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NHC–Cu-Catalyzed Protoboration of Mono-Substituted Allenes. Ligand-Controlled Site Selectivity, Application to Synthesis and Mechanism

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Abstract

Two different types of NHC–Cu complexes catalyze protoborations of terminal allenes to afford valuable 1,1- or trisubstituted vinylboron species with high site- and stereoselectivity. The scope of the method, application to natural product synthesis and mechanistic basis for the observed selectivity trends are presented.

Vinylboron compounds are used in a myriad of applications in chemical synthesis, most notably as cross-coupling partners;¹ development of methods for efficient and stereoselective preparation of such entities thus constitutes a compelling objective. Catalytic variants would be especially valuable, as the opportunity for accessing different selectivity profiles then becomes feasible through adjustment of catalyst structures. Herein, we outline protocols for efficient conversion of alkyl- and aryl-substituted allenes to either of the two possible vinylboron isomers, depending on the NHC–Cu complex used (Figure 1). Reactions are promoted by complexes derived from commercially available imidazolium salts and proceed in 8.0 hours at 22 °C to afford (pin)B-substituted olefins in up to 92% yield and >98% site- and stereoselectivity (pin = pinacolato). We demonstrate utility through synthesis of the C1–C10 fragment of a macrolide antibiotic elansolid A. Mechanistic rationales for the varying trends in selectivity and efficiency are provided.

In 2011, we demonstrated that by altering the structure of the NHC ligand of a Cu-based catalyst, terminal alkynes may be efficiently converted to α - or β -vinylboron entities (Figure 1).² Reactions involve site-selective addition of an NHC–Cu–B(pin) complex followed by protonation of the vinylcopper intermediate by MeOH (net protoboration).³ More recently, as shown in Figure 1, in conjunction with studies regarding NHC–Cu-catalyzed enantioselective allylic substitution reactions, we showed that the resulting allenes undergo

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

Cu-catalyzed allene protoboration to afford 1,1-disubstituted vinylboron products with ~90:10 selectivity.^{4,5} Considering the value of either isomeric form and the limited number of protocols for their preparation,²⁻⁵ we set out to establish the scope of the catalytic process (Figure 1), as well as determine whether the trisubstituted vinylboron compounds can be synthesized selectively with a different set of NHC ligands.

First, we examined the effect of catalyst structure on selectivity (Table 1). We chose allene **5** to probe the possibility of chemoselective protoboration. Reactions proceed favoring allene addition (<2% alkene reaction). Further, as shown in entries 1–4, NHCs with larger (farther spanning) aryl units deliver higher selectivity, with the Cu complex of **3** affording **6** with a 90:10 preference (Table 1, entry 4). As the N-alkyl moiety of the NHC is reduced in size, selectivity improves in favor of **7**, which is formed with complete *Z* selectivity.⁶ When the Cu complex derived from **4e** is used, the trisubstituted vinylboron **7** is obtained with 94% selectivity (Table 1, entry 9).

Chemoselective addition to the allene unit in **5** is noteworthy since Cu-catalyzed protoboration of β -alkyl styrenes proceed with similar efficiency as those presented in Table 1.⁷ Such observations imply that, although reactions of allenes might overall be similarly facile, these less hindered and more Lewis acidic substrates coordinate more efficiently with the nucleophilic NHC–Cu–B(pin) complexes⁸ (vs aryl olefins);⁹ DFT calculations indicate that the latter catalyst/allene association is indeed significantly more exothermic (by ~10 kcal/mol).¹⁰ Moreover, the lower efficiency with the less congested catalysts in entries 6–9 (Table 1) is probably due to the ability of the aryl olefin to compete better for the Cu complex; the reason why the protoborations products from aryl alkene are unobserved is under investigation.

An assortment of alkyl- and aryl-substituted allenes can be used in catalytic protoborations with the complex derived from **3** (Scheme 1). Transformations with sterically congested substrates, including those that carry a quaternary center (cf. **14–16** and **18a–b**) not only proceed efficiently but are more selective than those that contain a less hindered linear branch (cf. **8–10**, Scheme 1).

