

Enantioselective Synthesis of Allylboronates Bearing a Tertiary or Quaternary B-Substituted Stereogenic Carbon by NHC-Cu-Catalyzed Substitution Reactions

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Abstract: Allylic substitutions that afford α -substituted allylboronates bearing B-substituted tertiary or quaternary carbon stereogenic centers are presented. C–B bond-forming reactions, catalyzed by chiral bidentate Cu-NHC complexes, are performed in the presence of commercially available bis(pinacolato)diboron. Transformations proceed in high yield (up to >98%) and site selectivity (>98% S_N2'), and in up to >99:1 enantiomer ratio. Trans- or cis-disubstituted alkenes can be used; alkyl- (linear as well as branched) and aryl-trisubstituted allylic carbonates serve as effective substrates. Allylboronates that bear a quaternary carbon center are air-stable and can be easily purified by silica gel chromatography; in contrast, secondary allylboronates cannot be purified in the same manner and are significantly less stable. Oxidation of the enantiomerically enriched products furnishes secondary or tertiary allylic alcohols, valuable small molecules that cannot be easily obtained in high enantiomeric purity by alternative synthesis or kinetic resolution approaches.

Allylboronates are used as nucleophiles for additions to carbonyls or imines and can be converted to valuable allylic alcohols or amines.¹ Design of efficient catalytic protocols for enantioselective preparation of such B-containing unsaturated molecules thus represents a compelling objective in chemical synthesis. In their notable disclosure, Ito and Sawamura outlined an enantioselective protocol for synthesis of α -substituted allylboronates that contain a B-substituted tertiary carbon; this was accomplished by reactions of allylic carbonates with bis(pinacolato)diboron (**1**), catalyzed by a chiral copper–phosphine complex.^{2,3} Use of Z-allylic carbonates bearing a linear alkyl substituent was necessary, however, since enantioselectivity diminished substantially with E isomers; furthermore, boronate substitution was not observed with substrates containing a sterically hindered alkyl (e.g., cyclohexyl) or an aryl unit. Herein, we report methods for synthesis of an assortment of α -substituted allylboronates through reactions promoted by bidentate NHC-Cu complexes developed in these laboratories (eq 1).⁴ Transformations proceed with **1** and various allylic carbonates, delivering allylboronates carrying a tertiary or — for the first time — a *quaternary* α carbon stereogenic center,⁵ in >98% site selectivity and up to 99:1 enantiomer ratio (er). E-Disubstituted allylic carbonates as well as trisubstituted alkyl (linear or branched) or aryl alkenes are effective substrates. Subsequent oxidation furnishes enantiomerically enriched carbinols,⁶ including tertiary allylic alcohols, valuable entities not easily accessible by other synthesis⁷ or kinetic resolution strategies.⁸

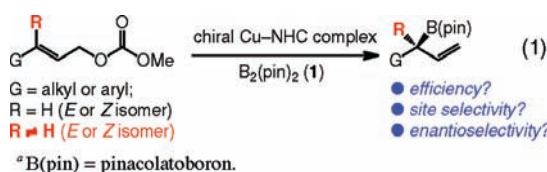
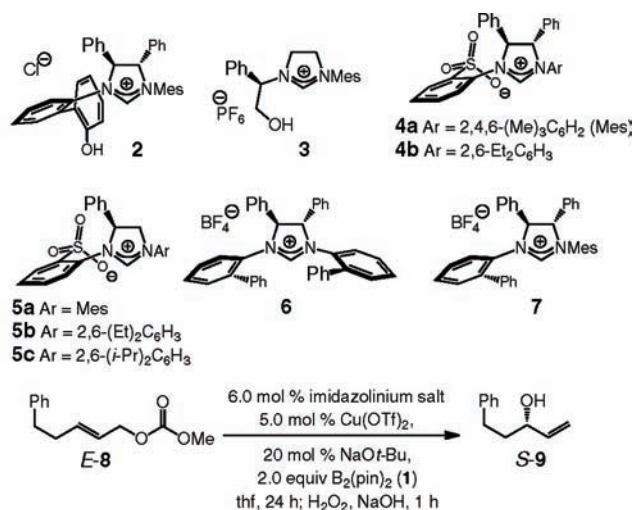


