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Vicinal Diboronates in High Enantiomeric Purity through Tandem Site-Selective NHC–Cu-Catalyzed Boron-Copper Additions to Terminal Alkynes

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Abstract

A Cu-catalyzed protocol for conversion of terminal alkynes to enantiomerically enriched diboronates is reported. In a single vessel, a site-selective hydroboration of an alkyne leads to the corresponding terminal vinylboronate, which undergoes a second site-selective and enantioselective hydroboration. Reactions proceed in the presence of two equivalents of commercially available bis(pinacolato) diboron [$B_2(\text{pin})_2$] and 5–7.5 mol % of a chiral bidentate imidazolinium salt, affording diboronates in 60–93% yield and up to 97.5:2.5 enantiomeric ratio (er). The enantiomerically enriched products can be functionalized to afford an assortment of versatile organic molecules. Enynes are converted to unsaturated diboronates with high chemo- (>98% reaction of alkyne; <2% at alkene) and enantioselectivity (e.g., 94.5:5.5 er).

We recently reported a site- and enantioselective Cu-catalyzed method for boron-copper addition to olefins carried out with bis(pinacolato)diboron [$B_2(\text{pin})_2$; **1**].¹ Transformations involve N-heterocyclic carbene (NHC) complexes and are performed in the presence of MeOH, which promotes in situ protonation of the C–Cu bond to regenerate the catalyst and deliver the hydroboration product. Aryl-substituted alkenes serve as effective substrates, since a low-lying π^* orbital is likely required for association of the substrate with the nucleophilic NHC–Cu complex.² We reasoned that if vinylboronates can be induced to undergo site-selective hydroborations, an efficient Cu-catalyzed protocol for enantioselective synthesis of the highly versatile vicinal diboronates would be in hand.^{3,4,5} Since vinylboronates might be prepared by alkyne hydroboration, we further envisioned a single-vessel Cu-catalyzed process for conversion of terminal alkynes to diboronates of high enantiomeric purity (eq 1).^{6,7} Herein, we disclose the realization of the strategy outlined above. Through the use of a Cu complex derived from a chiral bidentate NHC,^{8,9} a wide range of terminal alkynes are converted to vicinal diboronates in >98% site selectivity, 60–93% yield and up to 97.5:2.5 enantiomeric ratio (er).

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Supporting Information Available: Experimental procedures and spectral, analytical data for all products (PDF). This material is available on the web: <http://www.pubs.acs.org>

(1)

We began by examining the efficiency and site selectivity of alkyne hydroboration under conditions that would likely be optimal for the second enantioselective process [-15°C , tetrahydrofuran (thf)].¹ We established that, as illustrated in Scheme 1a, reaction of Cl-substituted alkyne **2** with 5.0 mol % chiral imidazolinium salt **3** and CuCl in the presence of 20 mol % NaOt-Bu and 0.9 equiv of **1** leads to >98% conv (based on **1**) in 24 hours, affording vinylboronate **4** with >98% site selectivity (<2% **5** by 400 MHz ^1H NMR analysis). Subjection of pure **4** to the same conditions (except with 1.1 equiv **1**) furnishes diboronate **6** with >98% site selectivity (<2% geminal diboronate) and in 94:6 er. As illustrated in Scheme 1, Cu-catalyzed tandem double-hydroboration of **2** with 2.1 equivalents of **1** leads to 90% conversion to **6**, which is formed in 95:5 er.

In addition to terminal alkynes bearing a halogen-substituted alkyl group (entry 1, Table 1), those carrying an O- or an N-based unit (entries 2–3), or an *n*-alkyl group (entry 4) undergo diboration to afford the desired products in 72–93% yield and up to 96.5:3.5 er. Comparison of the data in entries 5–6 with 7–8 (Table 1) indicates that transformations of alkynes containing a β -branched side chain (entries 5–6), where 7.5 mol % **3** is required for high conversion, proceed more slowly than those with the corresponding α -branched substituents (entries 7–8). In all cases, however, the desired products are isolated in 96.5:3.5 er.

Cu-catalyzed diborations presented in eq 2–3 demonstrate that the reaction can be carried out with terminal alkynes bearing a propargylic heteroatom, affording **15** and **16** in 71% and 82% yield and 97:3 and 95:5 er, respectively. These transformations, as well as those in Table 1, highlight a critical – and not immediately evident – attribute of the bidentate NHC–Cu complex derived from **3**: high site selectivity in alkyne hydroborations. This point is elucidated below.

