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Catalytic Enantioselective Protoboration of Disubstituted Allenes. Access to Alkenylboron Compounds in High Enantiomeric Purity

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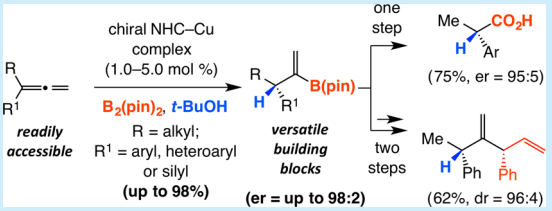
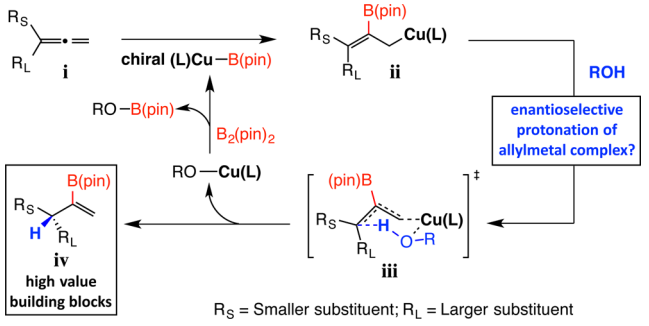
Supporting Information

ABSTRACT: Proto-boryl additions to 1,1-disubstituted allenes in the presence of 1.0−5.0 mol % of chiral NHC−Cu complexes, $B_2(pin)_2$, and *t*-BuOH proceed to afford alkenyl−B(pin) products in up to 98% yield, >98:2 site selectivity, and 98:2 er. The enantiomerically enriched alkenylboron products can be converted to otherwise difficult-to-access alkenyl bromides, methyl ketones or carboxylic acids. What's more, the corresponding boronic acids may be used in highly stereoselective NHC−Cu-catalyzed allylic substitution reactions.



Allylmetal complexes occupy a prominent position in organic chemistry;[1] reactions of these nucleophilic agents with carbonyl- and imine-containing compounds are a cornerstone of chemical synthesis. Nonetheless, methods for enantioselective protonation[2] of allylmetal species are scarce.[3] The difficulty in designing a catalytic enantioselective allyl anion protonation arises from the identification of a Brønsted acid that is compatible with the reaction conditions and contains a counterion component that allows proper acidity to be maintained while imparting sufficient bulk to cause stereochemical differentation. We envisioned that if a 1,1-disubstituted allene (**i**, Scheme 1) were to undergo selective

Scheme 1. Proposed Catalytic Cycle[a]

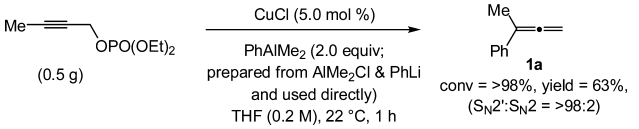


[a]B(pin) = (pinacolato)boron.

reaction with a chiral Cu−B(pin) complex (pin = pinacolato),[4] and the resulting allylcopper (**ii**) were to be γ-selectively and enantioselectively protonated via **iii**,[5] a Cu-catalyzed route to versatile unsaturated organoboron compounds (**iv**) would be in hand. The enantioselective C−H bond forming step would be distinct from other catalytic protoborations (i.e., γ proton transfer vs direct Cu−C bond protonation[4c]), affording entities that cannot be accessed by traditional hydroboration procedures.[6] Herein, we report the realization of the above plan.

We first established a practical method for preparation of 1,1-disubstituted allenes (Scheme 2). Treatment of a propargylic

Scheme 2. Preparation of Allene Substrates[a]



[a]See the Supporting Information for details.

phosphate, prepared in one step from the corresponding alcohol, with 5.0 mol % CuCl and an arylaluminum compound, accessed in situ by reaction of an aryllithium reagent and $AlMe_2Cl$, furnishes the desired allenes typically in >60% yield with complete control of S_N2' selectivity. Transformations proceed to completion in 5 min to 1 h (depending on the scale).[7]