Table 1. Evaluation of Chiral NHC Complexes^a



entry	imidazolium salt	temp (°C)	conv (%) ^b	yield (%) ^c	er ^d
1	2	22	10	9	61:39
2	3	22	22	19	62:38
3	4a	−30	81	76	85:15
4	4b	−30	54	50	84.5:15.5
5	5a	−30	70	70	81:19
6	5b	−30	34	33	85:15
7	5c	−30	69	68	94:6
8	6	22	53	52	63:37
9	7	22	42	41	61:39

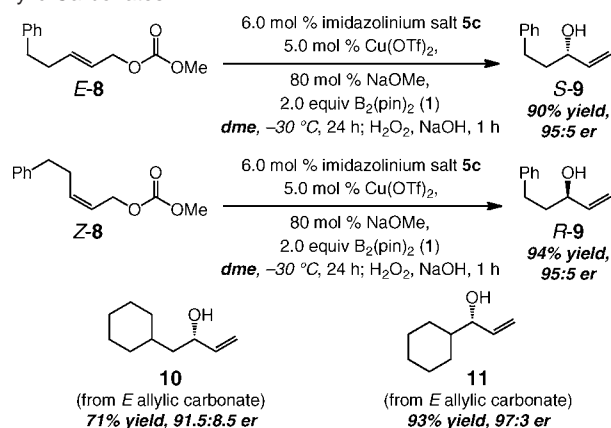
^a Reactions performed under N₂ atm; >98% site selectivity in all cases (e.g., <2% S_N2 product). ^b Values determined by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures. ^c Yields of purified products. ^d By GLC analysis; see the Supporting Information for details.

We began by examining the reaction of an E-disubstituted alkene in the presence of a representative set of chiral NHC-Cu complexes, generated in situ from treatment of an imidazolium salt with a sodium alkoxide and Cu(OTf)₂; initial screening had indicated that, somewhat surprisingly, high reactivity and selectivity can be obtained with the Cu(II) salt.⁹ Representative findings emerging from initial catalyst screening are summarized in Table 1. Reactions with complexes derived from bidentate hydroxyl-containing **2** or **3** are inefficient ($\leq 22\%$ conv). In contrast, sulfonates **4a,b** and **5a–c** give rise to significantly more effective catalysts: substantial conversion (34–81%) is observed despite reactions being performed at −30 °C (vs 22 °C for entries 1 and 2). Among the bidentate sulfonate-NHC-Cu complexes probed, **5c**, bearing a di-isopropyl-phenyl moiety, promotes the most enantioselective transformation (94:6 er). It should be noted that, although the reaction in the presence of **5c** proceeds to 69% conversion, the desired allylic alcohol S-9 is isolated in 68% yield after purification (including

the follow-up oxidation procedure); the allylic substitution thus proceeds without generating significant amounts of byproducts. As indicated in entries 8 and 9 of Table 1, C_1 - or C_2 -symmetric monodentate Cu complexes of **6** and **7**¹⁰ are relatively ineffective catalysts (63:37 and 61:39 er, respectively).

Subsequent optimization studies indicated that use of dme (vs thf used in Table 1) and excess amounts of NaOMe (80 vs 20 mol % NaOt-Bu) leads to significant improvement in reaction efficiency.¹¹ As shown in Scheme 1, under the new conditions, allylic alcohol **S-9** is isolated in 90% yield (>98% conv) and 95:5 er from reaction of **E-8**; the related transformation involving **Z-8** furnishes **R-9** in 94% yield and with identical enantioselectivity (95:5 er). Cu-catalyzed allylic boronate substitutions involving substrates that bear a β - or an α -branched alkyl substituent proceed readily; the allylic carbonate precursor to **11** is unreactive with the previously reported chiral copper–phosphine catalysts.² Allylic alcohols **10** and **11** (Scheme 1) are obtained from reactions of the corresponding *E*-disubstituted allylic carbonates in 71% and 93% yield and 91.5:8.5 and 97:3 er, respectively. In all cases, none of the achiral products derived from the S_N2 mode of C–B bond formation are detected (see below for more details regarding this selectivity issue).

