dioxaborolane) (**DB7**) provided the desired product **5a** in 93% yield and 39% ee (entry 7). A sterically more hindered diboron **DB8** containing two geminal methyl groups provided a diminished yield (75%) and a similarly low ee (37%, entry 8). Gratifyingly, a high yield (87%) and an excellent ee (93%) were achieved when a diboron **DB9** derived from (1*S*,2*S*)-1,2-diphenylethane-1,2-diol was employed (entry 9). Only a moderate yield (57%) was obtained when **DB10** derived from (*S*)-1,1,2-triphenylethane-1,2-diol was used, albeit with an excellent ee (94%, entry 10). A diminished ee was afforded when

Table 2. Asymmetric reductive coupling of isoquinoline mediated by chiral diboron compounds



2a DB1-12 5a

entries[a]	diboron	solvent	yield (%)	ee of **5a** (%)
1	**DB1**	dioxane	90	-
2	**DB2**	dioxane	70	-
3	**DB3**	dioxane	84	-
4	**DB4**	dioxane	9	-
5	**DB5**	dioxane	7	-
6	**DB6**	dioxane	6	-
7	**DB7**	dioxane	93	39
8	**DB8**	dioxane	75	37
9	**DB9**	dioxane	87	93
10	**DB10**	dioxane	57	94
11	**DB11**	dioxane	90	82
12	**DB12**	dioxane	35	80
13[b]	**DB9**	dioxane	82	93
14	**DB9**	MTBE	87	99

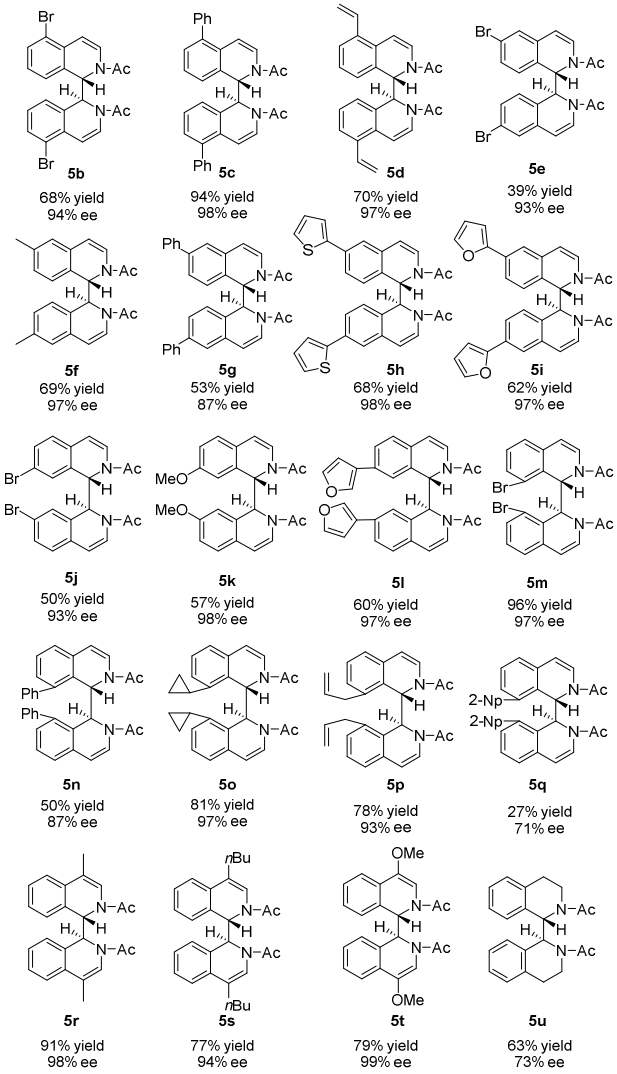


[a]Unless otherwise specified, the reactions were carried out at rt with **2a** (0.5 mmol, 1.0 equiv), diboron (0.375 mmol, 0.75 equiv) in the designated solvent for 0.5 h, and then AcCl (0.5 mL) was added. The mixture was stirred for additional 5 min before work-up. The absolute configuration of **5a** was determined by its X-ray crystallography. [b]The mixture was stirred for 5 min before the addition of AcCl.

