ORGANIC LETTERS

2013
Vol. 15, No. 6
1414–1417

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

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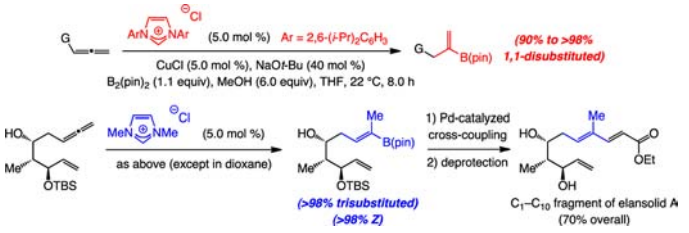
Received February 12, 2013

ABSTRACT



Two types of NHC–Cu complexes catalyze protoborations of terminal allenes to afford valuable 1,1- or trisubstituted vinylboron species with high site selectivity 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 after 8.0 h at 22 °C to afford (pin)B-substituted olefins in up to 92% yield and >98% site selectivity 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 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 available protocols

(1) For applications of vinylboron compounds in C–C bond formation, see: (a) Hall, D. G. In *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Wiley–VCH: Weinheim, 2005. (b) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565. For syntheses of cyclic and acyclic vinylborons by Pd-catalyzed cross-coupling reactions involving vinyl bromides and triflates, see: (c) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001. For a review on applications of vinyltrifluoroboron species, accessed via vinylborons, see: (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

(2) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859.

(3) For synthesis of vinylboron compounds by Cu-catalyzed protoboration of alkynes (in addition to ref 2), see: (a) Kim, H. R.; Jung, I. G.; Yoo, K.; Jang, K.; Lee, E. S.; Yun, J.; Son, S. U. *Chem. Commun.* **2010**, *46*, 758. (b) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem.—Eur. J.* **2012**, *18*, 4179. (c) Moure, A. L.; Arrayás, R. G.; Gárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2012**, *134*, 7219. (d) Park, J. K.; Ondrusek, B. A.; McQuade, D. T. *Org. Lett.* **2012**, *14*, 4790.

10.1021/ol4004178
Published on Web 03/05/2013

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.

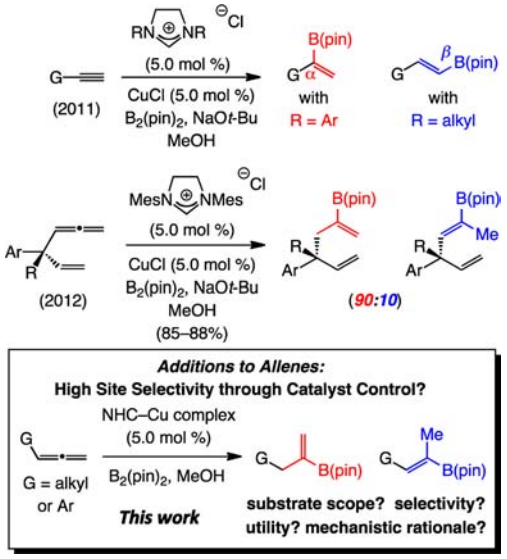
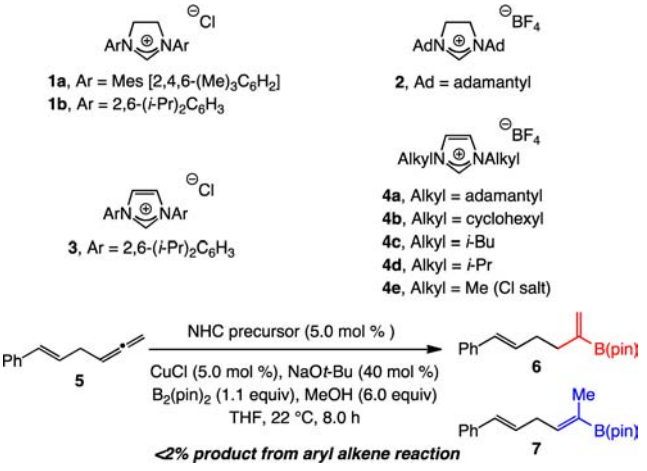


Figure 1. Previous findings and questions addressed in this study; NHC = N-heterocyclic carbene; B(pin) = (pinacolato)boron.