Scheme 1. NHC-Cu-Catalyzed Boronate Additions to Disubstituted Allylic Carbonates^a

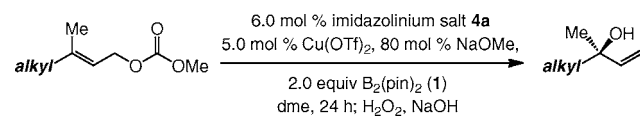


^a All >98% conversion by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures; >98% S_N2' in all cases. Er determined by GLC analysis (see the SI for details).

With an effective procedure for reactions of *E*- and *Z*-disubstituted allylic carbonates established, we turned to the more challenging issue of enantioselective synthesis of allylboronates with an α B-substituted quaternary carbon stereogenic center. The findings summarized in Table 2 illustrate that, in the presence of 6.0 mol % chiral imidazolium salt **4a**, alkyl-bearing trisubstituted allylic carbonates, including those that contain a sterically hindered substituent (e.g., entry 7), efficiently undergo reaction to afford the derived allylboronates in up to 98:2 er (86 to >98% conv, 81–97% yield of tertiary allylic alcohol).¹² Preliminary studies indicated that the reaction in entry 1 of Table 2 in the presence of **5c** (22 °C), used in the case of disubstituted alkenes,¹³ affords the desired product with somewhat lower enantioselectivity (89:11 er vs 95:5 er with **4a**).

Reaction rates and enantioselectivities can be sensitive to substrate structure. The more facile processes can be performed at -30 °C so that higher er values can be achieved; the representative comparison in entries 1 and 2, where (–)-linalool can be obtained in 82% yield and 97:3 er, illustrate this point. The lowest er value (81:19 er in entry 6, Table 2) corresponds to a substrate that contains a β -branched alkyl, a trend observed with reactions of disubstituted

Table 2. NHC-Cu-Catalyzed Enantioselective Synthesis of Alkyl-Substituted Tertiary Allylboronates and Alcohols^{a–d}



entry	substrate (alkyl)	temp (°C)	conv (%) ^b	yield (%) ^c	er ^d
1		22	>98	97	95:5
2		-30	86	82	97:3
3		22	>98	96	96.5:3.5
4		-30	>98	83	95:5
5		-30	>98	81	95:5
6		22	>98	89	81:19 ^e
7		-30	>98	95	98:2

^{a–d} See Table 1. ^e Enantioselectivity does not improve at -30 °C.

alkenes as well (see **S-9**, **10**, and **11**, Scheme 1). In further contrast to the less substituted alkenes, reactions of *Z*-trisubstituted allylic carbonates are less efficient and relatively nonselective. As an example, when the *Z* isomer of the substrate in entry 1 of Table 2 is used with the Cu complex of **4a** under the conditions shown in Table 2, (+)-linalool is isolated in 88% yield (>98% conv at 22 °C) and 76:24 er (vs >98% conv, 97% yield, and 95:5 er with the *E* isomer in entry 1 of Table 2).

Transformations of aryl-substituted alkenes, which pose a noteworthy mechanistic question, were subsequently investigated. We have reported that NHC-Cu complexes in the presence of $B_2(\text{pin})_2$ promote boron–copper additions with disubstituted aryl olefins (vs those in Table 1 and Scheme 1) with high site selectivity, affording benzylic C–Cu bonds exclusively (**I**, Figure 1). Reaction of an allylic carbonate ($R = \text{CH}_2\text{OCO}_2\text{Me}$ in **I**), bearing a disubstituted olefin, was found to afford only a homobenzylic C–B bond (>98% α to C–O).¹⁴ Such preferences were attributed to the stabilization of the developing electron density at the carbon of the benzylic C–Cu bond (**I**). The above considerations offer a rationale for the site selectivity in NHC-Cu-catalyzed reactions of alkyl-substituted carbonates discussed above: the intermediate C–Cu is likely stabilized by the adjacent C–O. With an aryl-containing trisubstituted allylic carbonate, C–Cu bond formation may be electronically favored at either the benzylic or the homobenzylic position (stabilization by aryl group or C–O, respectively). Partial positive charge developed at the site of the C–B bond formation, however, should be better accommodated at the more substituted benzylic carbon (**II**) and disfavored adjacent to the electron-withdrawing carbonate, thus culminating in site-selective allylic substitution.¹⁵

