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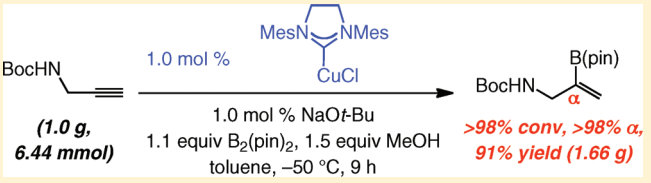
Highly Selective Methods for Synthesis of Internal (α-) Vinylboronates through Efficient NHC−Cu-Catalyzed Hydroboration of Terminal Alkynes. Utility in Chemical Synthesis and Mechanistic Basis for Selectivity

Hwanjong Jang, Adil R. Zhugralin, Yunmi Lee, and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

Supporting Information

ABSTRACT: Cu-catalyzed methods for site-selective hydroboration of terminal alkynes, where the internal or α-vinylboronate is generated predominantly (up to >98%) are presented. Reactions are catalyzed by 1−5 mol % of N-heterocyclic carbene (NHC) complexes of copper, easily prepared from *N*-aryl-substituted commercially available imidazolinium salts, and proceed in the presence of commercially available bis(pinacolato)diboron [$B_2(pin)_2$] and 1.1 equiv of MeOH at −50 to −15 °C in 3−24 h. Propargyl alcohol and amine and the derived benzyl, *tert*-butyl, or silyl ethers as well as various amides are particularly effective substrates; also suitable are a wide range of aryl-substituted terminal alkynes, where higher α-selectivity is achieved with substrates that bear an electron-withdrawing substituent. α-Selective Cu-catalyzed hydroborations are amenable to gram-scale procedures (1 mol % catalyst loading). Mechanistic studies are presented, indicating that α selectivity arises from the structural and electronic attributes of the NHC ligands and the alkyne substrates. Consistent with suggested hypotheses, catalytic reactions with a Cu complex, derived from an *N*-adamantyl-substituted imidazolinium salt, afford high *β* selectivity with the same class of substrates and under similar conditions.



INTRODUCTION

Vinylboron reagents, and vinyl(pinacolato)borons in particular, are employed in a range of C−C bond-forming reactions, including the widely utilized catalytic cross-coupling processes,[1,2] and are thus considered highly valuable entities in chemical synthesis. Whereas terminal or *β*-vinyl(pinacolato)borons can be prepared by a number of procedures, access to internal or α-vinylboronates is significantly more limited and the existing approaches involve stepwise and relatively demanding procedures. α-Vinylboronates may be synthesized by a three-step, two-vessel process that includes initial preparation of an α-vinyl halide, which is converted to the derived α-vinyllithiums and subsequently treated with isopropoxy(pinacolato)boron.[3] Alternatively, Pd-catalyzed cross-coupling in the presence of bis(pinacolato)diboron might be used to generate an internal vinyl−boron bond;[1e] formation of the requisite α-vinyl halides, however, requires strongly acidic conditions. α-Bromo alkenes, precursors to the aforementioned vinylmetals, can be obtained by reaction of an alkyne with BBr_3 and subsequent protonation of the terminal C−B bond with 15−20 equiv of HOAc, or through hydroiodination (HI generated in situ by reaction of TMSI with water).[4] As a result, α-vinylboron reagents that bear an acid-sensitive moiety cannot be utilized in the latter approach. Conversion of α-vinylhalides that carry an allylic C−N or C−O bond adjacent to the derived α-vinylmetals (such as vinylaluminums)[7] is usually not feasible because of facile and adventitious elimination reactions. Selective hydroboration of a terminal alkyne, especially one that is catalytic, would constitute one of the most direct routes for synthesis of an α-vinylboronate; such procedures, however, particularly the catalytic variants, have not been previously disclosed.[5,6]

Herein, we present a catalytic method for converting terminal alkynes to a variety of α-vinylboronates with high site selectivity (up to >98:2) and in up to 95% yield of the pure isomer (Scheme 1). Reactions are performed with bis(pinacolato)diboron [$(B_2(pin)_2$; **1**] and are efficiently catalyzed by N-heterocyclic carbene (NHC) complexes of Cu(I) obtained from *N*-aryl-substituted imidazolinium salts, which, similar to **1**, are commercially available. Terminal propargyl and α-amino alkynes, and their protected derivatives, as well as an assortment of aryl alkynes serve as effective starting materials; the earlier class of substrates cannot be utilized in the recently outlined Ni-catalyzed hydroalumination/boronate trap procedure.[7] We demonstrate that by altering the electronic attributes of the NHC−Cu complex, site selectivity can be controlled to the degree that either α- or *β*-vinylboronates are obtained in useful yields (Scheme 1); with catalysts derived from *N*-adamantyl-substituted imidazolinium salts, vinylboronates are obtained in up to >98% *β*-selectivity (vs strong preference for the α isomer with *N*-aryl-substituted

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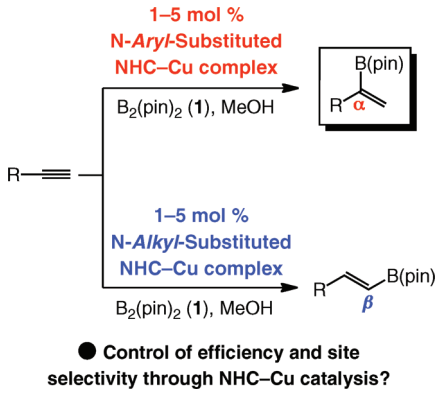
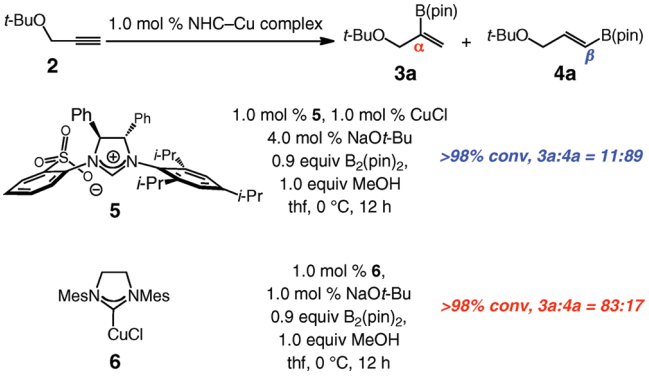
Scheme 1. Control of Site Selectivity in Cu-Catalyzed Hydroborations of Terminal Alkynes[a]



[a] $B_2(pin)_2$ = bis(pinacolato)diboron.

Scheme 2. Preliminary Observations



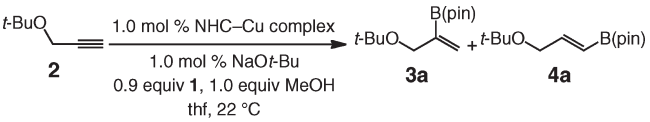
NHC−Cu complexes). We present a rationale for the unexpected α-selectivities and the dependence of selectivity on steric and electronic attributes of substrates and the NHC−Cu complexes.

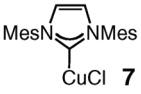
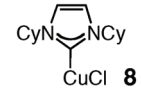
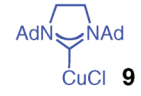
RESULTS AND DISCUSSION

1. NHC−Cu-Catalyzed α-Selective Hydroboration of Terminal Alkynes Derived from Propargyl Alcohol and Amine. *a. Initial Observations.* A key finding, which served as the foundation for the present investigations, emerged in the course of our studies regarding NHC−Cu-catalyzed double hydroboration of terminal alkynes, furnishing enantiomerically enriched diboronates.[8] Whereas Cu−B addition to propargyl ether **2**, catalyzed by the NHC−Cu complex derived from **5** and protonation of the resulting Cu−C (with MeOH), generates **4a** preferentially (**3a**:**4a** = 11:89), in the presence of monodentate NHC−Cu complex **6**, reaction proceeds with the *opposite* sense of selectivity, furnishing **3a** as the major isomer (**3a**:**4a** = 83:17, Scheme 2).

b. Examination of Various NHC−Cu Complexes. To explore further the aforementioned preference for generation of the α-vinylboronate, we examined the ability of a select number of monodentate NHC−Cu complexes to promote formation of **3a**. As the data summarized in Table 1 illustrate, reactions catalyzed by **7**−**9** (entries 2−4) give rise to larger amounts of the β-vinylboronate (vs entry 1). Although less efficient than the cyclohexyl-containing

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



entry	NHC–Cu	time	conv (%)[b]	3a:4a[b]
1	 **6**	30 min	>98	***77:23***
2	 **7**	30 min	80	50:50
3	 **8**	4.0 h	77	33:67
4	 **9**	24 h	33	***16:84***
5	 **10**	12 h	>98	***82:18***

[a] Reactions performed under N_2 atmosphere. [b] Conversion (based on **1** as the limiting reagent) and site selectivity (±2%) were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. Mes =2,4,6-Me_3-C_6H_2; Ad = adamantyl; Ar = 2,6-(i-Pr)$_2$-C_6H_3.

