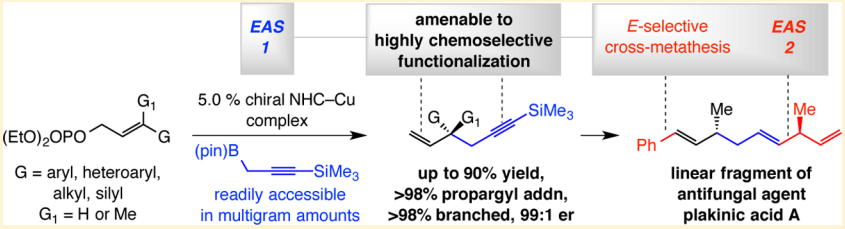
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

N-Heterocyclic Carbene–Copper-Catalyzed Group-, Site-, and Enantioselective Allylic Substitution with a Readily Accessible Propargyl(pinacolato)boron Reagent: Utility in Stereoselective Synthesis and Mechanistic Attributes

Ying Shi, Byunghyuck Jung, Sebastian Torker, and Amir H. Hoveyda*

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

Supporting Information



ABSTRACT: The first instances of catalytic allylic substitution reactions involving a propargylic nucleophilic component are presented; reactions are facilitated by 5.0 mol % of a catalyst derived from a chiral N-heterocyclic carbene (NHC) and a copper chloride salt. A silyl-containing propargylic organoboron compound, easily prepared in multigram quantities, serves as the reagent. Aryl- and heteroaryl-substituted disubstituted alkenes within allylic phosphates and those with an alkyl or a silyl group can be used. Functional groups typically sensitive to hard nucleophilic reagents are tolerated, particularly in the additions to disubstituted alkenes. Reactions may be performed on the corresponding trisubstituted alkenes, affording quaternary carbon stereogenic centers. Incorporation of the propargylic group is generally favored (vs allenyl addition; 89:11 to >98:2 selectivity); 1,5-enynes can be isolated in 75–90% yield, 87:13 to >98:2 S_N2'/S_N2 (branched/linear) selectivity and 83:17–99:1 enantiomeric ratio. Utility is showcased by conversion of the alkynyl group to other useful functional units (e.g., homoallenyl and *Z*-homoalkenyl iodide), direct access to which by other enantioselective protocols would otherwise entail longer routes. Application to stereoselective synthesis of the acyclic portion of antifungal agent plakinic acid A, containing two remotely positioned stereogenic centers, by sequential use of two different NHC–Cu-catalyzed enantioselective allylic substitution (EAS) reactions further highlights utility. Mechanistic investigations (density functional theory calculations and deuterium labeling) point to a bridging function for an alkali metal cation connecting the sulfonate anion and a substrate's phosphate group to form the branched propargyl addition products as the dominant isomers via Cu(III) π-allyl intermediate complexes.

INTRODUCTION AND BACKGROUND

Catalytic enantioselective allylic substitution (EAS) is a versatile transformation through which an alkene and a nucleophilic reagent may be converted to products with a newly formed olefin and an allylic stereogenic center. In principle, such processes allow for cross-coupling of alkenes with valuable (functionalizable) fragments.[1,2] Yet, despite notable advances, the majority of existing EAS reactions correspond to incorporation of an alkyl unit (Figure 1);[3] regardless of whether a tertiary (Figure 1a) or a quaternary carbon (Figure 1b) stereogenic center is desired, additions entailing the use of other C-based units are either uncommon or remain unknown.

To address the above shortcomings, we have introduced site- and enantioselective catalytic processes for addition of alkenylaluminum reagents to allylic phosphates;[4] this advance was enabled by the development of phosphine–Ni-catalyzed site- and stereoselective hydrometalation of terminal alkynes that furnish α- or β-substituted alkenylaluminum compounds.[5] We have demonstrated that under modified conditions terminal alkynes can be converted to alkynylaluminum species and used to synthesize enantiomerically enriched 1,4-enyne products site- and enantioselectively.[6] Nevertheless, the diisobutylaluminum hydride (dibal–H) needed in the latter transformations, although inexpensive, is a strong reducing agent that is intolerant of several key functional groups (e.g., ketones and carboxylic esters). We therefore shifted our focus to EAS processes that require milder organoboron reagents,[7] with an interest in utilizing those that contain a relatively robust (pinacolato)boron [B(pin)] unit.[8] This latest initiative has led to the development of enantioselective transformations with commercially available and easy-to-handle allenylboronic acid pinacol ester and allylic phosphates to form tertiary or quaternary carbon stereogenic centers (cf. Figure 1).[9] In the meantime, we have introduced protocols for site- and enantioselective additions of alkenylboron compounds,[10]

Received: November 20, 2014
Published: July 14, 2015

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948–8964

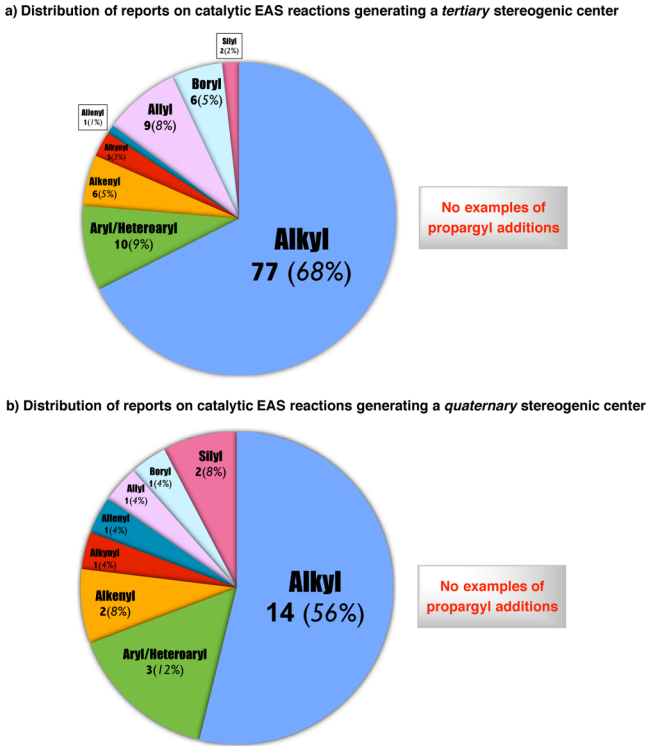
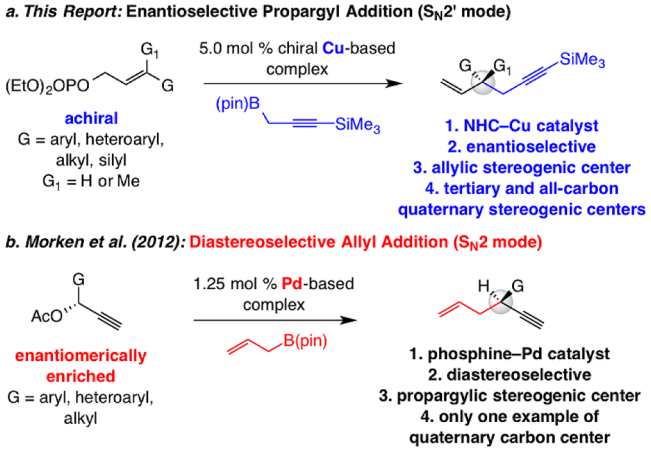


Figure 1. Functional units incorporated with product structures by catalytic EAS reactions (end of May, 2015). (See the Supporting Information for the complete listing.)

including those bearing *Z*-alkenes obtained by stereoselective cross-metathesis.[11] A significant advantage of boron-based reagents is that they render feasible additions of moieties that generate versatile products but would be appreciably more difficult to prepare through the use of organolithium[12] or Grignard reagents;[13] the latter organometallic species are substantially more reactive and thus, in addition to the noted matter of functional group incompatibility, often require severely low temperatures so that noncatalytic additions that diminish site selectivity as well as enantioselectivity are restrained.