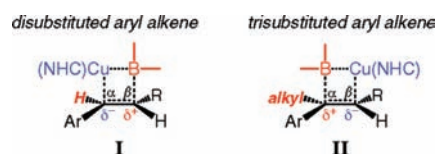


Figure 1. Effect of alkene substitution on selectivity of Cu–B addition to an aryl alkene.

As the data in Table 3 indicate, in sharp contrast to their disubstituted counterparts,¹³ aryl-containing carbonates containing a trisubstituted alkene undergo Cu-catalyzed boronate substitution with the opposite sense of site selectivity, in favor of benzylic C–B

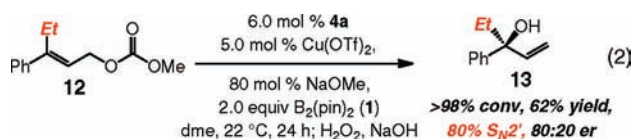
Table 3. NHC-Cu-Catalyzed Enantioselective Synthesis of Aryl-Substituted Tertiary Allylboronates and Alcohols^{a-d}

entry	aryl	temp (°C)	conv (%) ^b	α : β ^b	yield (%) ^c	er ^d
1	Ph	22	>98	>98:2	95	90:10 ^e
2	1-naphthyl	22	>98	>98:2	91	94.5:5.5 ^e
3	<i>o</i> -ClC ₆ H ₄	22	>98	>98:2	96	99:1
4	<i>o</i> -BrC ₆ H ₄	22	86	>98:2	84	99:1
5	<i>o</i> -MeC ₆ H ₄	22	>98	>98:2	88	98:2
6	<i>m</i> -MeC ₆ H ₄	-30	86	>98:2	77	93:7
7	<i>p</i> -MeC ₆ H ₄	-30	74	>98:2	72	92:8
8	<i>p</i> -CF ₃ C ₆ H ₄	22	<2			

^{a-d} See Table 1. ^e Enantioselectivity does not improve at -30 °C.

bond. Reactions afford the corresponding tertiary allylic alcohols (after oxidative workup) with >98% site selectivity and 72–96% yield. The desired allylboronates can be obtained in 90:10–99:1 er, with the highest selectivities being observed with the more sterically demanding aryl units; lower temperature can lead to improved enantioselectivity (entries 6 and 7 >98% conv and 89:11 er for both cases at 22 °C). The lack of reactivity with *p*-trifluoromethyl substrate (entry 8) supports the aforementioned scenario (cf. **II**, Figure 1); reaction via **I** could be energetically inaccessible, or MeOH may be required for effective turnover with such a mode of addition.¹³

A limitation of the present class of reactions is worthy of note. Cu-catalyzed reaction of Et-substituted alkene **12** (eq 2) delivers **13** in 62% yield and 80:20 er. Particularly noteworthy is that the reaction leads to — unlike all previous cases — the formation of the primary C–B bond (20% S_N2 addition). Generation of the achiral byproduct suggests the intermediacy of π -allylcopper complexes in reactions promoted by boronate-containing NHC-cuprates (vs neutral copper boronates) and, at least in certain instances, the intermediacy of Cu(III) complex (oxidative addition), followed by B-alkyl reductive elimination (vs Cu–B addition to the alkene proposed for neutral Cu complexes²). The above findings point to the need for still more effective chiral catalysts for transformations of highly congested alkenes.