NHC−Cu (compare entries 3 and 4), bis(adamantyl)-based complex **9** delivers 84% of the β product isomer **4a**. In contrast, Cu complex **10** (entry 5), which bears a more sterically demanding 2,6-(i-Pr)$_2$-phenyl (vs 2,4,6-(Me)$_3$-phenyl or Mes), promotes transformation with 82:18 α:β selectivity.

c. α-Selective Hydroborations of Propargyl Alcohols, Amines and Derivatives with NHC−Cu Complex ***6***. When reactions were subsequently performed at lower temperature in order to improve selectivity, hydroborations with complex **6** remained reasonably efficient whereas those performed in the presence of the more discriminating **10** become too sluggish. For example, >98% conversion to **3a** is observed when **6** is used [thf, −50 °C, 5.0 mol % Cu−NHC complex, 5.0 mol % NaO*t*-Bu], affording **3a** in 84% yield (entry 1, Table 2); in contrast, there is <10% **3a** generated with **10** under the same conditions. As shown in Table 2, in addition to **3a**, α-vinylboronates bearing a benzyloxy (**3b**, entry 2), a *tert*-butyldimethylsiloxy (**3c**, entry 3) or the parent hydroxyl group (**3d**, entry 4) can be isolated in 84:16−93:7 α:β selectivity and 76−82% yield in >98% purity after routine silica gel chromatography.

Cu-catalyzed additions to propargyl amine (entry 5, Table 2) proceeds with similar α selectivity compared to the corresponding alcohol and ethers (entries 1−4, Table 2); attempts to purify **11a**, however, did not result in isolation of the desired product in appreciable yield.[9] When the derived amides are used (entries 6−8, Table 2), α-vinylboronates form with substantially higher preference (≥95% α) and in 73−93% yield after purification. Two additional points are worthy of note: (1) The reaction with the parent alcohol (entry 4) does not require the use of MeOH, suggesting that the hydroxyl group remains available through the

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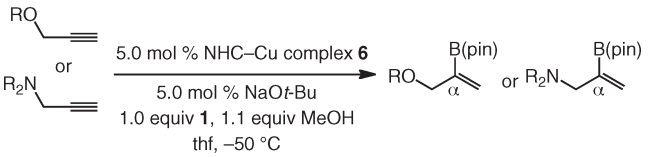
Table 2. α-Selective NHC−Cu-Catalyzed Hydroborations of Terminal Alkynes Bearing an Allylic O- or N-Based Substituent[a]



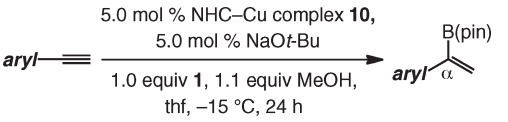
entry	major product	conv (%);[b] time (h)	α:β[b]	yield of pure α (%)[c]
1	t-BuO, B(pin) **3a**	>98; 9	89:11	84
2	BnO, B(pin) **3b**	93; 3	84:16	76
3	TBSO, B(pin) **3c**	>95; 24	85:15	78
4	HO, B(pin) **3d**	96; 21	93:7	82[d]
5	H_2N, B(pin) **11a**	69; 3	83:17	nd[e]
6	BocHN, B(pin) **11b**	>98; 9	>98:2	93
7	TsHN, B(pin) **11c**	92; 24	>95:5	73
8	PhthN, B(pin) **11d**	>95; 24	>98:2	79

[a] Reactions performed under N_2 atmosphere. [b] Conversion and site selectivity (±2%) were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. [c] Yields of isolated α isomer products (±5%). [d] MeOH was not used in this transformation; reaction quenched by addition of 4.0 N HCl in dioxane/MeOH. [e] Yield of isolated material not determined because of product instability to purification procedures.

course of the reaction to serve as the proton source (vs rapid conversion to the derived boronic ester by reaction with **1** prior to Cu−B addition). In contrast, hydroboration with propargyl amine requires the presence of MeOH, indicating that an amine is either not sufficiently acidic to protonate the vinylcopper intermediate or the resulting NHC−Cu-amide does not readily react with **1** to cause catalyst turnover.[10] (2) The products formed in reactions shown in Table 2 cannot be accessed by the previously mentioned Ni-catalyzed hydroalumination/methoxy(pinacolato)boron trap, presumably because of facile and adventitious elimination.[7] The alternative approach involving a vinyllithium (vinyl halide metal/halogen exchange/treatment with a boron-based electrophile) would suffer from the aforementioned complications with neighboring heteroatom substituents and require initial site-selective preparation of an α-vinyl halide (see above for associated drawbacks).[11]

2. NHC−Cu-Catalyzed α-Selective Hydroboration of Aryl- and Heteroaryl-Substituted Terminal Alkynes. Terminal aryl alkynes (entries 1−15, Table 3), including those containing a heterocyclic substituent (entries 16 and 17, Table 3), undergo Cu-catalyzed hydroboration in up to 96:4 α selectivity. Various types of α-vinylboronates can thus be obtained directly and in

Table 3. α-Selective NHC−Cu-Catalyzed Hydroborations of Aryl-Substituted Terminal Alkynes[a]



entry	aryl	conv (%)[b]	α:β[b]	yield of pure α (%)[c]
1	Ph	94	88:12	78
2	o-FC_6H_4	98	94:6	87
3	o-ClC_6H_4	79	91:9	72
4	o-BrC_6H_4	81	91:9	73
5	o-$CF_3C_6H_4$	54	83:17	35
6	o-MeC_6H_4	76	70:30	51
7	o-$MeOC_6H_4$	78	41:59	nd[d]
8	m-FC_6H_4	>98	94:6	78
9	m-$CF_3C_6H_4$	64	89:11	52
10	m-$MeOC_6H_4$	86	79:21	67
11	p-FC_6H_4	53	87:13	45
12	p-BrC_6H_4	85	91:9	73
13	p-$CF_3C_6H_4$	79	96:4	70
14	p-$NO_2C_6H_4$	89	91:9	71
15	p-$MeO_2CC_6H_4$	69	92:8	61
16	2-pyridyl	61	90:10	nd[d]
17	3-thienyl	89	78:22	nd[d]

[a−c] See Table 2. [d] nd = not determined because of complication in isolation.

high purity (<2% contamination with the β isomer) from the terminal alkynes in 35−87% yield. Several features of this class of transformations are noteworthy:

(1) High selectivity in reactions with aryl-substituted alkynes requires the less active but more discriminating 2,6-(*i*-Pr)$_2$phenyl-substituted NHC−Cu complex **10** (vs mesityl-substituted **6**; see Table 1). As illustrated in Table 3, reactions proceed to useful levels of conversion when performed at −15 °C, affording α-vinylboronates in high selectivity.