DB11 was applied as the diboron species (entry 11). The diboron **DB12** prepared from a chiral pinanediol only provided a low yield (35%) and a moderated ee (80%, entry 12). We then employed **DB9** as the reagent for further optimization. When **2a** and **DB9** were stirred at rt for only 5 min, a similarly high yield and enantioselectivity was achieved (entry 13). Finally, switch of solvent from dioxane to MTBE further enhanced the chiral induction, and product **5a** was isolated in 99% ee and 87% yield, whose absolute configuration was determined by X-ray crystallography (entry 14).

We then looked into the substrate scope of the reductive coupling with **DB9** as the chiral diboron reagent. A variety of quinoline derivatives with different substituents at various positions were applicable to form a series of chiral bisisoquinoline diacetamides in moderate to high yields and excellent ee's (up to 99%). It should be noted that no *meso* compounds were formed on all the substrates studied. As shown in Table 3, the reductive coupling was applicable to 5-substituted isoquinolines to provide

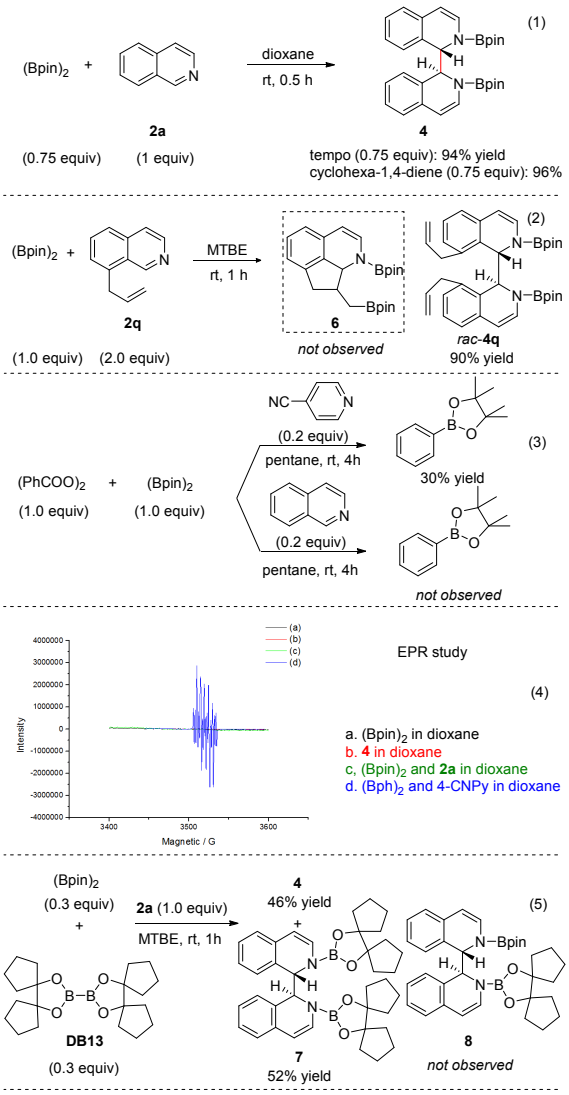
Table 3. Asymmetric reductive coupling of isoquinolines templated by chiral diboron **DB9**[a]



[a]Unless otherwise specified, the reactions were carried out at rt with **2b-u** (0.2 mmol, 1.0 equiv), diboron (0.15 mmol, 0.75 equiv) in MTBE (1 mL) for 0.5 h, and then AcCl (0.5 mL) was added. The mixture was stirred for additional 5 min before work-up.

products **5b-d** in good yields and excellent enantioselectivities. A series of 6,6'-disubstituted bisisoquinoline diacetamides **5e-i** were successfully formed in moderate yields and excellent ee's. Substituents such as bromo, phenyl, methyl, thiophenyl, and furyl groups were well tolerated. 7,7'-Disubstituted bisisoquinoline diacetamides **5j-l** were also smoothly formed. A series of 8,8'-disubstituted bisisoquinoline diacetamides **5m-q** were also prepared in high enantioselectivities. Products containing electronic-donating substituents such as alkyl or methoxy groups at 4,4'-positions **5r-t** were formed in excellent ees, while no reaction was observed on an isoquinoline bearing a bromo or trifluoromethyl substituent at 4-position. No reaction was observed on a 1-, or 3-substituted isoquinonline, probably due to the enhanced steric hindrance. Excitingly, dihydroisoquinoline was also a good substrate to provide **5u** in 63% yield and 73% ee.