Unlike the less substituted tertiary derivatives, allylic carbonates with a B-substituted quaternary carbon are sufficiently robust to be purified by silica gel chromatography. Alkyl- or aryl-substituted quaternary allylboronates can be obtained in high yields and er (Scheme 2). Such stability is likely the result of steric congestion at the B center, rendering it less susceptible to nucleophilic attack. Nonetheless, quaternary carbon-containing allyl boronates obtained by the present protocol do serve as nucleophilic reagents. Treatment of **14** with benzaldehyde (22 °C) affords the desired homoallylic alcohol in 98% yield and 97:3 er but as an equal mixture of alkene isomers (improvement not observed at -78 °C).

We put forth protocols for enantioselective synthesis of allyl boronates and allylic alcohols that were not easily attainable previously¹⁶ and further underline the special utility of sulfonate-bearing NHC-Cu catalysts.¹⁷ These studies, and a small number of other disclosures,¹⁸ underline the need for certain future developments.

Scheme 2. Stability of Enantiomerically Enriched Allyl Boronates

Identification of effective catalysts that promote reactions of sterically congested allylboronates (e.g., **14** and **15**) to a wide range of electrophilic substrates and introduction of effective procedures leading to efficient and stereoselective conversion of hindered C–B to C–N¹⁹ and C–C bonds are among such challenges. Investigations along these lines, mechanistic studies, development of more effective chiral catalysts, and application of the NHC-Cu-catalyzed C–B bond formation to other substrate classes are in progress.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (7) For example, see: (a) Uenishi, J.; Kubo, Y. *Tetrahedron Lett.* **1994**, *35*, 6697. (b) Wu, Y.-K.; Liu, H.-J.; Zhu, J.-L. *Synlett* **2008**, 621. A tertiary allylic alcohol has been prepared by Cu-catalyzed enantioselective vinyl addition to an α -ketoester. See ref 6a.
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- (9) For details of Cu screening, see the Supporting Information. It is noteworthy that a Cu(II) salt is reduced to the catalytic active Cu(I) complex by **1**. All previous Cu-catalyzed C–B bond-forming reactions involve use of a Cu(I) salt (e.g., refs 2, 13, and 18b). Related mechanistic details will be discussed in the full account of this work.
- (10) For use of C₁-symmetric chiral NHC-Cu complexes in enantioselective synthesis, see: (a) Lee, K.-s.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455. (b) Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898.
- (11) The exact reason for improvement in reaction efficiency due to use of larger excess of NaOMe is not clear, but may be partly the result of more efficient imidazolium salt deprotonation and Cu-NHC complex formation.
- (12) The stereochemical outcome of reactions in Table 2 (determined on the basis of formation of (–)-linalool in entry 1) differs from *E*-disubstituted

- alkenes (see Scheme 1). The origin of this difference is difficult to establish in the absence of mechanistic data (identity of turnover-limiting step).
- (13) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160.
- (14) When *alkyl*-containing (vs aryl) disubstituted olefins are subjected to Cu-NHC-catalyzed boron–copper additions (in the presence of MeOH), <2% hydroboration product is generated. See ref 13.
- (15) It is possible that boron–copper addition is reversible and only when mode of addition **II** occurs, copper–alkoxide elimination leads to the formation of the allylic substitution product. Studies carried out with products from additions to alkynes suggest that the boron–copper addition process is largely irreversible (Lee, Y.; Hoveyda, A. H., unpublished results); similar investigations corresponding to alkene substrates are in progress.
- (16) Reactions with the less air-sensitive $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, although at times less efficient, deliver similar enantioselectivities. For example, **9** and the product from the reaction in entry 3 of Table 2 are obtained in 52% yield, 94:6 er and 96% yield, 97:3 er, respectively, with the latter Cu salt.
- (17) For another example, see: Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446.
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- (19) Primary or secondary benzylic C–B bonds have been converted to C–N bonds. For representative cases, see: Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem.—Eur. J.* **2000**, *6*, 1840. However, application of such procedures to compounds bearing a B-substituted quaternary carbon has not been disclosed.

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