One type of catalytic EAS transformation that is yet to be introduced involves the addition of a propargyl group; such processes remain unknown (Scheme 1a).[14] The expected enantiomerically enriched 1,5-enynes would be of value as they could be converted to compounds that may be efficiently accessed by manipulation of the corresponding alkenyl,[10] allenyl,[9] allyl,[15] or alkynyl[6] products. As far as we are aware, only one example of such a reaction has been reported; this involves the reaction of allyl−B(pin) with a racemic propargylic acetate promoted by a phosphine−Pd complex (Scheme 1b).[16] Several key features distinguish the present set of reactions and the aforementioned diastereoselective allyl−propargyl cross-coupling transformations catalyzed by phosphine−Pd species (Scheme 1b):[16] (1) The former method gives access to 1,5-enyne compounds with a stereogenic center at the propargylic site (vs the allylic site here). (2) Transformations were carried out with enantiomerically enriched propargyl acetates (vs achiral allylic phosphates here). (3) Mainly diastereoselective processes involving secondary propargyl acetates were disclosed, leading to tertiary carbon stereogenic centers with only one instance of a reaction that affords a quaternary all-carbon stereogenic center. It should be noted that the products from

Scheme 1. 1,5-Enyne Synthesis by Catalytic Allylic Substitution



EAS with a propargylic reagent contain easily and fully differentiable alkyne and alkene units; this is unlike compounds furnished by enantioselective allyl−allyl coupling processes, wherein there are two terminal alkenes, site-selective modification of which, especially when tertiary carbon stereogenic centers are involved, could be difficult.[15]

A number of undesirable pathways, not applicable to previous EAS transformations with an organoboron compound and catalyzed by a Cu-based complex[4−6,8−10,12,13] (or the majority of those promoted otherwise[15a−c,16]), become feasible when considering reactions with a propargyl−B(pin) group. Such difficulties partly arise from the presence of two dissymmetric C-based ligands within the transition metal complex, one an allylic and the other a propargylic unit, allowing the possibility of the formation of an assortment of different isomeric products. Issues of group selectivity (e.g., propargyl vs allenyl addition) do not complicate additions of alkenyl,[10] allenyl,[9] alkynyl,[6] or symmetric allyl units.[15a−c] Additionally, the nucleophilicity of propargylcopper species is substantially higher than an alkenyl or allenyl variant; this demands that the catalyst preempts competitive addition by the uncatalyzed process that would likely afford achiral linear products preferentially.

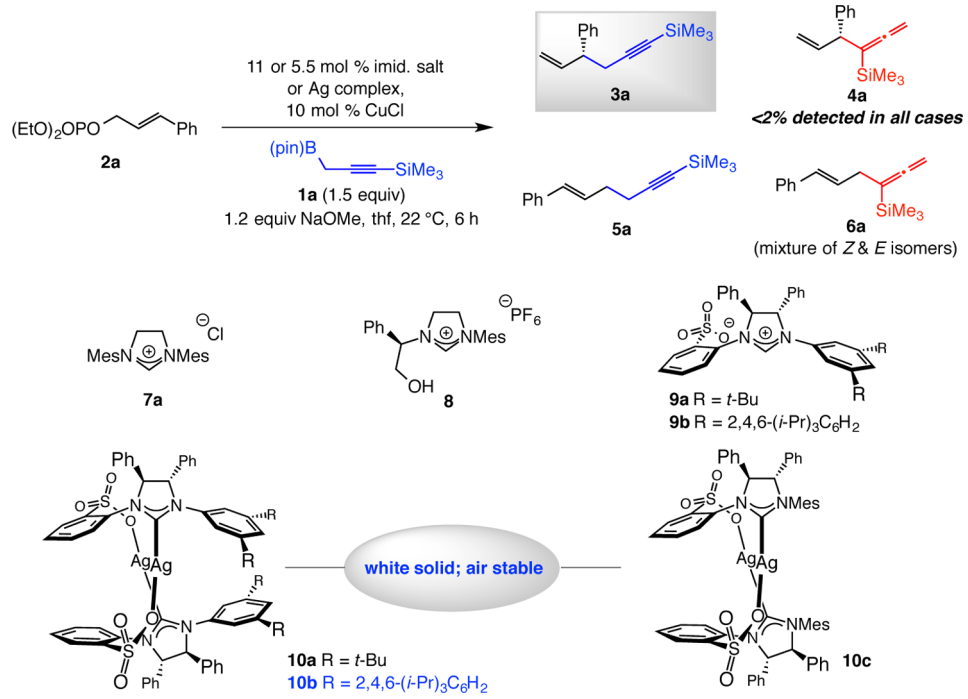
Here, we report the development and study of mechanistic attributes of N-heterocyclic carbene (NHC)−Cu-catalyzed EAS reactions that involve the use of a readily accessible propargylboron reagent.

RESULTS AND DISCUSSION

1. Synthesis of Propargyl-Substituted Tertiary Carbon Stereogenic Centers: Additions to Allylic Phosphates that Contain a Disubstituted Alkene. *1.1. Evaluation of NHC−Cu Complexes.* The reaction of **1a** with allylic phosphate **2a** to generate 1,5-enyne **3a** was selected as the representative process used for identifying an effective catalyst. Trimethylsilyl-substituted propargylboron compound **1a**, originally presented by Hoffman et al.[17] and its utility demonstrated extensively by Boehringer−Ingelheim researchers,[18] is utilized as the reagent; this entity can be prepared easily in multigram quantities and has been employed in a variety of applications.[18b,19] The "ligand-free" transformation proceeded efficiently without an NHC ligand to give the achiral linear propargyl addition product with 94% site selectivity (6:94 S_N2':S_N2; entry 1, Table 1); what is more, although a minor amount of achiral **6a** arising