(2) Although, in many cases, site selectivities shown in Table 3 do not vary to a significant degree, a brief analysis of variations as a result of the electronic attributes of the aryl groups is warranted. Electron-withdrawing aryl substituents, such as those that attract electrons through σ-bond framework as well as those that do so through resonance, generally give rise to higher α selectivity. Reactions of alkynes bearing an *o*-F and a *p*-F unit proceed with 94% and 87% α selectivity, respectively (entries 2 and 11, Table 3); with the electronegative halogen more proximal to the alkyne, α:β ratio is improved, underscoring the significance of the inductive effect. As another example, the reaction in entry 9, involving *m*-trifluoromethylphenylacetylene, is less discriminating (89% α) than that shown in entry 13, where the same substituent resides at the para position (96% α); in the latter case, stronger electron withdrawal is likely due to aryl $\pi \rightarrow \sigma^*_{C-F}$ donation. However, the influence of inductive effects is not always straightforward. For instance, as expected, with the less electronegative bromide (vs fluoride), somewhat lower α-selectivity is observed in reactions with alkynes that carry the

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halogen at the ortho position (91% vs 94% α, respectively; entries 2 and 4, Table 3); however, an alkyne with an *p*-Br unit is slightly more selective than one that contains an F atom at the same site (91% vs 87% α, respectively; entries 11 and 12, Table 3).

The negative impact of π-donor aryl units on α selectivity is manifested in the transformations shown in entries 7 and 10 of Table 3, involving the less discriminating reactions with substrates that contain a methoxy-substituted aryl groups (41:59 and 79:21 α:β for *o*- and *m*-MeO-phenylacetylene, respectively).[12] When *p*-methoxyphenylacetylene serves as the substrate (not shown, but the same conditions as in Table 3), only 62% α-selectivity is observed even when NHC−Cu complex **10** is used (58% conv). In contrast, reactions with alkynes that bear a *p*-NO_2 or *p*-carboxylic ester are significantly more α-selective (91−92% α; entries 14 and 15). The importance of electronic effects is further underlined by comparison of the data in entries 6 and 7: the smaller *o*-methoxy substituent leads to a preference for the β-vinylboronate (41:59 α:β) compared to the alkyne that carries an *o*-methylphenyl unit (70:30 α:β). Similar to the aforementioned inductive effects, changes in selectivities in Cu−B additions to aryl alkynes that bear a π-acceptor group are, at times, difficult to explain. As an example, there is a relatively small difference in selectivity between reaction of phenylacetylene (89% α; entry 1, Table 3) and *p*-nitrophenylacetylene (91% α; entry 14, Table 3). Considering that π-acceptor groups are typically expected to exert a stronger influence, it is curious that highest α-selectivity is observed in the case of an alkyne with a *p*-trifluoromethyl unit. It should be noted that, despite the recondite variations in selectivity, the data in Table 3 does point to the general trend that donor groups favor β selectivity and higher percentage of α-vinylboronates are formed with electron-withdrawing substituents.

(3) Steric effects play a notable role as well. For example, *o*-trifluoromethylphenylacetylene (entry 5) undergoes catalytic hydroboration to afford the α isomer with 83% selectivity, whereas the transformation with the substrate bearing a *p*-trifluoromethyl unit proceeds with 96:4 α:β selectivity (entry 13). Presumably, the stronger inductive effect of the more proximal *o*-CF_3 group is counterbalanced by the steric repulsion generated due to formation of a C−B bond involving a relatively sizable (pinacolato)-boron substituent at the benzylic site (repulsion between B(pin) and *o*-CF_3Ph). Mechanistic discussions and the significance of electronic and steric factors are provided below.

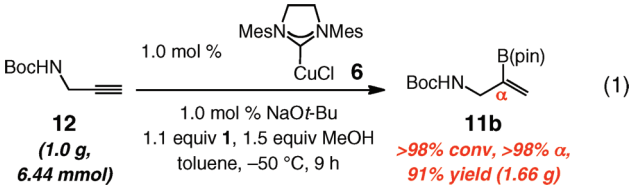
3. Complementarity of the Cu-Catalyzed Hydroboration with Ni-Catalyzed Hydroalumination/Boronate Trap Protocols to Access α-Vinylboronates. A comparison of the methods outlined above with the recently reported Ni-catalyzed alkyne hydroalumination/C−B bond formation [addition of methoxy(pinacolato)boron] developed in these laboratories[7] is warranted. Overall, the Ni(dppp)- and NHC−Cu-catalyzed protocols are complementary in connection with α-vinylboronate synthesis. The advantages of the present approach are two-fold:

(1) In contrast to the Cu-catalyzed hydroboration, with propargyl alcohol, propargyl amine and the related derivatives serving as the substrate (see Table 2), the Ni-catalyzed reactions are ineffective, presumably because of adventitious elimination of the intermediate vinylaluminum. Under the latter conditions, substrates are consumed entirely but desired products are not obtained (<5%).

(2) In cases where the substrate bears a functional group that can be concomitantly reduced by dibal-H, such as those shown in entries 14 and 15 of Table 3, the NHC−Cu-catalyzed hydroboration is the protocol of choice.

The catalytic hydroalumination protocol is preferred in certain cases. Higher α-selectivities are achieved through the Ni(dppp)-catalyzed hydroalumination/C−B formation when aryl alkynes are used[7] (95:5 to >98:2 α selectivity vs findings in Table 3). Ni-catalyzed hydrometalation is particularly effective with alkyl-substituted alkynes. For example, with homopropargyl alcohol (see eq 3, below), reaction in the presence of **6** affords 61% of the β-vinylboronate (−50 °C, toluene, 20 h, 81% conv); in contrast, there is 95% α-selectivity in the reaction of the same substrate with dibal-H, and 3 mol % Ni(dppp)Cl_2 [pure α-vinylboronate is isolated in 82% yield after treatment with methoxy(pinacolato)boron].[7]

4. The Utility of Cu-Catalyzed α-Selective Alkyne Hydroboration. *a. Cu-Catalyzed Alkyne Hydroboration on Gram Scale.* The present protocols are easy to perform; in addition to bis(pinacolato)diboron, the imidazolinium and imidazolium salts are air stable and commercially available, and the NHC−Cu complexes can be easily prepared.[13] The Cu-catalyzed processes are amenable to gram scale procedures; the example shown in eq 1 is illustrative. Only 1.0 mol % of the readily accessible NHC−Cu complex and 1.1 equiv of $B_2(pin)_2$ suffice, affording vinylboronate **11b** in 91% yield after purification with exclusive α selectivity (>98% α).



b. An Efficient Route for Conversion of Terminal Alkynes to Methyl Ketones. As stated above, the most significant utility of α-vinylboronates accessed through the NHC−Cu-catalyzed method relates to various metal-catalyzed cross-coupling reactions.[1] Additionally, the present protocol offers a convenient route for the conversion of terminal alkynes to the corresponding methyl ketones, in a net transformation that is analogous to the Pd-catalyzed Wacker oxidations performed with alkenes.[14] The example presented in Scheme 3 is illustrative. Catalytic hydroboration of the terminal alkyne that resides within enyne **13** proceeds to afford **14** in 95% yield after purification with >98% α selectivity and with exceptional chemoselectivity (<2% reaction of the alkene). Subsequent oxidation delivers methyl ketone **15** in 82% yield. The Cu-catalyzed hydroboration and the follow-up oxidation may be performed in a single vessel, without isolation or purification of the α-vinylboronate **14**, affording **15** in 69% yield after purification.

c. Synthesis of Cyclic Vinylboronates through Sequential Cu-Catalyzed Hydroboration/Ru-Catalyzed Ring-Closing Metathesis. The availability of α-selective catalytic hydroboration of alkynes can be utilized toward preparation of cyclic vinylboronates that would otherwise be less easily accessible.[15] The example shown in Scheme 4 is illustrative. α-Vinylboronate **17**, obtained in 88% yield and >98% site selectivity through Cu-catalyzed hydroboration of enyne **16**, is converted to cyclic vinylboronate **19** in 71% yield by ring-closing metathesis promoted by 5 mol % Ru carbene **18**.[16]