Scheme 2. Mechanistic investigation



A series of experiments were conducted in order to elucidate the mechanism of the asymmetric reductive coupling (Scheme 2). Firstly, the reductive coupling was performed in the presence of a radical quencher tempo or cyclohexa-1,4-diene and the coupling product **4** was isolated without deterioration of the yield; Secondary, 8-allylisoquinoline (**2q**) was subjected for reductive coupling. Only *rac*-**4q** was isolated and no formation of compound **6** or related cyclic products was observed; Thirdly, both 4-cyanopyridine and isoquinoline were used as catalyst for the radical coupling reaction between $(PhCOO)_2$ and B_2pin_2. Phenylboronic ester was formed as reported with 4-cyanopyridine as an additive,[7a] whereas no coupling was observed with isoquinoline as the additive, indicating no involvement of radical intermediates; Fourthly, an EPR experiment of the mixture of isoquinoline/B_2pin_2 revealed no radical signals, while a mixture of 4-cyanopyridine/B_2pin_2 (g = 2.0038, 298 K) cleared showed radical signals as reported by Zhu & Li.[7a] All the above experiments suggested no involvement of a radical intermediate in the diboron-templated reductive coupling, which was in contrast to the radical formation in 4-cyanopyridine/B_2pin_2 system.[7] To test whether only a single diboron was involved in the reductive coupling, both B_2pin_2 (**DB1**) and **DB13** were subjected in one pot for reductive coupling of isoquinoline and only products **4** and **7** were isolated with no formation of the cross-over product **8**. This result indicated that the reductive coupling occurred with a single diboron compound as the template. Lastly, DFT (M06 method) calculations were performed on reaction of **DB9** and **2a** (Figure 1 and Figure S1 in SI). The computed most favorable pathway initiates with coordination of two **2a** to chiral diboron **DB9** to cooperatively activate the B-B bond, followed by a concerted [3,3]-sigmatropic rearrangement via 6-membered chair-form $\mathbf{TS_{INTa\text{-}4a}}$ with a low barrier of 10.8 kcal/mol in solution to afford reductive coupling product **4a** (ΔG_{sol} = -38.2 kcal/mol). The formation of **ent-4a** requires a higher barrier than **4a** by 2.1 kcal/mol, mainly due to steric congestion of the two Ph groups and a lower stability of **ent-4a** (-35.3 kcal/mol). The formation of a *meso* product would require a boat-form and higher-energy transition state (16.2 kcal/mol). These results are consistent with the experimental observations, and show how the chiral diboron template guides the formation of the observed chiral coupling product.

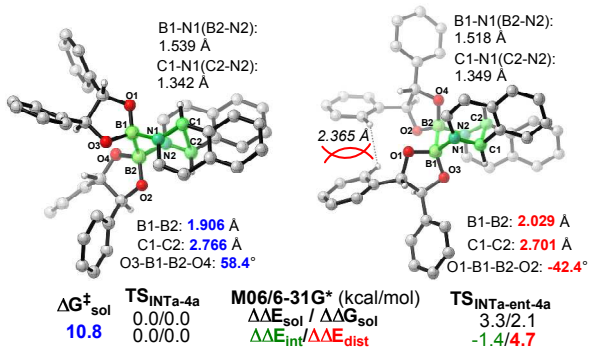
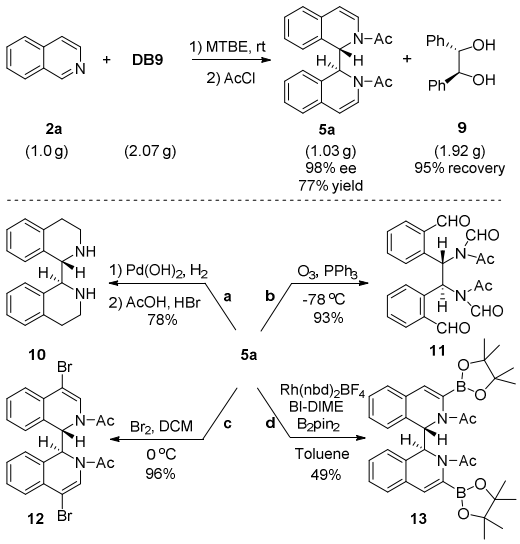


Figure 1. DFT-computed energies and structures of the two most lowest (reductive coupling) concerted [3,3]-sigmatropic rearrangement transition states with the key geometrical parameters.