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

Table 1. Formation of Tertiary Carbon Centers: Study of Different NHC−Cu Complexes[a]



entry	ligand/complex; mol %	conv (%);[b] yield (%)[c]	$S_N2':S_N2$ (3a:5a)[b]	(3a + 5a):6a[b]	er[d]
1	none	86; 67	6:94	86:14	na
2	**7a**;[e] 11	>98; 77	5:95	88:12	na
3	**8**; 11	86; 71	16:84	87:13	nd
4	**9a**; 11	92; 68	95:5	84:16	90:10
5	**9b**; 11	>98; 75	91:9	89:11	97:3
6	**10a**; 5.5	>98; 70	96:4	84:16	91:9
7	**10b**; 5.5	>98; 75	97:3	89:11	97:3
8	**10c**; 5.5	>98; 74	>98:2	87:13	31:69

[a]Reactions performed under N_2 atm. [b]Conversion (allylic phosphate consumption) and group (propargyl/allenyl addition) selectivities (±2%) were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. Site selectivities were determined by analysis of 400 MHz ^{1}H NMR spectra of purified material. [c]Yield (±5%) of propargyl addition products after silica gel chromatography (includes inseparable linear isomer **5a** but no allenyl compounds). [d]Enantioselectivity (±1%) determined by GC analysis. See the Supporting Information for experimental and analytical details. [e]Preformed NHC−Cu complex was used; see the Supporting Information for details. Mes, 2,4,6-$(Me)_3C_6H_2$; na, not applicable; nd, not determined.

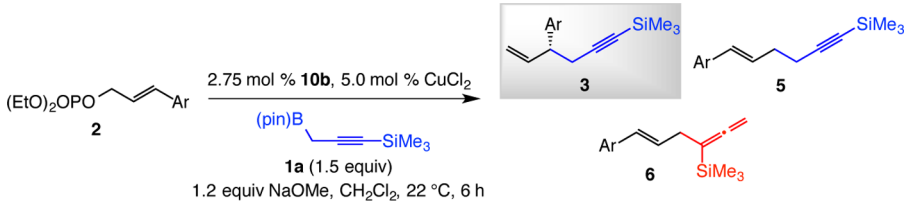
from addition of the allenyl moiety in the S_N2 fashion [86:14 (**3a** + **5a**)/**6a**] was obtained, none of the corresponding chiral allene **4a** was detected (<2%, as judged by analysis of 400 MHz ^{1}H NMR spectra of the unpurified mixture). This finding shows that, contrary to processes involving allenyl−[9] or alkenyl−B(pin)[5] entities, undesired linear isomers can be produced by competitive "background" processes. Our suspicion that an effective enantioselective propargyl addition catalyst would have to be able to compete readily with a relatively facile nonselective alternative pathway was thus substantiated.

Investigation of different Cu complexes, a sample of which is illustrated in Table 1, underscored the importance of a complex bearing a sulfonate-containing NHC ligand if high branched selectivity were to be observed (see below for a discussion of the related mechanistic aspects). With the monodentate species derived from imidazolinium salt **7a** the linear isomer from propargyl addition was formed selectively (95% S_N2; entry 2, Table 1), an 88:12 ratio of propargyl/allenyl products [(**3a** + **5a**)/**6a**] was obtained and, again, **4a** was not detected (<2% by ^{1}H NMR analysis). The aforementioned selectivity pattern remained nearly constant throughout the screening studies (84:16−89:11). Reactions with imidazolinium salts bearing an alkoxy linker (e.g., **8**), similar to transformations in entries 1 and 2, gave similarly unfavorable degrees of S_N2' selectivity (84% S_N2, entry 3).

It was only with NHC−Cu catalysts derived from sulfonates **9a**,**b** that the chiral branched product was formed preferentially (95:5 and 91:9 $S_N2':S_N2$, respectively; entries 4 and 5); the desired 1,5-enyne was obtained in 90:10 and 97:3 er, respectively. Since, as already mentioned, allylic substitution proceeds relatively efficiently in the absence of an NHC ligand, giving way to competitive linear-selective addition (cf. entry 1), we investigated the use of dimeric Ag complexes **10a**,**b** as catalyst precursors;[20] because Ag/Cu ligand exchange is facile, we surmised that the possibility of the presence of NHC−free organocopper species and the competing reactions would be largely (if not entirely) obviated. Under the latter conditions, site selectivities improved (e.g., 97% vs 91% S_N2' for **10b** vs **9b**) and the er values remained nearly the same (entries 5 and 7, Table 1). With the NHC−Cu catalyst generated from dimeric Ag complex **10c**, the desired product was formed in lower and, notably, with a preference for the alternative product

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

Table 2. EAS Reactions with Aryl-Substituted Substrates[a]



entry	substrate (Ar)	conv (%);[b] yield (%)[c]	$S_N2':S_N2$ (3:5)[b]	3:6[b]	er[d]
1	**2a** (Ph)	>98; 75	97:3	91:9	97:3
2	**2b** (*o*-FC_6H_4)	>98; 82	96:4	92:8	97:3
3	**2c** (*o*-BrC_6H_4)	>98; 80	97:3	95:5	97:3
4	**2d** (*o*-$MeOC_6H_4$)	>98; 81	98:2	94:6	96:4
5	**2e** (*o*-MeC_6H_4)	>98; 89	97:3	92:8	96:4
6	**2f** (*m*-BrC_6H_4)	>98; 85	98:2	93:7	98:2
7	**2g** (*m*-MeC_6H_4)	>98; 76	98:2	92:8	98:2
8	**2h** (*m*-$CF_3C_6H_4$)	>98; 79	93:7	89:11	98:2
9	**2i** (2-naphthyl)	>98; 81	96:4	96:4	97:3
10	**2j** (*p*-ClC_6H_4)	>98; 80	96:4	92:8	97:3
11	**2k** (*p*-MeC_6H_4)	>98; 83	97:3	93:7	97:3
12	**2l** (*p*-$NO_2C_6H_4$)	>98; 83	87:13	90:10	95:5

[a]Reactions performed under N_2 atm. [b]Conversion (allylic phosphate consumption) and group (propargyl/allenyl addition) selectivities were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification; site selectivities (±2%) were determined by analysis of 400 MHz ^{1}H NMR spectra of purified products. [c]Yields (±5%) are the lowest obtained after a minimum of three runs and are of products after purification (includes inseparable linear isomer **5**). [d]Enantioselectivities (±2%) were determined by HPLC or GC analysis. See the Supporting Information for all experimental and analytical details.

enantiomer (31:69 er). It merits mention that NHC−Ag complexes **10a−c** are air-stable white solids that can be stored for extended periods of time without decomposition.[21]