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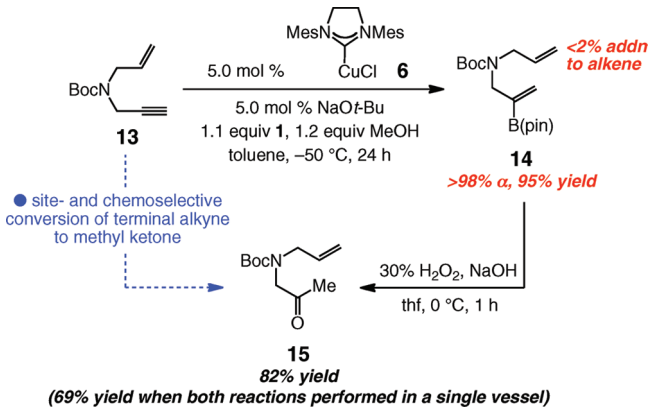
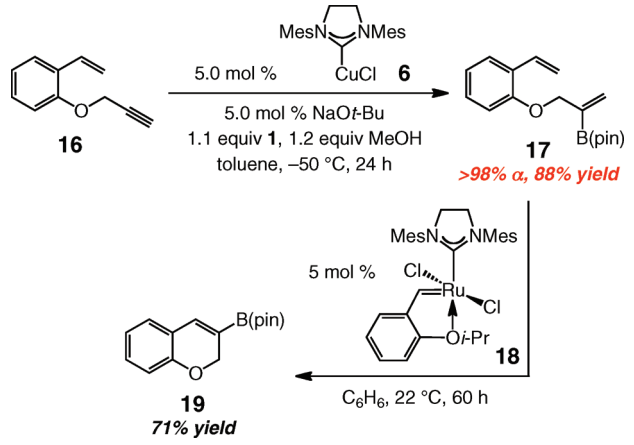
Scheme 3. Site- and Chemoselective NHC−Cu-Catalyzed Hydroboration of an Enyne. Conversion of a Terminal Alkyne to a Methyl Ketone



Scheme 4. Synthesis of Cyclic Vinylboronates

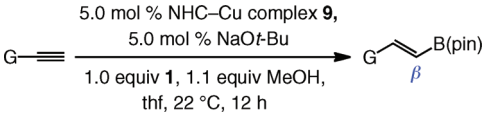


It should be noted that synthesis of **19** through alternative procedures, such as Pd-catalyzed cross-coupling with $B_2(pin)_2$ (**1**),[17] would require a vinyl halide or an enol triflate substrate, selective synthesis of which might prove to be less than straightforward.

5. β-Selective NHC−Cu-Catalyzed Hydroborations of Terminal Alkynes. Several strategies have been developed for synthesis of terminal vinyl(pinacolato)borons. β-Selective hydroborations of terminal alkynes by reaction with catecholborane,[18] di(isocamphenyl)borane,[19] pinacolatoborane,[20] or di(isopropylprenyl)borane[21] have been reported. There are methods for synthesis of β-vinylboronates through Rh-catalyzed dehydrogenative borylation.[22] Boron hydride additions to terminal alkynes promoted by Rh, Ir,[23] Ti,[24] or Zr[25] complexes have been disclosed as well. Reactions of vinylmetal reagents with B-based electrophiles is another strategy for accessing terminal vinylboronates.[26] The aforementioned Pd-catalyzed cross-coupling with enol triflates or halides[17] and Ru-catalyzed cross-metathesis[27] are catalytic protocols that can furnish β-vinylboronates from alkene-containing substrates.

Initial screening of representative NHC−Cu complexes (cf. Table 1) indicated that when *N*-adamantyl-substituted **9** is used, high β selectivity is observed in the reaction with *tert*-butylpropargyl ether **2** (84% β at 22 °C). Although a number of β-selective alkyne hydroborations have been previously reported,[18−27]

Table 4. β-Selective NHC−Cu-Catalyzed Hydroborations of Terminal Alkynes Promoted by NHC−Cu Complex 9[a]



entry	G	conv (%)[b]	α:β[b]	yield of pure β (%)[c]
1	Cl	85	18:82	63
2	MeO_2C	85	19:81	64
3	*c*-pent	83	11:89	65
4	*t*-$BuOCH_2$	>98	12:88	80
5	$HOCH_2$	82	13:87	65[d]
6	$PhthNCH_2$	84	27:73	56
7	$TsHNCH_2$	82	13:87	70
8	Ph	89	<2:>98	81
9	*o*-FC_6H_4	>98	7:93	80
10	*o*-$CF_3C_6H_4$	90	5:95	71
11	*o*-MeC_6H_4	90	3:97	75
12	*o*-$MeOC_6H_4$	95	<2:>98	88
13	*m*-$CF_3C_6H_4$	82	<2:>98	78
14	*p*-$CF_3C_6H_4$	82	<2:>98	80

[a−b] See Table 2. [c] Yields of isolated β isomer products (±5%). [d] MeOH was not used in this transformation; reaction quenched by addition of 4.0 N HCl in dioxane/MeOH.

we judged that establishing the generality of such Cu-catalyzed processes would be valuable for two reasons: (1) The trends in reactivity and selectivity might be useful for establishing the origins of α-selective variants promoted by NHC complexes **6** and **10** (detailed below). (2) The catalytic transformations described in this study represent more than a hydroboration process; protonation of the intermediate vinylcopper is only one of several possible modes of functionalization. Catalytic reactions that place a (pinacolato)boron at the terminal (β) carbon and a Cu−NHC at the internal site of a terminal alkyne may be trapped by other classes of electrophiles, allowing access to a range of valuable organic molecules. Investigations along these lines are in progress.

A variety of terminal alkynes undergo β-selective reactions at ambient temperature within 12 h to afford the desired vinylboronates after purification in up to 88% yield and >98% selectivity (Table 4). Appreciable site selectivities (81−89% β) are observed in transformations with alkyl-substituted acetylenes (entries 1−3, Table 4) and substrates derived from propargyl alcohol and amine (73−88% β, entries 4−7), allowing the corresponding β-vinylboronates to be isolated in 56−80% yield. β selectivities are higher when arylacetylenes are employed as substrates (93% to >98% β, entries 8−14).

6. Chemoselectivity of NHC−Cu-Catalyzed Hydroboration of Terminal Alkynes. As was described previously,[28] olefins that do not bear an aryl or a (pinacolato)boron substituent do not undergo NHC−Cu-catalyzed hydroboration; in contrast,

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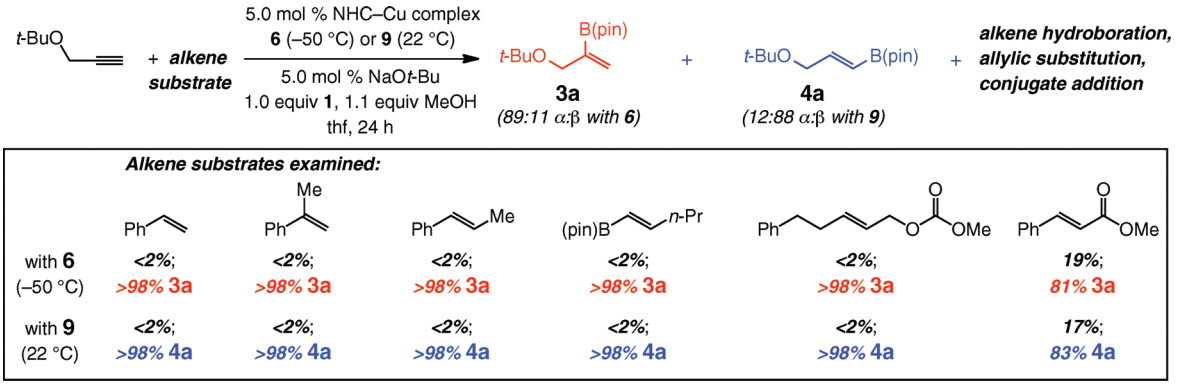
Scheme 5. Chemoselectivity in NHC−Cu-Catalyzed Hydroboration Reactions



and as illustrated above, alkynes bearing an alkyl unit can serve as effective substrates. Such difference in reactivity is manifested in the complete chemoselectivity observed in the reaction of enyne **13**, illustrated in Scheme 3. A more competitive scenario involves transformations of alkynyl substrates in the presence of alkenes that do participate in NHC−Cu-catalyzed hydroborations.[28−30] As summarized in Scheme 5, regardless of whether Cu complex **6** or **9** is used, transformation with a terminal alkyne appears to be significantly more efficient than styrene, α- or β-methylstyrene,[28a] α-vinylboronate,[28b] an allylic carbonate,[29] or an α,β-unsaturated carboxylic ester.[30] These findings bode well for applications where site-selective functionalization of a polyfunctional substrate is required.