Scheme 3. Scalability and derivatization of **5a**



In order to demonstrate the practicality of this method, the reductive coupling was performed at a gram scale and product **5a** was obtained in 98% ee and 77% isolated yield (Scheme 3). Despite the requirement of a stoichiometric amount of **DB9** for the reaction, the chiral diol **9** was recovered in 95% yield, which could be easily converted back to **DB9**. The chiral bisisoquinolines are versatile building blocks for further transformation. For example, **5a** could be hydrogenated and hydrolyzed under acidic conditions to provide chiral diamine **10**. Alternatively, it could be transformed to an acyclic diamine derivative **11** by ozonolysis. Bromination of **5a** provided product **12**, which was not accessible

directly by reductive coupling. Excitingly, borylations[13] at 3,3'-positions were realized under rhodium catalysis with BI-DIME[14] as the ligand to form **13** in an acceptable yield.

In conclusion, we have discovered a chiral diboron-templated highly diastereoselective and enantioselective reductive coupling of isoquinolines, which have provided an expedite access to a series of chiral substituted bisisoquinoline diacetamides in good yields and excellent enantioselectivities under mild conditions. This simple and practical method enjoys a broad substrate scope and good functional group compatibility. Mechanistic investigation suggests that the reaction proceeds through a concerted [3,3]-sigmatropic rearrangement via a 6-membered chair-form transition state. Because of the synthetic versatility of chiral bisisoquinolines, this method is expected to facilitate further development of chiral diamine chemistry and applications in asymmetric catalysis.

Supporting Information

Full experimental and computational details, characterization data, NMR spectra of **2**, **4**, **5** and related intermediates, chiral HPLC of **5a-u** and related chiral intermediates, cif files of **4**, **5a**, **DB9**. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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References

1. Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091.
2. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
3. Selected reviews on transition-metal-catalyzed reactions with diboron: (a) Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, *3*, 271. (b) Irvine, G. J.; Lesley, M. J.; Marder, T. B.; Norman, N. C.; Rice, C. R.; Robins, E. G.; Roper, W. R.; Whittell, G. R.; Wright, L. J. *Chem. Rev.* **1998**, *98*, 2685.
4. For reviews: (a) Cuenca, A. B.; Shishido, R.; Ito, H.; Fernández, E. *Chem. Soc. Rev.* **2017**, *46*, 415. (b) Cid, J.; Gulyás, H.; Carbó, J. J.; Fernández, E. *Chem. Soc. Rev.* **2012**, *41*, 3558. (c) Dewhurst, R. D.; Neeve, E. C.; Braunschweig, H.; Marder, T. B. *Chem. Commun.* **2015**, *51*, 9594.
5. For recent examples: Diboration of olefins, (a) Fang, L.; Yan, L.; Haeffner, F.; Morken, J. P. *J. Am. Chem. Soc.* **2016**, *138*, 2508. (b) Blaisdell, T. P.; Caya, T. C.; Zhang, L.; Sanz-Marco, A.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 9264. (c) Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, G.; Fernández, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 7158. Borylation of Michael acceptors, (d) Rodomkit, S.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3387. (e) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 8277. (f) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2010,** *49*, 5130. Diboration or borylation of alkynes, (g) Morinaga, A.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 15859. (h) Nagashima, Y.; Hirano, K.; Takita, R.; Uchiyama, M. *J. Am. Chem. Soc.* **2014**, *136*, 8532. (i) Kojima, C.; Lee, K.-H.; Lin, Z.; Yamashita, M. *J. Am. Chem. Soc.* **2016**, *138*, 6662. (j) Yang, K.; Song, Q. *Green Chem.* **2016**, *18*, 932. Borylation of allylic alcohols, (k) Miralles, N.; Alan, R.; Szabó, K.; Fernández, E. *Angew. Chem., Int. Ed.* **2016**, *55*, 4303. Borylation of imines, (l) Solé, C.; Gulyás, H.; Fernández, E. *Chem. Commun.* **2012**, *48*, 3769. Borylation of diazo compouds, (m) Li, H.; Shangguan, X.; Zhang, Z.; Huang, S.; Zhang, Y.; Wang, J. *Org. Lett.* **2014**, *16*, 448.
6. Ohmura, T.; Morimasa, Y.; Suginome, M. *J. Am. Chem. Soc.* **2015**, *137*, 2852.
7. (a) Wang, G.; Zhang, H.; Zhao, J.; Li, W.; Cao, J.; Zhu, C.; Li, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 5985. (b) Wang, G.; Cao, J.; Gao, L.; Chen, W.; Huang, W.; Cheng, X.; Li, S. *J. Am. Chem. Soc.* **2017**, *139*, 3904. (c) Köster, R.; Bellut, H.; Ziegler, E. *Angew. Chem., Int. Ed.* **1967**, *6*, 255.
8. For radical-related coupling, (a) Zhang, L.; Jiao, L. *J. Am. Chem. Soc.* **2017**, *139*, 607. (b) Mfuh, A. M.; Doyle, J. D.; Chhetri, B.; Arman, H. D.; Larionov, O. V. *J. Am. Chem. Soc.* **2016**, *138*, 2985. (c) Chen, K.; Zhang, S.; He, P.; Li, P. *Chem. Sci.* **2016**, *7*, 3676. (d) Zhang, J.; Wu, H.-H.; Zhang, J. *Eur. J. Org. Chem.* **2013**, 6263. (e) Mo, F.; Jiang, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1846.
9. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.
10. (a) Elliott, I. W., Jr.; McGriff, R. B. *J. Org. Chem.* **1957**, *22*, 514. (b) Nielsen, A. T. *J. Org. Chem.* **1970**, *35*, 2498. (c) Siegfried, M.-A.; Hilpert, H.; Rey, M.; Dreiding, A. *Helv. Chim. Acta.* **1980**, *63*, 938. (d) Elliott, M. C.; William, E.; Howard, S. T. *J. Chem. Soc., Perkin Trans. 2*, **2002**, 201. (e) Arai, S.; Takita, S.; Nishida, A. *Eur. J. Org. Chem.* **2005**, 5262. (f) Wilckens, K.; Lentz, D.; Czekelius, C. *Organometallics* **2011**, *30*, 1287.
11. (a) Hu, N.; Zhao, G.; Zhang, Y.; Liu, X.; Li, G.; Tang, W. *J. Am. Chem. Soc.* **2015**, *137*, 6746. (b) Tang, W.; Keshipeddy, S.; Zhang, Y.; Wei, X.; Savoie, J.; Patel, N. D.; Yee, N. K.; Senanauyake, C. H. *Org. Lett.* **2011**, *13*, 1366.
12. For previous reports on chiral diboron, see: (a) Clegg, W.; Johann, T. R. F.; Marder, T. B.; Norman, N. C.; Orpen, A. G.; Peakman, T. M.; Quayle, M. J.; Rice, C. R.; Scott, A. J. *J. Chem. Soc., Dalton Trans.,* **1998**, 1431. (b) Roy, C. D.; Brown, H. C. *J. Organomet. Chem.* **2007**, *692*, 784.
13. (a) Cuenca, A. B.; Fernández, E. *Top. Organomet. Chem.* **2016**, 1. (b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M. Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.
14. (a) Tang, W.; Capacci, A. G.; Wei, X.; Li, W.; White, A.; Patel, N. D.; Savoie, J.; Gao, J. J.; Rodriguez, S.; Qu, B.; Haddad, N.; Lu, B. Z.; Krishnamurthy, D.; Yee, N. K.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5879. (b) Zhao, Q.; Li, C.; Senanayanke, C. H.; Tang, W. *Chem. Eur. J.* **2013**, *19*, 2261.

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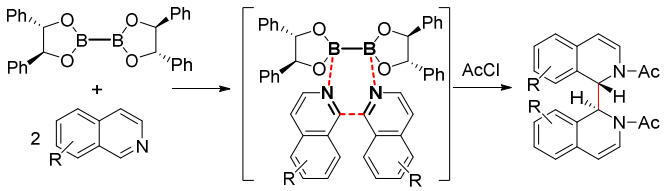

- *First reductive coupling templated by chiral diborons*
- *Excellent diastereoselectivities and enantioselectivities*
- *Concerted [3,3]-sigmatropic rearrangement*
- *Broad substrate scope and ease of derivatization*

73-99% ee
29-96% yield
21 examples