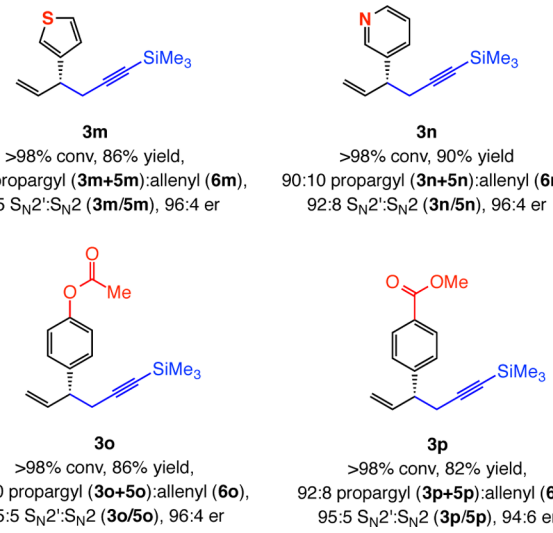
The initial screening revealed an unusual selectivity pattern. Unlike the products derived from propargyl addition, where the branched isomer (**3a**) is formed in preference to the linear product (**5a**), when an allenyl unit is introduced, it is only the achiral linear adduct (**6a**) that is generated (i.e., <2% **4a** by analysis of ^{1}H NMR spectra of the unpurified mixtures). This unexpected dichotomy in site selectivity, which persisted throughout these investigations, including in the case of additions to trisubstituted alkenes to give all-carbon quaternary stereogenic centers (see below), has notable mechanistic implications that will be discussed below.

1.2. Transformations with Aryl Alkenes. With aryl-substituted allylic phosphates, reactions proceeded to >98% conversion with 2.75 mol % NHC−Ag complex **10b**, 5.0 mol % $CuCl_2$, and 1.5 equiv of propargyl−B(pin) reagent **1a**. Enantioselective additions were complete within 6 h at ambient temperature,[22] and the desired products were isolated in ≥75% yield (Table 2; >98% conversion throughout). Even in cases where the substrate carries a sizable aryl unit (cf. entries 3−5, Table 2), products were obtained in >80% yield without the need for higher catalyst loading and/or extended reaction times.

Allenyl isomers could be readily removed (silica gel chromatography); thus, the values shown for yield of the products correspond to pure alkynyl products (mixture of branched and linear isomers). The propargyl/achiral allenyl product ratio [(**3** + **5**):**6**] did not drop below the 89:11 mark; a strong preference for generation of the branched products was observed in nearly every case (≥93:7 S_N2'/S_N2 except 87:13 in entry 12). Enantioselectivity was uniformly high (≥95:5 er).

1,5-Enynes possessing a heteroaromatic moiety were synthesized efficiently (Scheme 2). Thienyl-substituted **3m** was isolated in 86% yield (pure propargyl product) through a reaction that proceeds with 95% site selectivity and 96:4 er. Addition to a pyridyl substrate took place without any adverse influence by the Lewis basic amine site[23] on the activity of the Cu complex: Enyne **3n** was isolated in 90% yield, 92% site selectivity, and 96:4 er. Of note is the efficient formation of 1,5-enyne **3o** and **3p** in 96:4 er and 94:6 er, demonstrating that the

Scheme 2. Reactions with Heteroaryl-Containing Substrates[a]



[a]Reactions conditions and methods of product analysis identical to those indicated in Table 2. Yields (±5%) are the lowest obtained after a minimum of three runs and are of propargyl addition products (branched and linear), except for **3n**, where the propargyl and allenyl product could not be separated. See the Supporting Information for all experimental and analytical details.

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

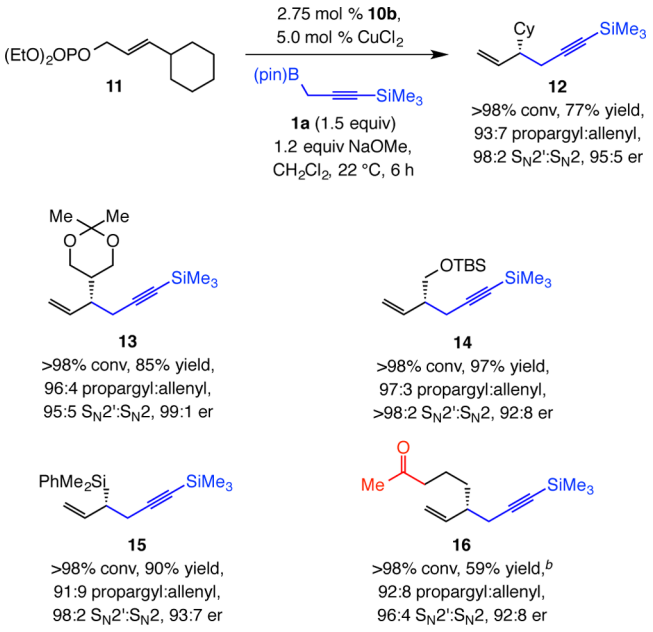
catalytic process tolerates comparatively electrophilic moieties, such as an acylated phenol or a carboxylic ester (more on functional group compatibility below).

1.3. Transformations with Aliphatic Allylic Phosphates. Reactions with alkyl-substituted allylic phosphates were similarly facile and selective (Scheme 3). Additions were complete within 6 h with 2.75 mol % **10b**, affording the expected 1,5-enynes in up to 90% yield, 96:4 propargyl/allenyl and >98:2 S_N2'/S_N2 selectivity, and 99:1 er. Reactions of alkenes with a comparatively sizable substituent (cf. **12** and **13**) as well as those that contain a silyl-protected hydroxymethyl moiety (cf. **14**) proved to be efficient and selective. Preparation of allylsilane **15** in 90% yield, 91:9 propargyl/allenyl and 98:2 branched/linear selectivity, and 93:7 er shows that alkenylsilanes are suitable substrates as well.

Preparation of methyl ketone **16** in 59% yield, 92:8 propargyl/allenyl and 96:4 branched/linear selectivity, and 92:8 er in 2 h (vs 6 h) further underscores the tolerance of the catalytic protocol toward electrophilic/enolizable units. To gain additional insight vis-à-vis compatibility of the method toward other commonly occurring functional groups, we performed the studies summarized in Table 3. We find that, whereas alkyl ketone **17a** (entry 1), Weinreb amide **17b** (entry 2), aryl ester **18c** (entry 5), and phenyl cyanide (entry 6) survive the EAS conditions reasonably well (74% to >98% unreacted electrophilic additive), the more reactive acetophenone (entry 3) and benzophenone (entry 4) underwent side reactions competitively. In all cases, **3a** was generated with the same selectivity levels as was observed in the absence of the additives (cf. entry 1, Table 2).