7. Mechanistic Basis for Site Selectivity in NHC−Cu-Catalyzed Hydroboration of Terminal Alkynes. The original observation regarding the preference for formation of α-vinylboronates with monodentate NHC−Cu catalysts was somewhat unexpected, since Cu-catalyzed processes involving other substrate classes, including those promoted by NHC-based complexes, exhibit preference for the formation of β isomers. Indeed, NHC−Cu-mediated reactions of mono-[31] and NHC−Cu-catalyzed processes with disubstituted styrenes[32] afford β-boryl products exclusively.[33] To elucidate the origins of the unusual α-selectivities, we first set out to identify factors that govern site selectivity in NHC−Cu-catalyzed C−B bond formation. These initial investigations are summarized below, followed by a scheme proposed to account for the origin of selectivity in α- as well as β-selective catalytic hydroborations. The studies detailed below will illustrate that site selectivity in Cu−B additions to alkynes depends not only on the steric and electronic attributes of the NHC ligands, but also on the steric and electronic characteristics of the alkyne substrates; it is as a result of subtle balance involving all the aforementioned factors that site selectivity is determined. Two additional points regarding our mechanistic investigations should be noted: (1) Our studies suggest that, unlike reactions with alkenes, in transformations promoted by aryl-substituted NHCs and involving substrates derived from propargyl alcohol and amine as well as aryl alkynes, Cu complex association with the substrate molecule may be product-determining. (2) Although similar to processes with olefins, it appears that, overall, the alkyne serves as the electrophilic component, factors involving donation of electrons from the acetylene π-cloud to the available low energy orbitals of the transition metal must also be considered.

a. The Identity of the Product-Determining Event. As the first step toward developing a plausible mechanistic model, we set out to ascertain that the identity of the hydroboration reactions is not due to thermodynamic difference between the two Cu−B addition products; rather it is either the coordination or the insertion step that determines the identity of the predominant isomer. As shown in Scheme 6, crossover experiments point to the Cu−B addition to an alkyne as being irreversible.[34] It is therefore likely that the identity of the major vinylboronate isomer is not due to rapid protonation of the C−Cu bond of one of the two intermediate isomers (e.g., **21** in Scheme 6) by the proton source (MeOH in the catalytic processes).[35] Consistent with the latter findings, computational investigation of the mechanism indicate that formation of insertion products **21** and **22** is strongly exoergic (ΔG° between −36.4 and −43.8 kcal/mol); the reverse reaction is thus not likely to occur.[13] Furthermore, and importantly, computational studies of substrate coordination to copper, involving an *aryl-substituted* alkyne, and the subsequent insertion step indicates that *catalyst−substrate association is product-determining*.[13]

b. Correlation of Electron-Donating Ability of the NHC Ligands to Site Selectivity. At this juncture, we sought to elucidate factors that cause reactions performed in the presence of alkyl-substituted NHC−Cu complexes (**8** and **9**) to afford β-vinylboronates predominantly but favor generation of the α isomers with aryl-substituted NHC (**6** or **10**; Table 1). We thus examined the correlation between α:β ratios and the electronic characteristics of the NHC ligands; the results of these studies are depicted in Figure 1. Since the electron-donating ability of an NHC is inversely proportional to Tolman electronic parameter (TEP), the data are presented with inverted TEP values.[36] The analysis illustrated in Figure 1 points to an inverse correlation between α:β product ratios and the ability of the carbene ligands to serve as two-electron donors. That is, the more Lewis basic NHC−Cu complex (i.e., alkyl-substituted NHCs) promote preferential formation of the β-vinylboronates, whereas α products are preferred with catalysts that carry the less donating variants (i.e., Ar-substituted NHC ligands).

*c. Correlation of Electronic Attributes of Alkyne Substituents to α Selectivity in Reactions with NHC−Cu Complexes **6** or **10**.* Analysis of the data presented in Tables 2−4 underscores the sensitivity of the product distribution to electronic characteristics of the substrates and the NHC ligands used in generating the Cu-based catalysts. We therefore investigated the effect of the electronic attributes of the aryl alkyne substrates on the level and direction of site selectivity. We limited our analysis to the

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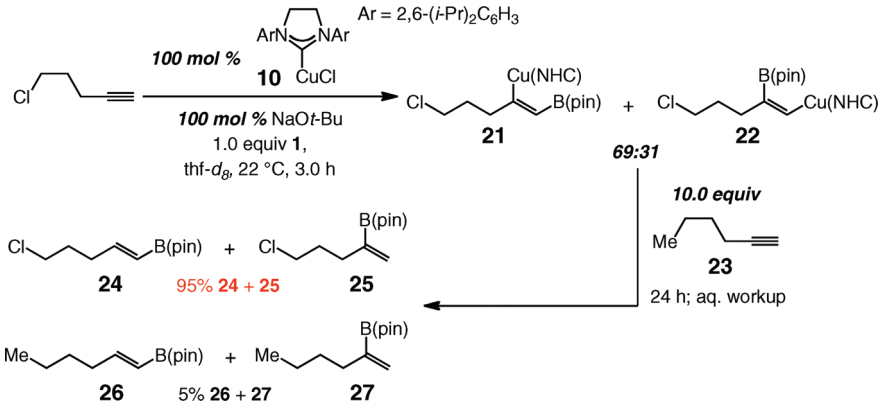
Scheme 6. Crossover Experiment To Investigate the Reversibility of the Cu−B Addition Step in the Related NHC−Cu-Catalyzed Processes[a]



[a] Product ratios were determined by analysis of the 400 MHz ^{1}H NMR spectra of the unpurified product mixtures.

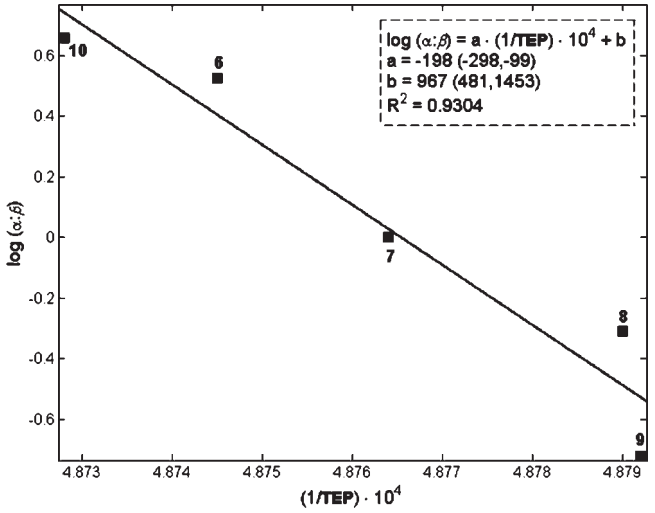


Figure 1. Correlation of α:β vinylboronate ratios to inverse Tolman electronic parameters (TEP) for various NHC ligands. Values in parentheses are the 95% confidence interval; numbers correpond to the NHCs (cf. Table 1) of the Ni complexes for which measurements were made.

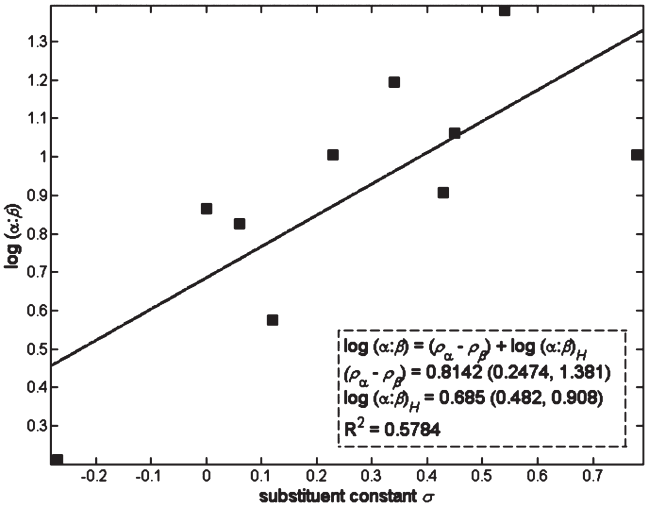


Figure 2. Correlation of α:β vinylboronate ratios to substituent constants (σ). Values in parentheses correpond to 95% confidence interval.

data for Cu−B additions promoted by *N*-aryl-containing complexes **6** or **10**, since the high selectivities with aryl-substituted alkynes obtained through transformations with adamantyl-substituted Cu complex **9** (≥93% β; Table 4, entries 8−14) do not permit for extraction of significantly meaningful ratios.