(2)

(3)

The first-stage hydroboration of alkynes **14a–b** proceeds readily with 1.0 mol % monodentate NHC–Cu complex **17** (Scheme 2), which result in the formation of *secondary* vinylboronates **19a** and **19b** as major isomers (**18:19** = 17:83 and 10:90, respectively). In contrast, when imidazolium sulfonate **3** is used, **18a** and **18b** are produced predominantly (**18:19** = 89:11).¹⁰ Control experiments indicate that secondary boronates (e.g., **19**) undergo Cu-catalyzed hydroboration less readily and afford products of substantially lower enantiomeric purity (with Cu complex of **3**). For example, treatment of a pure sample of **5** to the conditions in Scheme 1 results in 13% conversion to **6**, which is formed in only 55:45 er. The high enantioselectivity afforded by the Cu derived from **3** is thus partly due to its ability to promote preferential formation of the terminal vinylboronates selectively. Consistent with the above findings, chiral monodentate NHC–Cu complexes **20** and **21** (Scheme 2) give rise to less efficient and nonselective transformations. The basis for site selectivity in NHC–Cu-catalyzed alkyne hydroborations is under investigation.

The diboronates obtained through the present method are versatile, providing access to other useful enantiomerically enriched molecules. The example in eq 4 involving diboronate **15** and β -bromoenone **22** is illustrative; site-selective Pd-catalyzed cross-coupling¹¹ of the less hindered C–B bond followed by

(4)

oxidation of the remaining alkylboronate delivers **23** in 72% yield without loss of enantiomeric purity (96.5:3.5 er).

Enantiomerically enriched diboronates can be synthesized with through catalytic diborations of terminal alkenes with one equivalent of **1** or the derived biscatecholates^{3,6} (vs two equiv used in this study). Bis(pinacolato)diboron is, however, commercially available in ample quantities and inexpensive. The alternative protocols require the use of chiral phosphines and salts of precious metals (e.g., Pt-, Pd- or Rh-based), which are significantly more costly than CuCl. Finally, as demonstrated through synthesis of unsaturated diboronate **25** in eq 5, the present approach complements the abovementioned protocols involving alkene substrates;^{3,6} the Cu-catalyzed reaction thus allows for chemoselective diboration of an alkyne in the presence of an olefin (<2% reaction of the alkene).

(5)

Development of other NHC–Cu-catalyzed boron-copper additions and examination of mechanistic issues are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1. Initial Investigations

Scheme 2. Influence of NHC Structure on Site Selectivity and Enantioselectivity of Boron-Copper Additions^a

^a Conversions for reactions with 0.9 equiv **1** are based on the amount of this reagent and determined by ¹H NMR analysis. Mes = (2,4,6)-trimethylphenyl.

Table 1

Cu-Catalyzed Enantioselective Diboration of Terminal Alkynes^a

entry	product	mol % 3	conv (%) ^b diboronate (%) ^b	yield (%) ^c	er ^d
1		5.0	>98; >98	32	94.5:5.5

entry	product	mol % 3	conv (%) ^a ; ^b diboronate (%) ^b	yield (%) ^c	er ^d
2		5.0	>98; 75	74	96.5:3.5

entry	product	mol % ³	conv (%) ^b diboronate (%) ^b	yield (%) ^c	er ^d
3		5.0	>98; 82	72	93.5:6.5

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entry	product	mol % ³	conv (%) ^a ; ^b diboronate (%) ^b	yield (%) ^c	er ^d
4		5.0	>98; 93	84	95.5:4.5

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entry	product	mol % 3	conv (%) ^a ; ^b diboronate (%) ^b	yield (%) ^c	er ^d
5	10	7.5	>98; 81	78	96.5:3.5
6	11	7.5	>98; 66	60	96.5:3.5

entry	product	mol % ³	conv (%) ^b diboronate (%) ^b	yield (%) ^c	er ^d
7		5.0	>98; 82	76	97:3
8		5.0	>98; 65	61 ^e	97.5:2.5

B(pin) = pinacolatoboron.

- ^aReactions under N₂ atm at -15 °C (48 h, thf), except for entry 2 (-30 °C).
- ^bDetermined by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures.
- ^cYield of purified products.
- ^dDetermined by HPLC analysis (see the Supporting Information for details).
- ^eContains ~5% geminal diboronate.