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)

Table 1. Screening of NHC−Cu Complexes[a]



entry	NHC precursor	conv (%)[b]	yield (%)[c]	**6**:**7**[b]	*Z*/*E* (**7**)[d]
1	**1a**	>98	74	84:16	>98:2
2	**1b**	94	75	88.5:11.5	>98:2
3	**2**	>98	78	68:32	>98:2
4	**3**	>98	73	*90:10*	>98:2
5	**4a**	>98	80	56:44	>98:2
6	**4b**	73	58	22:78	>98:2
7	**4c**	73	60	10:90	>98:2
8	**4d**	89	69	16:84	>98:2
9	**4e**	79	62	*6:94*	*>98:2*

[a] Reactions at 22 °C under N_2. [b] By analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Yields of mixtures of **6** and **7** after purification. [d] By analysis of 400 MHz ^{1}H NMR spectra of purified materials.

complexes[8] (vs aryl olefins);[9] DFT calculations indicate that the latter catalyst/allene association is indeed significantly more exothermic (by ∼10 kcal/mol).[10] 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 protoboration 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 also 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 monosubstituted 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**

(4) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490.

(5) Subsequent to studies in ref 4, a disclosure regarding site selective synthesis of vinylboron products by Cu-catalyzed protoboration of monosubstituted 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 SI for details of stereochemical identity determination (NOE studies).

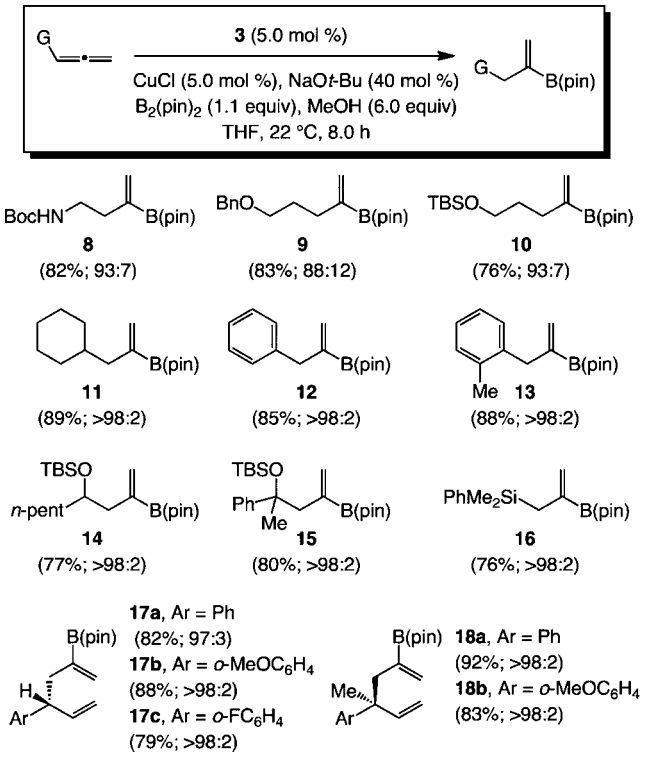
(7) For example, β-isopropylstyrene undergoes >98% conv in 3.0 h with 5.0 mol % **1a**; see: Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160.

(8) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443.

(9) Similarly, although Cu−B addition to monosubstituted 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, A. H. *Angew. Chem., Int. Ed.* **2013** DOI: 10.1002/anie.201301018.

(10) See the SI for details of DFT calculations.

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 those in Table 1. See the Supporting Information (SI) for details.