The stereoelectronic effects of aryl-alkyne substituents were gauged through the use of a Hammett equation.[37] Although, detailed kinetic studies have not been performed, ratios of α and β products represent the data for a competition experiment. Subtraction of the Hammett equation derived for β-vinylboronates from that which corresponds to the formation of α product isomers furnishes an equation that relates electronic properties of the aryl substituents to site selectivity. As shown in eq 2:

$$\log(\alpha{:}\beta) = \sigma(\rho_\alpha - \rho_\beta) + \log(\alpha{:}\beta)_H \qquad (2)$$

where α:β is a product molar ratio, ρ_α is the reaction constant for a pathway that results in the formation of the α-vinylboronate, ρ_β corresponds to the constant relating to a transformation that affords the β isomer, and $\log(\alpha{:}\beta)_H$ corresponds to α:β ratio generated through NHC−Cu-catalyzed reaction of phenylacetylene. The resulting Hammett plot is illustrated in Figure 2.

The positive value obtained for $\rho_\alpha - \rho_\beta$ (i.e., $\rho_\alpha > \rho_\beta$; see Figure 2) arises from preferential formation of α-vinylboronates in reactions of alkynes containing an electron-withdrawing substituent [Table 3; see discussion above (Section 2), regarding the influence of electronic factors on α selectivity].[38] Furthermore, the experimentally determined $\rho_\alpha = +1.55$ translates to $\rho_\beta = +0.74$ based on the equation shown in Figure 2. The above considerations suggest that, *overall*, and regardless of the trend in site selectivity, an alkyne serves as the electrophilic entity in NHC−Cu-catalyzed additions. Nonetheless, such an effect should be viewed as the *net* outcome of different substrate−catalyst interactions (electron reorganization or electrostatic as well as charge transfer or covalent);[39] that is, associations that represent electron flow from the alkyne to the NHC−Cu complex, such as donation from the alkyne π cloud to the low-lying Cu s orbital (see Scheme 8), should also be considered.[40] Accordingly, we turned to identifying additional electronic parameters, particularly those that correspond to the overlap of frontier orbitals (i.e., covalent

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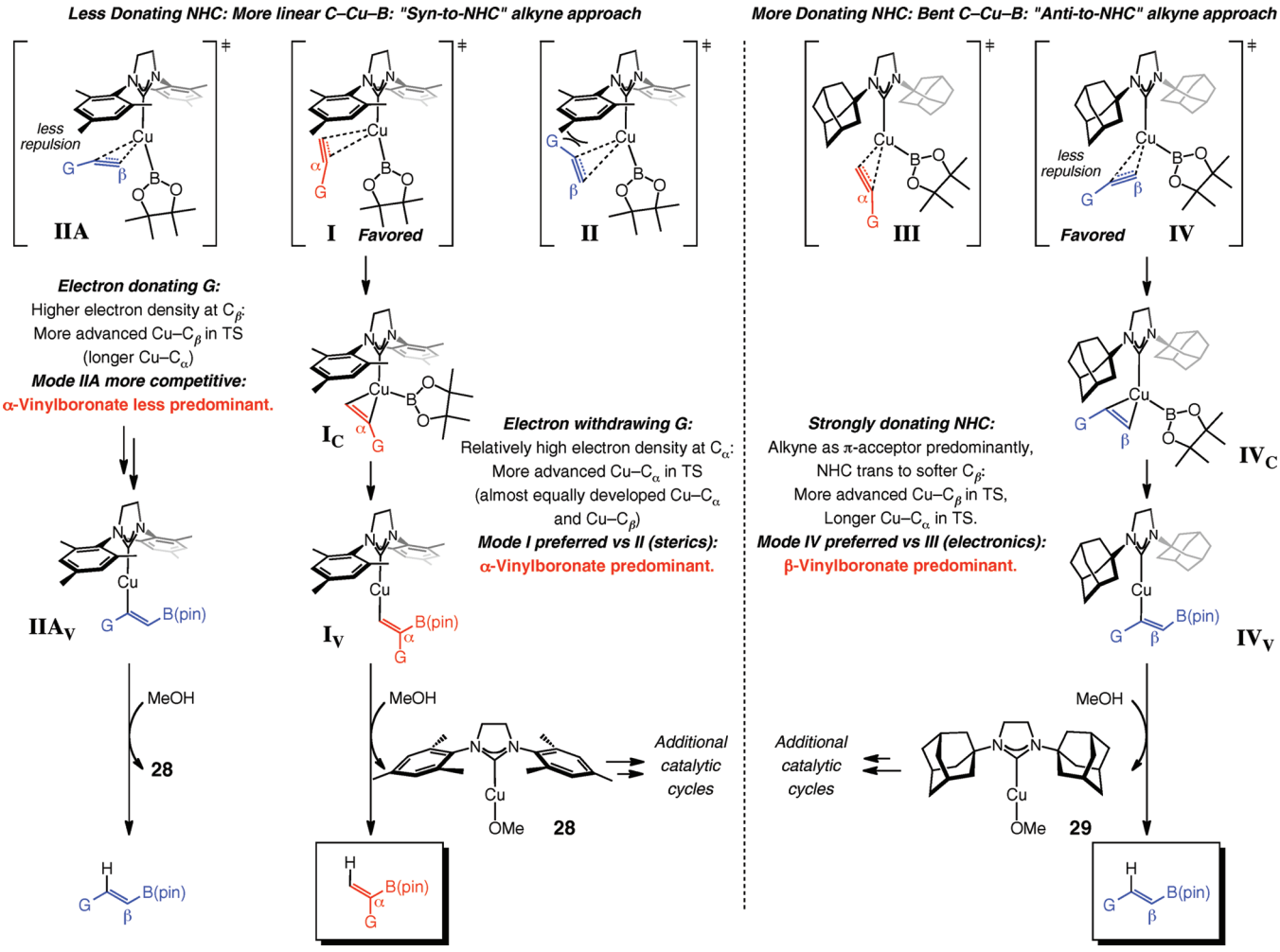
Scheme 7. Electronic and Steric Effects Influence the Sense and Level of Selectivity in NHC−Cu-Catalyzed Cu−B Additions to Terminal Alkynes



interactions) and which can influence product distribution. We calculated local softness indices for the alkyne's two carbon atoms in the substrates shown in Table 3.[41] The softness index of an atom provides an estimate of the degree to which bond formation involving the said atom has advanced in a transition state (e.g., s_α = softness index at C_α);[42] nucleophilic or electrophilic softness index (e.g., s^- or s^+) can serve as qualitative measurement of the HOMO or LUMO coefficient,[39] respectively, at that particular atom. Thus, s_α^-:s_β^- estimates the contribution of Cu−C_α and Cu−C_β bond formations to the overall energy of the transition state for alkyne coordination to an NHC−Cu complex, where the substrate serves as the electron donor.