We began by investigating the possibility of a chiral Cu catalyst promoting protoboration of **1a** in a site-selective (**2a** vs **3a** or **4a**) and enantioselective fashion (Table 1). In our previous studies involving Cu−B(pin) additions to monosubstituted allenes in the presence of aldehydes and ketones,[8] a chiral phosphine proved to be most effective (vs nonselective chiral NHCs). Accordingly, we first examined the representative protoboration process under the same parameters.[9] Reaction with bis-phosphine **5** (*R*-SEGPHOS) generated **2a** in 88:12 er along with 9% of **4a** (entry 1, Table 1). Consistent with earlier investigations, the reaction with imidazolinium salt **6a** was much less enantioselective (63:37 er; entry 2), affording 14% of **3a** as the byproduct. We reasoned that use of a more sizable alcohol might exacerbate the steric interactions within

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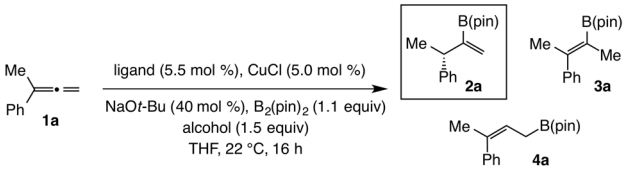
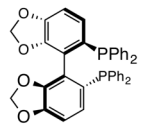
Table 1. Evaluation of Chiral Complexes[a]



Results of catalyst screening:

Most effective chiral phosphine



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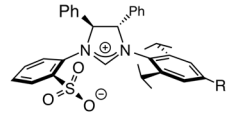


6a R = *i*-Pr
6b R = 1-naphthyl

Most effective chiral NHCs

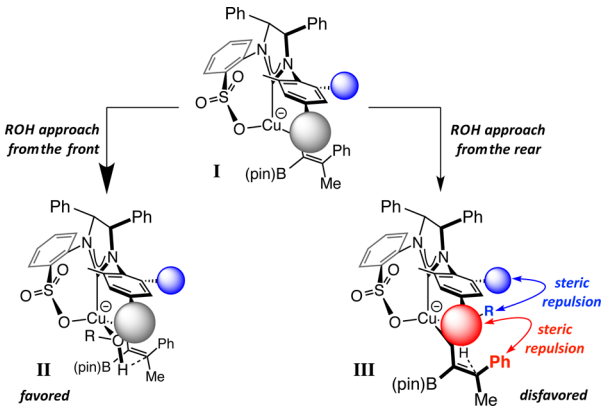
entry	ligand; alcohol	conv (%)[b]	yield (%)[c]	**2a**/**3a**/**4a**[b]	er[d]
1	**5**; MeOH	>98	71	89:2:9	12:88
2	**6a**; MeOH	>98	89	86:14:<2	63:37
3	**5**; *t*-BuOH	97	53	91:3:6	7:93
4	**6a**; *t*-BuOH	>98	77	98:2:<2	93:7
5	**6b**; *t*-BuOH	>98	79	>98:<2:<2	95:5

[a]Reactions performed under a N_2 atmosphere. [b]By analysis of ^{1}H NMR spectra of the unpurified (for conv) or purified (for selectivity) mixtures (±2%). [c]Yields of purified products (±5%). [d]By GC analysis.

the competing transition states for enantioselective protonation, leading to a rise in enantioselectivity. We therefore examined protoboration of **1a** with *t*-BuOH (entries 3−4, Table 1); this resulted in a substantial improvement in enantioselectivity with bis-phosphine **5** (93:7 er). To our surprise, catalytic protoboration promoted by the NHC−Cu complex derived from **6a** delivered the desired product not only in a similarly high er but also in a significantly improved yield (77% vs 53%) with superior site selectivity (98% vs 91% **2a** and 3% **3a**).