Transformations with the NHC–Cu complex derived from **4e** can be carried out with a variety of mono-substituted allenes to generate trisubstituted vinylborons efficiently with high site selectivity (89:11 to >98:2) and exclusively as *Z* isomers (Scheme 2). Without a resident aryl olefin, reactions are more efficient than with **5** (cf. Table 1). In several ways, however, reactions with the **4e**-derived catalyst are distinct (vs the larger **3**). Unlike those performed with aryl-substituted **3** (Scheme 1), transformations involving allenes with a linear alkyl group are highly site-selective (**19–21**, 94:6). A sterically demanding substituent can be detrimental to site selectivity: tolyl-containing **24** forms in 89:11 ratio (vs 93:7 with phenyl-substituted **23**) or more dramatically, vinylsilane **27** is obtained with a preference for the 1,1-disubstituted isomer (73% of the mixture). In further contrast to reactions in Scheme 1, allylic ethers are not tolerated: attempts to access allyl silyl ethers **25–26** results largely leads to unidentifiable products (details below).

The utility of the method, particularly in relation to that of alkyl-substituted allenes, is demonstrated by synthesis of the C1–C10 fragment of the macrolide elansolid A, a recently identified antibiotic natural product (Scheme 3).¹¹ Efficient preparation of **31**¹² is illustrative of the ease with which mono-substituted allenes are accessed. NHC–Cu-catalyzed protoboration with hydroxyl-containing **31** with **4e**, followed by Pd-catalyzed cross-coupling (without isolation/purification of the vinylboron intermediate) affords triene **32** with >98% site selectivity, in 72% overall yield and as only the *E* stereoisomer (>98%). A total synthesis of elansolid A has not been reported.

The observed selectivity trends, dictated by catalyst structure, can be rationalized by the pathways outlined in Figure 2, as supported by DFT calculations.¹⁰ With either catalyst type (derived from **3** or **4e**), Cu–B addition places the NHC–Cu initially at the less hindered site of the mono-substituted allene ($\rightarrow$ **i**). Subsequent γ -protonation via **ii**, the favorability of which is indicated by calculations,¹⁰ causes preferential formation of the 1,1-disubstituted vinylboron product.¹³ The latter part of the above route, however, pertains mainly to catalysts with the larger NHC ligand (i.e., **3**). With the smaller catalyst derived from **4e**, conversion of the complex **i** to isomeric **iii**,¹⁴ bearing a secondary Cu–C bond, becomes sufficiently favored; theoretical studies reveal that allylcopper **iii** is higher in energy and can more swiftly undergo protonation via **iv**¹⁰ (vs **ii**) to afford trisubstituted B(pin)-substituted alkenes (Curtin–Hammett kinetics). The greater reactivity of **iii** appear to be partially the result of the higher-energy HOMO of the more substituted Cu–C bond;¹⁰ moreover, since the trisubstituted olefin is energetically favored, the activation barrier to protonation that furnishes such entities would be lower (Hammond's postulate). Transition structure **iv**, engendering high stereoselectivity, allows for minimization of steric repulsion between the allene substituent (G) and the B(pin) and NHC–Cu units; there is little 1,3-diaxial repulsion to discourage formation of **iv**. Based on the above scenario, with the larger NHC ligand **3**, protonation of the kinetically-generated allylcopper species is faster than equilibration between **i** and **iii** and is therefore product-determining (non-Curtin-Hammett); with smaller catalysts, it is the more facile protonation of the higher energy allylcopper (**iii**) that determines the identity of the major product.