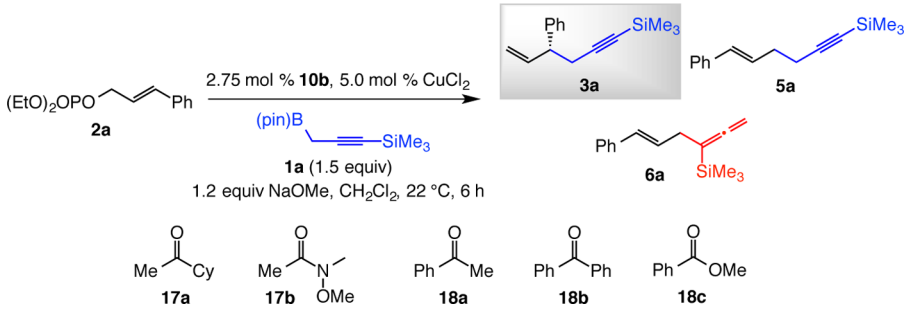
2. Synthesis of Propargyl-Substituted Quaternary Carbon Stereogenic Centers: Reactions with Allylic Phosphates Bearing a Trisubstituted Alkene. We then examined the possibility of applying the EAS process to the formation of all-carbon quaternary stereogenic centers.[24] Preliminary catalyst screening (Table 4) again revealed that sulfonate-based NHC−Cu complexes have the unique ability to favor the formation of the desired chiral, branched isomers (compare entries 5−7 vs 1−3). However, there are two noteworthy differences between the data shown in Tables 4 and 1 (with disubstituted alkene **2a**). The complex derived from **9a** delivers inferior site selectivity (39:61 S_N2':S_N2 vs 95:5 in the

Scheme 3. EAS Reactions with Alkyl-Substituted Substrates[a]



[a]Reactions conditions and methods of product analysis identical to those indicated in Table 2. Yields (±5%) are the lowest obtained after a minimum of three runs and are of propargyl addition products (branched and linear). See the Supporting Information for all experimental and analytical details. [b]Reaction time was 2 h.

Table 3. Further Examination of Functional Group Compatibility in EAS with 2a[a]

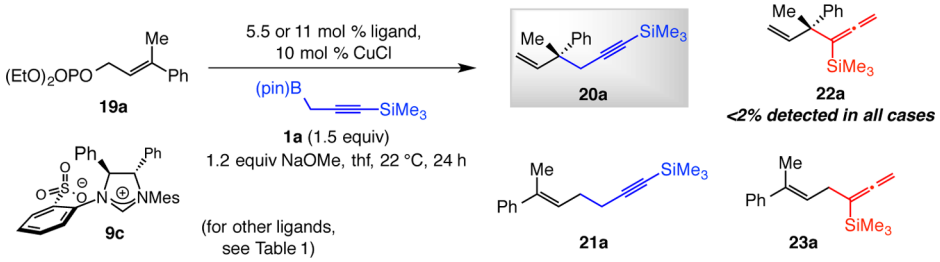


entry	electrophile	conv (%);[b] yield (%)[c]	S_N2':S_N2 (**3a**:**5a**)[b]	(**3a** + **5a**):**6a**[b]	recovered electrophile[d]
1	**17a**	>98; 79	97:3	89:11	>98
2	**17b**	92; 76	96:4	89:11	90
3	**18a**	89; 38	97:3	88:12	25[e]
4	**18b**	79; 48	97:3	89:11	41[e]
5	**18c**	>98; 75	96:4	90:10	>98
6	PhCN	>98; 76	96:4	89:11	74

[a]Reactions performed under N_2 atm. [b]Conversion levels (allylic phosphate consumption) and group (propargyl/allenyl addition) selectivities were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification; site selectivities (±2%) were determined by analysis of 400 MHz ^{1}H NMR spectra of purified products. [c]Yields (±5%) are the lowest obtained after a minimum of three runs and are for propargyl addition products after purification (includes inseparable linear isomer **5a**). [d]On the basis of analysis of 400 MHz ^{1}H NMR spectra of product mixtures and the use of *N*,*N*-dimethylformamide as the internal standard (±2%). [e]Product mixture contained the corresponding homopropargylic alcohol. See the Supporting Information for all experimental and analytical details.

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

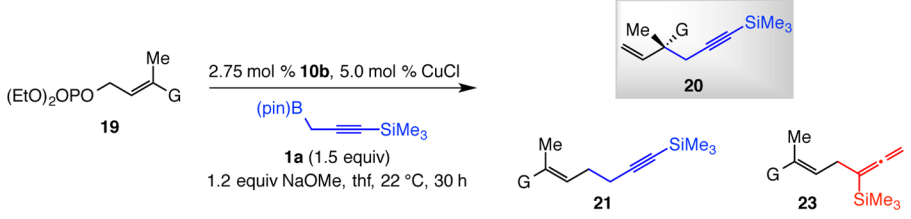
Table 4. Formation of Quaternary Carbon Centers: Examination of Different NHC–Cu Complexes[a]



entry	ligand/complex; mol % catalyst	conv (%);[b] yield (%)[c]	$S_N2':S_N2$ (20a:21a)[b]	(20a + 21a):23a[b]	er[d]
1	none; 10	45; 35	<2:98	82:18	na
2	**7a**; 10	49; 47	<2:98	92:8	na
3	**8**; 10	57; 50	3:97	91:9	nd
4	**9a**; 10	93; 83	39:61	89:11	86:14
5	**9c**; 10	48; 31	85:15	85:15	32:68
6	**10a**; 5.0	>98; 82	91:9	92:8	87:13
7	**10b**; 5.0	>98; 84	94:6	88:12	92:8

[a]Reactions performed under N_2 atm. [b]Conversion (allylic phosphate consumption), group (propargyl/allenyl addition), and site selectivity (±2%) were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. [c]Yields (±5%) are the lowest obtained after a minimum of three runs and are for propargyl addition products (±5%) after silica gel chromatography (includes inseparable linear isomer **22a** but no allenyl compounds). [d]Enantioselectivity (±1%) determined by HPLC or GC analysis. See the Supporting Information for experimental and analytical details. See the Supporting Information for details. Mes, 2,4,6-$(Me)_3C_6H_2$; na, not applicable; nd, not determined.

Table 5. Enantioselective Synthesis of Enynes with a Quaternary Carbon[a]



entry	substrate (G)	conv (%);[b] yield (%)[c]	$S_N2':S_N2$ (20:21)[b]	(20 + 21):23[b]	er[d]
1	**19a** (Ph)	>98; 81	94:6	89:11	91:9
2	**19b** (*o*-$MeOC_6H_4$)[e]	98; 95	94:6	91:9	83:17
3	**19c** (*m*-BrC_6H_4)	95; 93	>98:2	89:11	92:8
4	**19d** (*p*-ClC_6H_4)	>98; 91	96:4	90:10	93:7
5	**19e** (Cy)	>98; 78	>98:2	90:10	94:6

[a]Reactions performed under N_2 atm. [b]Conversion levels (allylic phosphate consumption) and group selectivities were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification; site selectivities (±2%) were determined by analysis of 400 MHz ^{1}H NMR spectra of purified products. [c]Yields (±5%) are the lowest obtained after a minimum of three runs and are for products after purification (includes inseparable linear product **21**). [d]Enantioselectivities (±1%) were determined by HPLC or GC analysis. [e]The complex derived from **10a** was used; see text for details. See the Supporting Information for all experimental and analytical details.