To account for the selectivity trends observed with the NHC−Cu complex derived from **6a**, as well as the positive influence of a large alcohol reagent, we arrived at the stereochemical models depicted in Scheme 3. We surmised that two interactions could render **III** less favorable (vs **II**). One is engendered by the tilt of the NAr, causing the ortho unit of the NAr (blue sphere) to interact with the alcohol substituent (R); **III** might be less favored because of steric repulsion between the NAr's para unit (red sphere) and the aryl group of the allene. The latter point led us to prepare and study

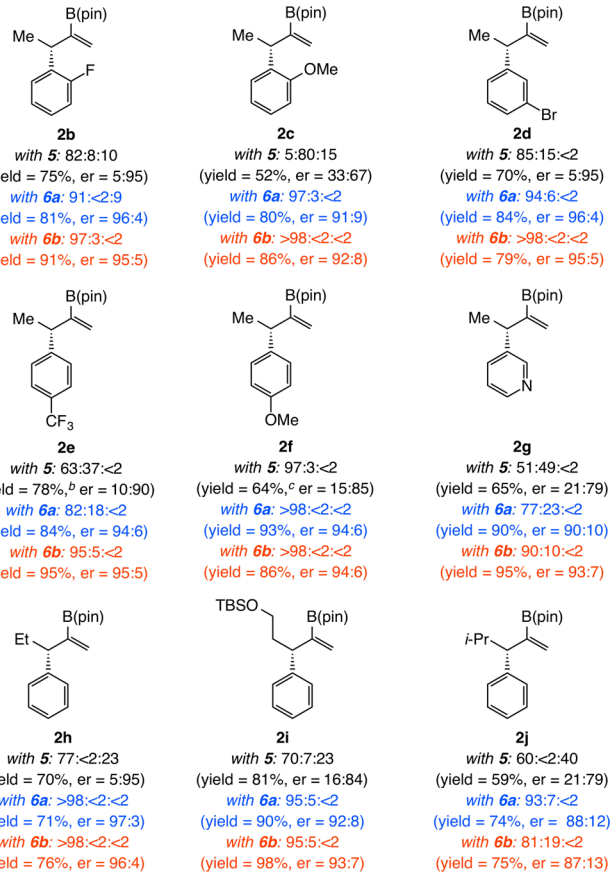
Scheme 3. Stereochemical Models



imidazolinium salt **6b**, which delivered some increase in enantioselectivity (95:5 vs 93:7 er). As will be demonstrated below, **6b**, while requiring a longer synthesis route (6 vs 3 steps), in some cases delivers a better stereoselectivity profile.

Different 1,1-disubstituted allenes underwent catalytic protoboration efficiently and with high enantioselectivity (Scheme 4; for additional cases, see the Supporting

Scheme 4. Enantioselective Protoboration of Aryl-Substituted Allenes[a]



[a]Same conditions as those in Table 1; all conv = >98%, except otherwise noted. Yields are of purified products (**2** and **3**; ± 5%). Site selectivities determined by analysis of ^{1}H NMR spectra of the unpurified mixtures. Enantioselectivities determined by GC analysis. [b] Conv = 88%. [c] Conv = 91%.

Information). Allenes containing an ortho-, meta-, or para-substituted aryl group (**2b−f**) and those that bear a heteroaromatic moiety (e.g., **2g**) were suitable substrates. Synthesis of **2h−j** illustrates that reactions of allenes with larger alkyl units (vs Me) are facile. The data for the Cu complexes derived from bis-phosphine **5** as well as NHC ligands obtained from **6a−b** highlight the characteristics of each system and illustrate that in all cases the NHCs are the ligands of choice. In many instances, the phosphine−Cu complex generated substantial amounts of inseparable isomeric products (i.e., **3** and **4**); with methoxy-substituted **2c**, the desired product constituted only 5% of the mixture, and in reactions to generate **2h−j**, the corresponding allylboron compounds (**4h−j**) were formed. On several occasions, use of bis-phosphine **5** resulted in low to moderate enantioselectivity (e.g., 33:67 er for **2c**, 16:84 er for **2f**, 21:79 er for **2g** and **2j**). While **6a−b** were often

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similarly effective, in some cases, the latter afforded significantly higher site selectivities in favor of **3** (cf. **2e** and **2g**). The general effectiveness of the NHC−Cu species is in stark contrast to additions of allylcopper species derived from Cu−B(pin) additions to aldehydes and ketones, where bis-phosphines such as **5** are optimal. These results underline the fundamental steric and geometric distinctions between the transition states involved in the reactions of B(pin)-substituted allylcopper species with aldehydes or ketones vs those involving proton addition.