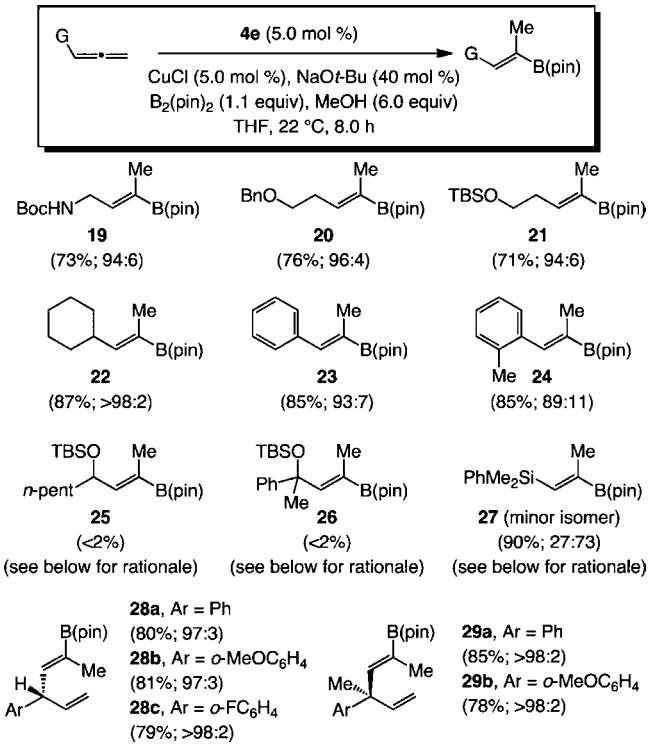
(cf. Table 1). In several ways, however, reactions with the **4e**-derived catalyst are distinct (vs the larger **3**). Unlike those performed with aryl-substituted **3** (Scheme 1), transformations involving allenes with a linear alkyl group are highly site-selective (**19-21**, ≥94:6). A sterically demanding substituent can be detrimental to site selectivity: tolyl-containing **24** forms in an 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** largely lead to unidentifiable products (details below).

The utility of the method, particularly in relation to that of alkyl-substituted allenes, is demonstrated by the 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 monosubstituted 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.

(11) Steinmetz, H.; Gerth, K.; Jansen, R.; Schläger, N.; Dehn, R.; Reinecke, S.; Kirschning, A.; Müller, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 532.

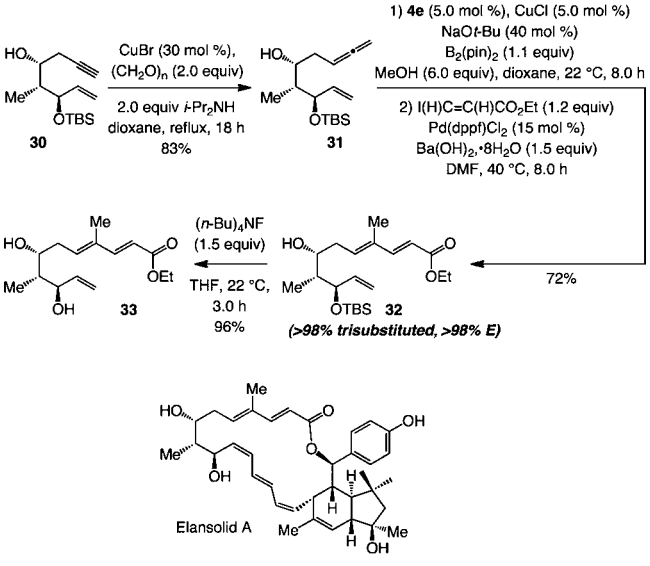
(12) See the SI for synthesis of alkyne **30**.