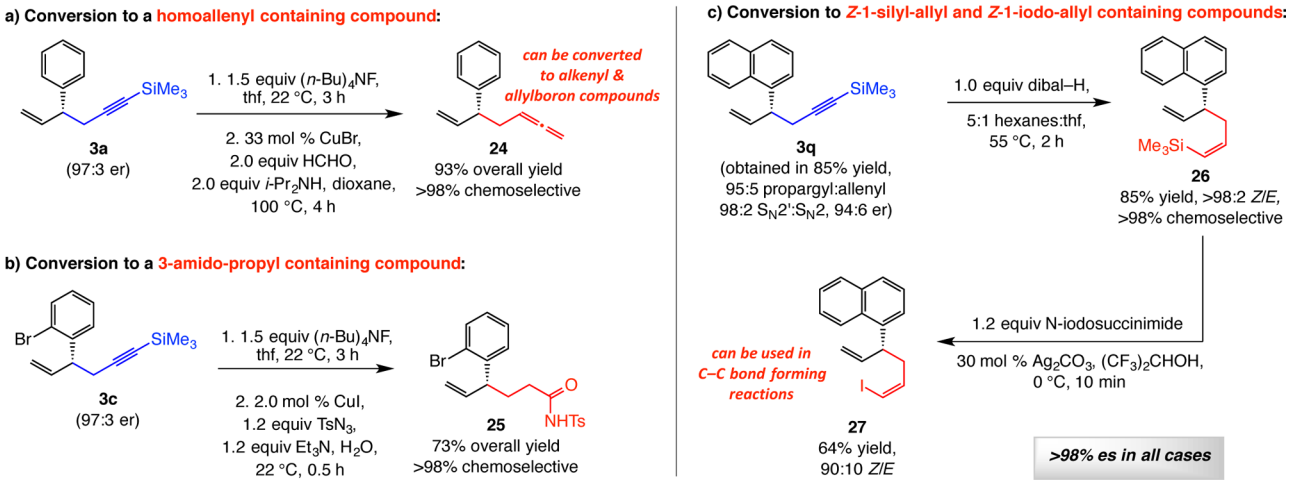
case of **2a**). When imidazolinium salt **9c** was used (entry 5, Table 3), the opposite enantiomer was generated predominantly (32:68 er); as will be detailed later, this observation offers an important clue regarding mechanism of the EAS process. The reversal in selectivity was observed in the related allenyl additions [with allenyl–B(pin)] as well, although the er values were higher (12:88 er).[9] Unlike the transformations with allenyl–B(pin),[9] EAS with the complex derived from **10b** afforded **22a** in 92:8 er (entry 7, Table 4); in the former study,[9] the EAS product was obtained in 67:33 er (94:6 $S_N2':S_N2$). These findings underscore the clear distinction between the transformations involving the allenyl–B(pin) and **1a**.

Transformations with trisubstituted allylic phosphates proceeded to ≥95% conversion after 30 h at ambient temperature in THF[25] in the presence of 5.0 mol % of catalyst derived from **10b** (Table 5). Propargyl addition products were isolated in 78–95% yield after purification; as before, the 9–11% of the allenyl byproduct (**23a**) formed could be removed by silica chromatography. Site selectivity was as high as that obtained with disubstituted allylic phosphates (cf. Table 2, Schemes 2 and 3), while er values were somewhat lower (up to 94:6). The most challenging case, shown in entry 2 of Table 5, involved an ortho-substituted aryl group; in this instance, it was the less hindered Cu complex derived from **10a** that emerged as the most effective. With Ag complex **10b**, utilized in all other cases in Table 5, there was 75% conversion, and a 60:40 ratio of branched/linear products was generated (vs 98% conversion and 94% S_N2' selectivity). Alkyl-substituted trisubstituted allylic phosphates can be utilized effectively (**20e** in 78% yield, >98:2 $S_N2':S_N2$, and 94:6 er). As with reactions of disubstituted alkenes (cf. Scheme 3), only the linear allenyl isomers were observed (see below for mechanistic analysis).

The slower rates of EAS reactions that afford all–carbon quaternary stereogenic centers versus those that involve 1,2-

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948–8964

Scheme 4. Representative Functionalization of EAS Product by Reactions Involve Chemoselective Modification of the Alkyne[a]



[a]Yields (±5%) are the lowest obtained after a minimum of three runs and are for propargyl addition products after silica gel chromatography (includes inseparable linear isomers but no allenyl compounds). See the Supporting Information for details. es = enantiospecificity (product enantiomeric excess/substrate enantiomeric excess) × 100.

disubstituted alkenes render the corresponding conditions less conducive to the presence of other electrophilic functional groups than was formerly illustrated (cf. Table 3). We find that carboxylic ester **18c** (1.0 equiv) present in the solution for the formation of **20a** can be recovered in >98% yield with minimal influence on the efficiency of the EAS (81% yield, 94% S_N2', 89:11 [(**20a** + **21a**):**23a**, 91:9 er]. In contrast, when methyl ketones **17a** and **18a** were added to the mixture, **20a** was obtained in 67% and 29% yield, respectively, and the carbonyl additive were recovered in 30% and 15% yield, respectively (other selectivities for **20a** remained the same).

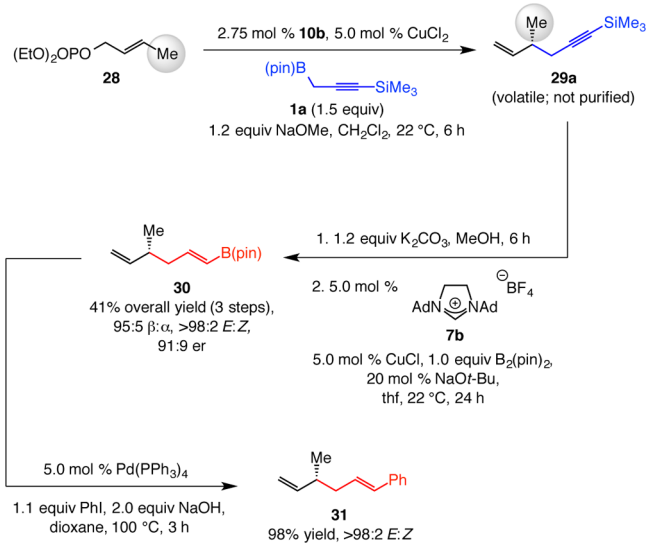
3. Chemo- and Stereoselective Functionalization of the Propargyl Group of the EAS Products. This segment of investigations was designed to demonstrate that the propargyl unit may be manipulated to access to a host of useful functional units. We focused on illustrating the straightforwardness with which an alkyne unit may be modified without any adventitious side reactions that involve the resident alkene group. This is a critical advantage that might not be available if the enantiomerically enriched dienyl products derived from allyl–allyl coupling reactions were to be utilized.[15] We therefore chose to focus on transformations of 1,5-enynes that contain a tertiary carbon stereogenic center, as differentiation of the alkenes of a 1,5-diene would be particularly challenging in such instances.[26]