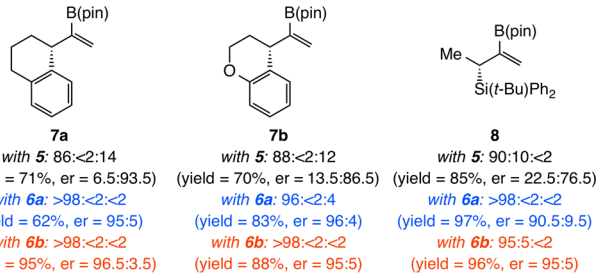
The examples in Scheme 5 show that reactions of exocyclic 1,1-disubstituted allenes are efficient as well as site selective and stereoselective (cf. **7a**−**b**).[10] Similar efficiency and stereoselectivity levels were observed with substrates with an alkyl and a silyl substituent (cf. **8**).[11]

The alkenyl−B(pin) products are versatile, as underscored by the transformations in Scheme 6. The first category deals with synthesis of alkenyl bromides (cf. **9a**−**b**), precursors to many catalytic or noncatalytic C−C bond forming reactions; such entities cannot be easily accessed by alternative protocols.[12] Exceptional enantiospecificity (es) was observed for reactions performed with $CuBr_2$. The second set entails preparation of enantiomerically enriched α,α'-disubstituted ketones (cf. **10a**−**b**).[13] The mild oxidation process is complete in 30 min, furnishing ketones with >97% es. The alternative catalytic strategies (e.g., enantioselective alkylations) have not been employed to prepare this type of α-substituted enantiomerically enriched methyl ketones.[14] We have also developed a catalytic method[15] for direct oxidation of enantiomerically enriched alkenyl−B(pin) products to carboxylic acids (Scheme 6).[16] Enantioselective synthesis of nonsteroidal anti-inflammatory agent (*S*)-naproxen was carried out on 2.0 mmol scale with 1.0 mol % of **6b**, affording the acid in 75% overall yield and 95:5 er (94% es).

We then investigated the possibility of directly using the alkenylboron compounds in stereoselective C−C bond formation. We selected allylic substitutions, partly because, to the best of our knowledge, chiral nucleophiles (enantiomerically enriched or otherwise) have not been utilized in this reaction class.[17] However, our attempts to effect allylic substitutions involving **2a** with various Cu-based complexes (achiral or chiral) led to <2% conversion (Scheme 7). Neopentyl glycol ester **12** and the trifluoroborate **13** were equally ineffective.

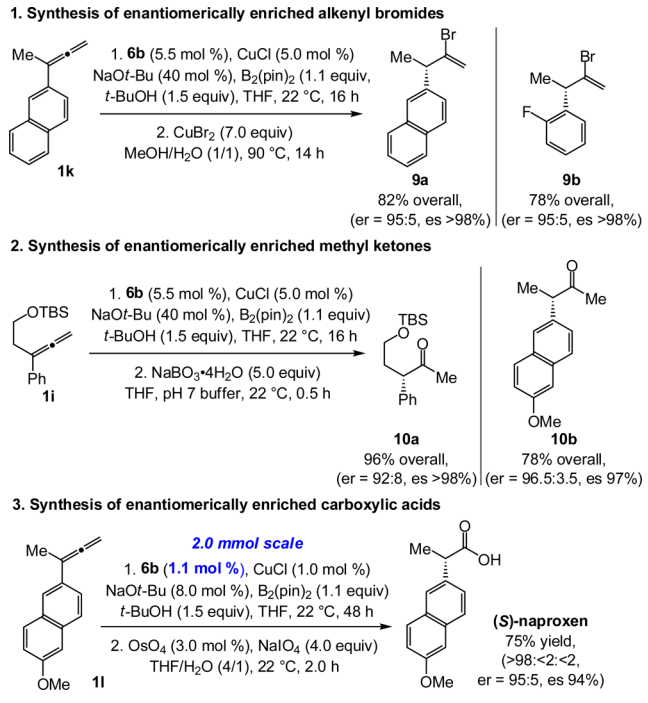
We subsequently prepared the less congested boronic acid *R*-**14** ($NaIO_4$, NH_4OAc;[18] 83% yield) and determined that, with 5.0 mol % NHC−Cu complex derived from **6c**, it reacts to