In all cases, we find that s_α:s_β < 1,[13] indicating that an asynchronous coordination transition state is operative wherein the Cu−C_α bond is less advanced than the Cu−C_β bond. The log(α:β) values were plotted versus s_α^-:s_β^-, as illustrated in Figure 3, allowing us to identify a correlation between the experimental α:β and calculated s_α^-:s_β^- ratios. These measurements imply that C_α−B bond formation is more favored (higher α selectivity is observed) in reactions which involve alkynes possessing increased electron density at their C_α and that can proceed via transition states that more easily accommodate such an attribute. The aforementioned considerations suggest that the incipient Cu···C_α is longer than Cu···C_β, but *to varying degrees*: elevated s_α^-:s_β^- ratios (i.e., larger electron density at the C_α) indicate that Cu···C_α is relatively more advanced (shorter) and bond formation at both carbon atoms is similarly developed in the corresponding transition states. Comparison of α:β ratios to s_α^+:s_β^+ values gives an inverse correlation as well, albeit with a low coefficient of determination (R^2 = 0.0657).[13] The significance of the above findings, vis-à-vis the suggested model for the selectivity trends, is described above (Scheme 7).

d. Proposed Mechanistic Scenarios Accounting for the Observed Site Selectivities. Plausible pathways for the generation of α-vinylboronates in reactions performed with NHC−Cu **6** or **10** derived from *N*-aryl-substituted imidazolinium salts (via **I**→$\mathbf{I_C}$→$\mathbf{I_V}$) as well as β-vinylboronates, generated in transformations with complex **9** (via **IV**→$\mathbf{IV_C}$→$\mathbf{IV_V}$), are illustrated in Scheme 7.[43] In the case of less electron-donating *N*-aryl-substituted NHC−Cu complexes and terminal alkynes with an electron-withdrawing group, the mode of coordination represented by **I** is favored (vs **II**), where steric repulsion between the alkyne substituent (G) and the large NAr moieties of the NHC are destabilizing elements. The size of the NAr unit accounts for the faster rate but lower selectivity observed with **6** compared to

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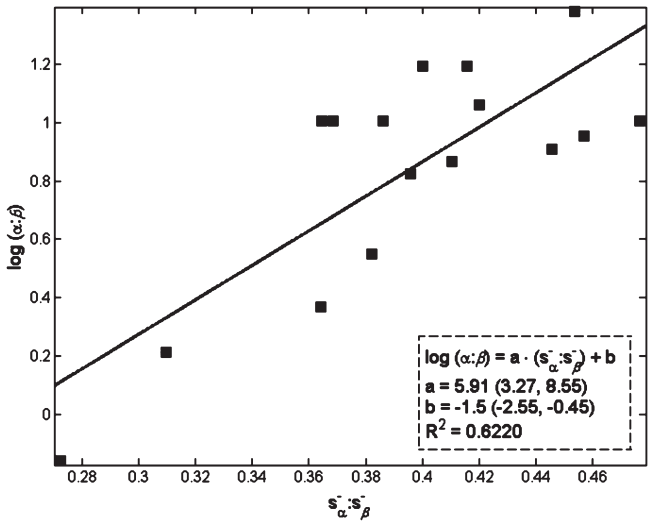
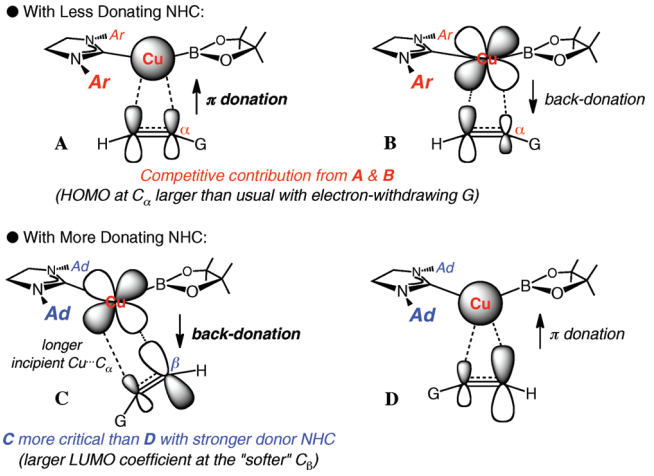


Figure 3. Correlation of α:β vinylboronate product to s_α^-:s_β^- ratios. Values in parentheses correpond to 95% confidence interval.

Scheme 8. Interactions Involving Cu and Alkyne Frontier Orbitals[a]



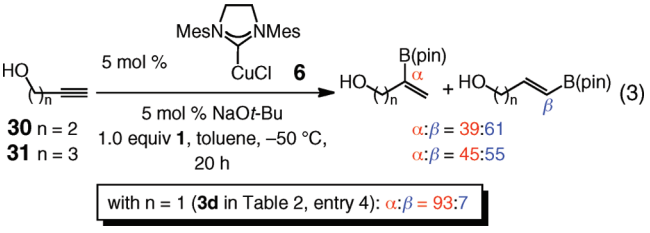
[a] Ar = 2,4,6-$Me_3C_6H_2$ or 2,6-$(i\text{-Pr})_2C_6H_3$; Ad = adamantyl.

10 (Mes vs $(i\text{-Pr})_2$Ph-substituted NHC; see entries 1 and 5 of Table 1). The transformation may proceed via metallacyclopropene $\mathbf{I_C}$,[44] which is subsequently converted to (pinacolato)boron-substituted vinylcopper $\mathbf{I_V}$; in situ protonation of $\mathbf{I_V}$ affords the α-vinylboronate product, regenerating NHC−Cu−OMe complex **28**, which can initiate additional catalytic cycles.

Based on the Dewar−Chatt−Duncanson model,[45] and as mentioned previously, coordination of an alkyne to a Cu atom involves donation of electron density from the π C≡C (**A** or **D**, Scheme 8) as well as back-donation from the transition metal to the alkyne π^* (**B** or **C**, Scheme 8) in various degrees of significance. We emphasize such dual interaction through depiction of the intermediacy of metallacyclopropenes $\mathbf{I_C}$ and $\mathbf{IV_C}$ (Scheme 7).[44] In the case of complex **I**, involving a relatively less electron-donating NHC (vs the more Lewis basic adamantyl-substituted variant), π-donation from the alkyne to the Cu s-orbital plays a more dominant role (**A**, Scheme 8 vs **B**, involving donation from Cu d-orbital to the alkyne π^*). Since, as described above, C_β is softer (possesses a larger HOMO coefficient), a more advanced Cu···C_β bond can be expected in the transition state (**I**) leading to metallacyclopropene $\mathbf{I_C}$. As depicted in Schemes 7 and 8 (**I** and **A**, respectively), the net result is a *relatively* symmetric transition state, because with an electron-withdrawing substituent (G = CH_2OR, CH_2NR_2 or aryl), there is enhanced electron density at C_α, which causes more similar HOMO coefficients at the two alkynyl carbons (softness index ratios closer to unity). The proposed scenario may be considered from a different vantage point: as C_β is "softer", dissipation or accumulation of electron density at C_α and C_β is *not* equivalent; electronic alteration, regardless of its origin, is stronger at the alkyne's β carbon. The influence of a substrate's electronic attributes is therefore more pronounced at the C_β, engendering a stronger lack of electron density at the β carbon with an electron-withdrawing alkyne substituent; this leads to a similar level of electron density at the two carbon sites and a relatively symmetric transition state (**I**).

The presence of electron-donating alkyne substituents translate to diminution in α selectivities (Tables 2 and 3). Increased electron density at C_β may result in a higher HOMO coefficient at this site and a relatively less advanced Cu···C_α, as depicted in **IIA** (Scheme 7); such electronic variation, originating from the alkyne substituent, leads to a longer Cu···C_α and amelioration of the steric factors in **I**, responsible for preferential generation of α-vinylboronates. Reduced α selectivities are thus observed with methoxy-substituted phenylacetylenes (41:59 and 79:21 α:β with *o*- and *m*-methoxy substitution, respectively; entries 7 and 10, Table 3).