One transformation of note generates homoallenyl compounds, as represented by **24** in Scheme 4a. The product was secured in 93% yield obtained in a single operation without loss of enantiomeric purity and with complete chemoselectivity (<2% reaction at the alkene site), through treatment of **3a** with $(n\text{-Bu})_4NF$ and then 33 mol % CuBr, 2.0 equiv of paraformaldehyde, and 2.0 equiv of $(i\text{-Pr})_2NH$ (100 °C, 4 h). The difficulties associated with converting the product of an allyl–allyl coupling process to the corresponding homoallenyl compounds,[27] and the increasing number of catalytic stereoselective transformations that involve monosubstituted allenes[28] renders this functionalization especially striking. Another notable Cu-catalyzed process converts the EAS products with exclusive chemoselectivity (>98% reaction at the alkyne unit) to enantiomerically enriched tosylamides such as **25** (Scheme 4b);[29] such electronically activated functional units, accessible in a single step only from an alkyne unit (unlike an olefin), are readily amenable to further modification.[30] The silyl alkyne group may be converted to the corresponding *Z*-alkenyl silane (cf. **26**) by treatment with dibal–H at 55 °C for 2.0 h (Scheme 4c).[4b] As in the previous cases, competitive reaction involving the alkene group was not detected (<2% by 400 MHz ^1H NMR). Subsequent treatment with *N*-iodosuccinimide, 30 mol % Ag_2CO_3, and hexafluoroisopropyl alcohol for 10 min at 0 °C led to the formation of the derived *Z*-alkenyl iodide, albeit with ∼10% loss in alkene stereoisomeric purity (cf. **27**, Scheme 4c).[19c,31] This latter sequence demonstrates that the silyl unit of the propargyl–B(pin) reagent (**1a**) can impart attractive characteristics to the catalytic approach that extend beyond serving as a protecting unit.

Alkenyl iodide **27** corresponds to the product of a hitherto unknown EAS reaction that culminates in site-selective and enantioselective addition of an easily adaptable allyl group,[15] one that can be used to access compounds containing a *Z*-alkene (e.g., through catalytic cross-coupling).[32] Another example is demonstrated in Scheme 5. We chose to investigate EAS with methyl-substituted allylic phosphate **28**; such methyl-substituted products, as will be illustrated below, are commonly occurring in biologically active compounds. And yet, to our surprise, this particular substrate type has not been used in any catalytic enantioselective allyl–allyl[15] or allyl–propargyl[16] coupling and been scarcely utilized in EAS processes that involve "hard" nucleophiles;[33] such paucity might partly be because the comparatively diminutive size of the substituent can lead to minimal enantiotopic differentiation, requiring a particularly effective chiral catalyst and enantioselective process. In the event, exposure of **28** to NHC–Cu-catalyzed EAS conditions resulted in its complete consumption and formation of trimethylsilyl-substituted **29a**, which is volatile and cannot be easily isolated in high yield. Accordingly, we treated the unpurified mixture containing **29a** to mildly basic methanol to remove the silyl unit, followed by NHC–Cu-catalyzed protoboryl addition of the resulting terminal alkyne;[34] *β*-alkenyl–B(pin) **30** was obtained in 41% overall yield (for three

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948–8964

Scheme 5. EAS with a Key Substrate and Conversion to 1,5-Dienes[a]



[a]Yields (±5%) are for the products after silica gel chromatography. For enyne **29a** the yield reported is the lowest obtained after a minimum of three runs and are for propargyl addition product isomers after silica gel chromatography (includes inseparable linear isomer but no allenyl compounds). See the Supporting Information for experimental and analytical details. Ad, adamantyl.

steps starting with allylic phosphate **28**), 95% β selectivity, >98% E selectivity, and 91:9 er. Because the terminal alkyne unit of the 1,5-enyne could be induced to undergo protoyl-boron addition with complete chemoselectivity, β-substituted styrene **31** could then be prepared in 98% yield by means of phosphine−Pd-catalyzed cross-coupling with iodobenzene. Alkenylboron derivatives, such as **30**, may not be accessed with the same ease and efficiency through the use of dienyl products obtained from EAS reactions that incorporate an allyl[15] moiety, since differentiation of two alkene units would be less straightforward than that of an alkyne and an olefin [e.g., by site- and stereoselective cross-metathesis with vinyl−B(pin)];[35] this is particularly the case with a relatively diminutive methyl group at the allylic site (see Scheme 6 for a specific application).

4. Stereoselective Synthesis of the Acyclic Fragment of Plakinic Acid A. *4.1. Sequential Catalytic EAS as a Synthesis Strategy.* As was demonstrated, a distinguishing mark of the present catalytic EAS protocol is that it delivers products with easily differentiable alkene and alkyne moieties. Thus, as illustrated in Scheme 6a, transformations involving the latter two sites can be designed, depending on the desired target. For instance, catalytic cross-metathesis involving the α-alkene might be followed by NHC−Cu-catalyzed site- and E-selective protyl-boron addition to the desilylated alkyne[34] to afford an enantiomerically enriched alkenyl−B(pin) that can then be used in a subsequent transformation (e.g., catalytic EAS[36]). That is, conversion of the product of the first EAS reaction to the substrate of another catalytic EAS allows for enantio- and diastereoselective synthesis of a syn or anti relative stereochemistry (depending on the catalyst enantiomers selected).

4.2. Illustration of the Concept of Sequential Catalytic EAS. To demonstrate the utility of the protocol further as well as exhibit its complementary relationship with other catalytic and stereoselective processes, we undertook a diastereo- and enantioselective synthesis of the acyclic segment of antifungal natural product plakinic acid A (Scheme 6b).[37,38] The route began with NHC−Cu-catalyzed EAS involving methyl-substituted allylic phosphate **27** and tri(isopropylsilyl)-substituted propargyl−B(pin) reagent **1c**. Enyne **29c** was isolated in quantitative yield with complete control of group selectivity (<2% allenyl product) in 97:3 S_N2'/S_N2 selectivity and in 90:10 er. Cross-metathesis (CM) with styrene and 5.0 mol % of molybdenum alkylidene **32**[39] delivered enyne **33c** in 80% yield, without contamination by the Z olefin isomer (>98:2 E/Z) and, importantly, with complete chemoselectivity in favor of reaction at the alkene site (<2% enyne cross-metathesis).[40]