Scheme 5[a]



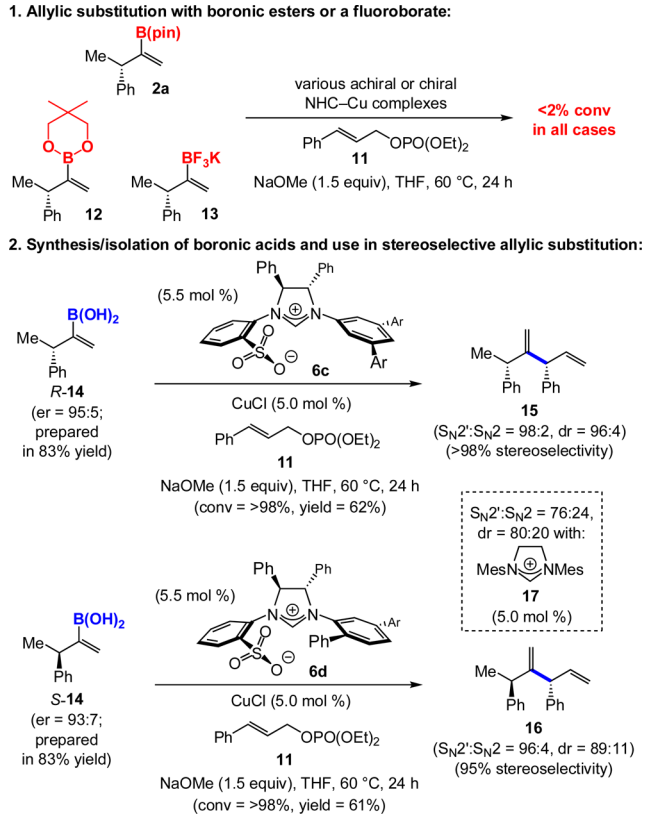
[a]Same conditions used as those indicated in Table 1 and Scheme 4.

Scheme 6. Representative Functionalization Procedures[a,b]



[a]See the Supporting Information for experimental and analytical details. [b] Yield values correspond to conversion of alkyl-B(pin) to ketones or alkenyl bromides; es = enantiospecificity (product enantiomeric excess/substrate enantiomeric excess) × 100.

Scheme 7. Catalytic Allylic Substitution Reactions[a]



[a]Ar = 2,4,6-$(i\text{-Pr})_3C_6H_2$.

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afford 1,4-diene **15** in 62% yield with 98% S_N2' selectivity and in 96:4 dr (>98% stereoselectivity). Cross-coupling with *S*-**14** gave anti isomer **16** with similar site selectivity and efficiency (i.e., nearly complete catalyst control); here, **6d** proved to be the more effective ligand. By comparison, when an achiral NHC−Cu complex, such as that derived from **17**, was used, site selectivity (76:24 $S_N2':S_N2$) and stereoselectivity (80:20 dr) were substantially diminished.

Development of other catalytic proto-boryl additions and further mechanistic investigations are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

†H.J. and B.J. contributed equally.

Notes

The authors declare no competing financial interest.

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(9) See the Supporting Information for additional details.

(10) Reactions with allenes that contain two alkyl groups are less efficient and proceed with low site selectivity and enantioselectivity. For example, reaction of Me- and Cy-substituted allene proceeds to 66% conversion (41% yield), affording a 57:41 ratio of di-/tetrasubstituted alkenyl-B(pin), 2% of the allyl-B(pin), and 46:54 er for the first isomer (>98% conv, 47% yield, 22:76:2 and 48:52 er with **6b**).

(11) Related B(pin)-substituted allylsilanes have been accessed by Pd-catalyzed silaborations of monosubstituted allenes. See: Ohmura, T.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2006**, *128*, 13682.

(12) For conversion of C−B(pin) into C−Br bonds, see: (a) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434. (b) Reference 2.

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