The above considerations offer an explanation for the low α selectivity in catalytic addition to *o*-tolyl alkyne (70:30 α:β; entry 6, Table 3); in comparison, it is likely due to the aforementioned electronic effects that reaction with the alkyne bearing the electron-withdrawing *o*-trifluoromethylphenyl group, despite the larger substituent (CF_3 vs Me), leads to a stronger preference for the derived α isomer (83:17 α:β in entry 5, Table 3 vs 70:30 in entry 6). To challenge the validity and/or establish further evidence in support of the proposed scenario, we carried out the additional transformations depicted in eq 3. In contrast to processes with propargyl alcohol and derivatives (entries 1−4, Table 2), reactions of homopropargyl alcohol (**30**, eq 3) and bis(homopropargyl) alcohol (**31**, eq 3) are substantially less selective (39:61 α:β and 45:55 α:β, respectively, vs 93:7 α:β obtained for propargyl alcohol; Table 2, entry 4).[46] Thus, by the same token, reactions of propargyl ethers in entries 1−3 of Table 2 (84:16−89:11) are less selective than the propargyl amides illustrated in entries 6−8 of the same table (>95:5); the more electron-withdrawing amides exert a stronger electronic influence than a *tert*-butyl, benzyl, or a silyl ether.[47]



When the more electron-donating alkyl-substituted NHC−Cu complex **9** is used, mode of coordination **IV** may become favored

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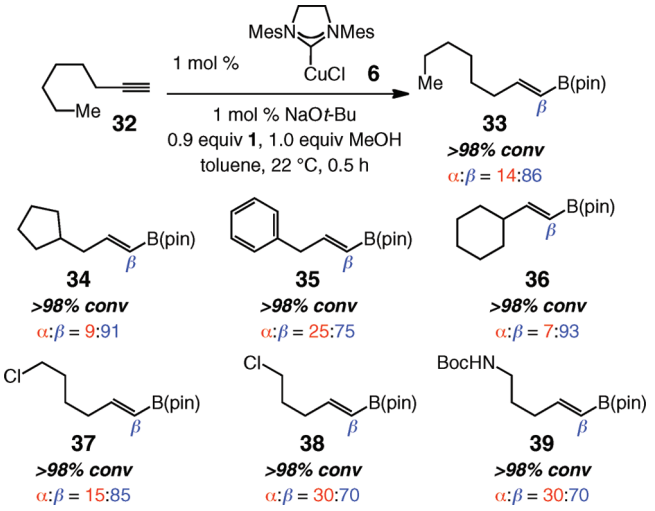
Scheme 9. β-Selective Reactions of Alkyl-Substituted Alkyne with Complex 6[a]



[a] Reactions performed under N_2 atmosphere. Conversion (based on **1** as the limiting reagent) and site selectivity (±2%) were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification.

(Scheme 7, right column); β-vinylboronate products might therefore be generated via metallacyclopropene $\mathbf{IV}_C$ and vinylcopper intermediate $\mathbf{IV}_V$. A number of electronic and steric principles might serve to establish a rationale for the preference for the above mode of reaction. One critical factor is the departure from linearity[48] of NHC−Cu−B(pin)[49] imposed by the more strongly donating NHC ligand (vs **I** with NAr substituted variant). Such distortion would likely be due to the relatively strong trans-influence imposed by the heterocyclic carbene,[48,50] leading to the formation of an available coordination site that is anti to the heterocyclic ligand. As a result, and as shown in **III** and **IV** (Scheme 7), the alkyne substrate approaches the NHC−Cu−B(pin) from an angle that positions it more distal to the NHC (labeled as "anti-to-NHC" vs **I**−**II** labeled as "syn-to-NHC"). Electronic factors can be called upon to explain the preference for reaction through **IV** (vs **III**). In the case of a more strongly electron-donating NHC (i.e., Cu complex **9**), as illustrated by **C** in Scheme 8, an alkyne serves as a π-acceptor. Accordingly, mode of alkyne−catalyst association **IV** (Scheme 7), where the softer C_β (larger LUMO) is positioned anti to the heterocyclic ligand (more effective hyperconjugation), becomes favorable. Since the C_β has a larger LUMO coefficient than the C_α (but to varying levels; see below), β selectivity is rendered less sensitive to the electronic attributes of the alkyne substituent compared to reactions with NAr-substituted Cu complexes **6** or **10** (compare the data in Table 4 vs Tables 2 and 3 and eq 3). Furthermore, the lower selectivity with propargyl alcohol, amines, and derivatives (73−88% β in entries 4−7, Table 4), contrary to those observed in additions to aryl acetylenes (93 to >98% β in entries 8−14, Table 4), are likely connected to the more dominant electronic influence of the resonance-based effects of the aryl substituents versus the inductive effects by the former set.

It is possible that in reactions of alkyl-substituted alkynes (those that do not contain an electron-withdrawing unit proximal to the triple bond), regardless of the nature of the NHC−Cu complex, the Cu−B insertion step (vs Cu−alkyne coordination) serves as the product-determining step. Such a hypothesis does offer an explanation for the β selectivity observed with Cu complexes derived from NHCs that contain an *N*-alkyl (entries 1−3, Table 4) or an *N*-aryl group, represented by the processes shown in Scheme 9. Our calculations (NHC−Cu···alkyne coordination product-determining)[13] as well as experimental findings, however, indicate that a similar scenario likely does not apply to reactions of aryl alkynes illustrated in Table 4 and should not be used to explain the higher β selectivity observed with this substrate class. Accordingly, in contrast to the related reactions involving aryl-substituted olefins, where Cu−B addition to the alkene is believed to be product-determining,[28a,51] there is little difference in the rate of reaction between a substrate that bears an electron-withdrawing or donating unit (entry 12 vs 14, Table 4).

Subtle structural modifications within the substrate regarding the position of electron-withdrawing substituents, which in certain cases are relatively distal to the alkyne, can have a notable impact on site selectivity (e.g., **32** or **34** vs **35**, **32** vs **37** vs **38**; Scheme 9). If Cu−B addition to the alkyne were consistently the step that determines product identity, the presence of the electronegative substituents would lead to a *preference* for β-vinylboronate generation, since accumulation charge density at the α position would be more stabilized, favoring Cu−C_α bond formation (β selectivity). In contrast, however, the presence of electron withdrawing units result in diminution of β selectivity (Scheme 9); such variations can be explained by the mechanistic picture presented above in connection with increased stability of the developing electron density at the C_α site.

CONCLUSIONS

The present investigations introduce hydroboration reactions of a range of terminal alkynes promoted by easily accessible NHC−Cu complexes and a commercially available B-containing reagent to afford α-vinylboronates in up to >98% site selectivity. The catalytic method should prove to be of value in chemical synthesis, since the Cu-catalyzed reactions are amenable to gram-scale processes and because the majority of previously reported protocols deliver the alternative terminally boron-substituted β-vinylboronates either exclusively or in high selectivity (>90%). The catalytic reactions selectively deliver intermediates that arise from the addition of NHC−Cu and (pinacolato)boron across terminal alkynes, and because the C−Cu, as well as the C−B bond, can be used in subsequent bond-forming processes, the implications of the transformations described herein extend beyond hydroboration.

Mechanistic studies suggest that the unusual α selectivities arise from steric and electronic effects that originate from the NHC ligands of the Cu-based catalysts and the substituents of terminal alkyne substrates. Theoretical investigations reported previously imply that the rate- and product-determining step in NHC−Cu-catalyzed Cu−B additions to alkenes might involve alkene insertion into a Cu−B bond.[51] However, the unusual selectivity patterns observed in Cu−B additions to terminal alkynes might best be accounted for through a mechanistic regime where the rate- and product-determining step is alkyne coordination to a NHC−Cu−B(pin) complex. The investigations presented above illustrate that, by altering the electronic nature of the latter transition metal system, considerable variations in site selectivity can be achieved such that the more difficult-to-access α-vinylboronates or the alternative β-vinylboronates are generated in up to >98% α or β selectivity.

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Development of catalytic Cu−B additions to other classes of alkynes and alkenes, alternative protocols for functionalization of the resulting organometallic products, and further mechanistic investigations are in progress.[52]

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author
amir.hoveyda@bc.edu

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(9) See the Supporting Information for a 400 MHz ^{1}H NMR spectrum of the product mixture prior to purification attempts.

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(11) For an example of vinyl halide conversion to a vinyllithium followed by (pinacolato)-isopropoxyboron utilized in the course of a natural product total synthesis, see: Murelli, R. P.; Cheung, A. K.; Snapper, M. L. *J. Org. Chem.* **2007**, *72*, 1545–1552.

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