Scheme 2. Site Selective and *Z*-Selective Synthesis of Trisubstituted Vinylboron Compounds[a]



[a] >98% conv (allene disappearance) and >98% *Z* in all cases; same conditions as those 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



The observed selectivity trends, dictated by catalyst structure, can be rationalized by the pathways outlined in Figure 2, as supported by DFT calculations.[11] With either catalyst type (derived from **3** or **4e**), Cu–B addition

places the NHC−Cu initially at the less hindered site of the monosubstituted allene (→**i**). Subsequent γ-protonation via **ii**, the favorability of which is indicated by calculations,[11] 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**[11] (vs **ii**) to afford trisubstituted B(pin)-substituted alkenes (Curtin−Hammett kinetics). The greater reactivity of **iii** appears to be partially the result of the higher-energy HOMO of the more substituted Cu−C bond;[11] 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 controls the identity of the major product.

The proposal in Figure 2 offers an explanation for several 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 the γ-protonation rate (vs **ii**) to disfavor the Curtin−Hammett pathway.

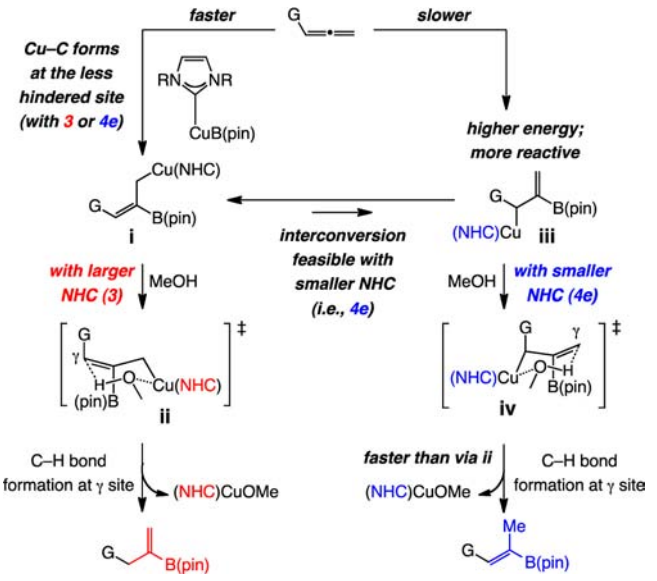
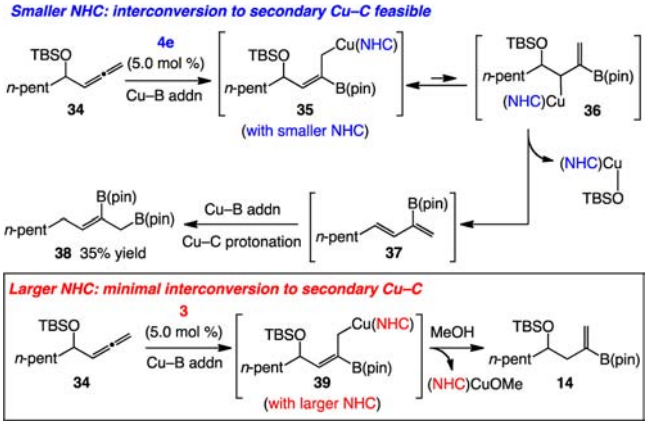


Figure 2. Rationale for the site selectivity trends; Curtin−Hammett kinetics with smaller NHC ligand **4e**.

Scheme 4. Effect of Site Selectivity on Efficiency



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

Acknowledgment. F.M. and B.J. contributed equally to this research. Financial support was provided by the NSF (CHE-1111074) and the NIH (GM-47480). We thank Hwanjong Jang (Boston College) for helpful discussions and Frontier Scientific for generous gifts of $B_2(pin)_2$.

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

The authors declare no competing financial interest.

(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 SI) and a recent report regarding the electronically related allylzinc systems by Okuda; see: Lichtenberg, C.; Engel, J.; Spaniol, T. P.; Englert, U.; Raabe, G.; Okuda, J. *J. Am. Chem. Soc.* **2012**, *134*, 9805. η^1-to-η^1 Interconversion 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 sizable bis-phophine−Cu complexes afford 1,1-disubstituted vinylboronates, whereas when monodentate phosphines are used trisubstituted isomers are formed predominantly; see ref 5.