The proposal in Figure 2 offers an explanation for other observations.¹⁵ The lower selectivity with the less hindered allenes in Scheme 1 (**8-10**) might be because the intermediacy of **iii** (Figure 2) is slightly competitive. In contrast, with **4e** (Scheme 2), all transformations proceed with high selectivity, since it is the rate of allylcopper protonation that is critical (vs which is generated favorably). The inefficiency of syntheses of silyl ethers **25-26** (Scheme 2) is likely due to facile Cu–alkoxide elimination of intermediates such as **36** in Scheme 4 (perhaps by syn elimination), resulting in the eventual generation of **38** (among other products). In reactions with **3**, the Cu–C bond in **39**, remote from the silyl ether, undergoes γ -protonation, as isomerization is relatively disfavored. Vinylsilane **27** is formed mainly as a 1,1-disubstituted olefin likely since stabilization of electron density at the adjacent Cu–C site by the low-lying C–Si σ^* orbitals in **iv** more effectively retards γ -protonation rate (vs **ii**) to disfavor the Curtin-Hammett pathway.

Development of related catalytic protocols and further mechanistic investigations are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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5. Subsequent to studies in ref. 4, a disclosure regarding site selective synthesis of vinylboron products by Cu-catalyzed protoboration of mono-substituted allenes appeared. However, catalysts were exclusively phosphine-based, substrates were almost all aryl-substituted, application to complex molecules synthesis was not demonstrated and detailed rationale for the origin of the observed selectivities was not provided. See: Yuan W, Ma S. *Adv Synth Catal.* 2012; 354:1867.
6. See the Supporting Information for details of stereochemical identity determination (nOe studies).
7. For example, β -*i*-propylstyrene undergoes >98% conv in 3.0 h with 5.0 mol % **1a**; see ref 6
8. Dang L, Lin Z, Marder TB. *Organometallics.* 2008; 27:4443.
9. Similarly, although Cu–B addition to mono-substituted allenes/in situ 1,2-additions of allylcopper species to enals requires 8.0 h, the enal is fully consumed in 4.0 h in the absence of an allene. For reactions in the presence of aldehydes and ketones, see: Meng F, Jang H, Jung B, Hoveyda AH. *Angew Chem Int Ed.* 201310.1002/anie.201301018
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12. See the Supporting Information for synthesis of alkyne **30**.
13. Direct Cu–C (vs γ -) protonation is implausible; it is unlikely that reactions with the more hindered catalysts favor Cu–C bond formation at the more substituted site and vice versa.
14. Allyl–Cu(I) complexes likely exist in the η^1 form (vs π -allyl), based on our computational studies (see the Supporting Information) and a recent report regarding the electronically related allylzinc systems by Okuda; see: Lichtenberg C, Engel J, Spaniol TP, Englert U, Raabe G, Okuda J. *J Am Chem Soc.* 2012; 134:9805. [PubMed: 22591244] . η^1 -to- η^1 Inter-conversion can occur by an intramolecular process where the B(pin) can present a steric barrier. Another possibility is an exchange mechanism involving two complexes, which underscores the significance of a smaller NHC to the rate of interconversion
15. The arguments provided here can be used to explain why the more sizeable bis-phosphine–Cu complexes afford 1,1-disubstituted vinylboronates, whereas when monodentate phosphines are used trisubstituted isomers are formed predominantly; see ref 5.

Figure 1. Previous findings and questions addressed in this study; NHC = N-heterocyclic carbene; B(pin) = (pinacolato)boron.

Figure 2.

Rationale for the site selectivity trends; Curtin–Hammett kinetics with smaller NHC ligand **4e**.

Scheme 1.

Synthesis of 1,1-Disubstituted Vinylborons by NHC–Cu–Catalyzed Protoborations of Allenes^a

^a >98% conv in all cases; same conditions as in Table 1. See the Supporting Information (SI) for details.

Scheme 2. Site- and *Z*-Selective Synthesis of Trisubstituted Vinylboron Compounds^a^a >98% conv (allene disappearance) and >98% *Z* in all cases; same conditions as in Table 1, except 1,4-dioxane used as solvent. See the SI for details.

Scheme 3.

Application to Stereoselective Synthesis of the C1–C10 Fragment of Macrolide Antibiotic Elansolid A

Smaller NHC: interconversion to secondary Cu-C feasible **Larger NHC: minimal interconversion to secondary Cu-C**

Scheme 4.
Effect of Site Selectivity on Efficiency

Table 1

Screening of NHC–Cu Complexes^a

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