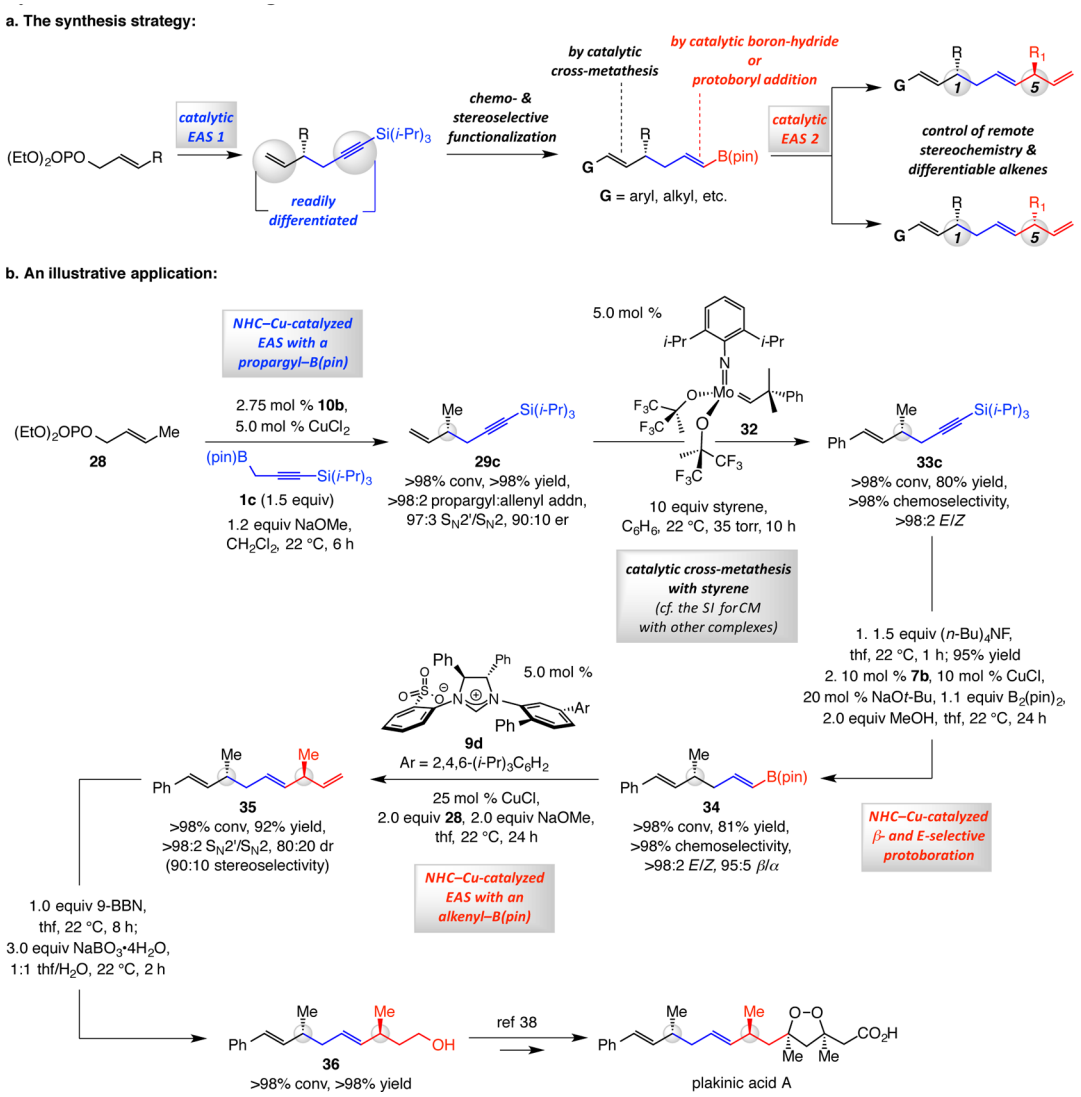
The next objective was to transform the acetylene moiety into an alkenylboron unit to be utilized in an NHC−Cu-catalyzed EAS that would generate the other methyl-substituted stereogenic center. Removal of the silyl group and site- and stereoselective NHC−Cu-catalyzed proto-boryl addition to the resulting terminal alkyne, which proceeded with >98% chemoselectivity (<2% reactions at the styrenyl group), afforded E-β-alkenyl−B(pin) intermediate **34** in 81% yield, >98:2 E/Z and 95:5 β/α selectivity. Treatment of **34** with 5.0 mol % enantiomerically pure imidazolinium salt **9d** and 25 mol % CuCl with 2.0 equiv of allylic phosphate **28** generated triene **35** in 92% yield, with complete branched selectivity (>98% S_N2') and in 80:20 diastereomeric ratio (dr; 90:10 selectivity).[41] Site-selective hydroboration of the monosubstituted alkene afforded primary alcohol **36** in >98% yield (Scheme 6b).

5. Mechanistic Attributes of the Catalytic EAS Process. *5.1. Regarding the Origin of High Group Transfer (Propargyl vs Allenyl) Selectivity.* There are several mechanistic issues that are particular to the present set of catalytic EAS reactions. One relates to possible intermediacy of a Cu(I)−propargyl (**A**) as opposed to a Cu(I)−allenyl (**B**) complex (Scheme 7).[42] Considering the numerous potential reactive intermediates following oxidative addition to either **A** or **B** (**i**−**viii**, Scheme 7), it is not a priori clear that the transformation should exhibit high group transfer (propargyl vs allenyl) selectivity. Fandrick et al. have shown that reactions of aryl aldehydes and ketones with organoboron reagent **1a** and catalyzed by bis(phosphine)−Cu complexes, likely involve species related to **A** or **B**, depending on the identity of the associated ligand.[43] In another study, we have demonstrated that enantioselective NHC−Cu-catalyzed coupling of **1a** and phosphinoylimines can be used to generate homoallenylamides by efficient and enantioselective γ addition pathways; these processes probably proceed via Cu(I)−propargyl complex **A**.[44] However, there is a key difference between the allenyl additions to phosphinoylimines and the present set of EAS reactions; this originates from the distinct redox chemistry of the two types of processes. In the case of Cu(I) (d^{10}) complexes, which operate by means of a single oxidation state when promoting imine additions, π-allyl species $\mathbf{TS_{iso}}$ (Scheme 7) represents a transition state through which Cu(I)−propargyl (**A**) and Cu(I)−allenyl (**B**) systems can interconvert. However, EAS reactions are further complicated due to the possibility of Cu(III)−dialkyl intermediates (cf. **i**−**iv**, Scheme 7), which may be in equilibrium with metastable Cu(III)−π-allyl (d^8) isomeric species (cf. **v**−**viii**, Scheme 7).

5.2. General Considerations Regarding the Mechanistic Studies. To gain an appreciation of the unique effectiveness of the sulfonate-containing NHC−Cu complexes, especially in

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

Scheme 6. Sequential Catalytic EAS as a Strategy in Stereoselective Synthesis: Application to Stereoselective Synthesis of the Diene Fragment of Plakinic Acid A[a]



[a]Yields (±5%) are for products after silica gel chromatography. For compound **29c**, the yield is the lowest obtained after a minimum of three runs and is for propargyl addition products (±5%) after silica gel chromatography (includes inseparable linear isomer but no allenyl compounds). See the Supporting Information for experimental and analytical details. CM, cross-metathesis.

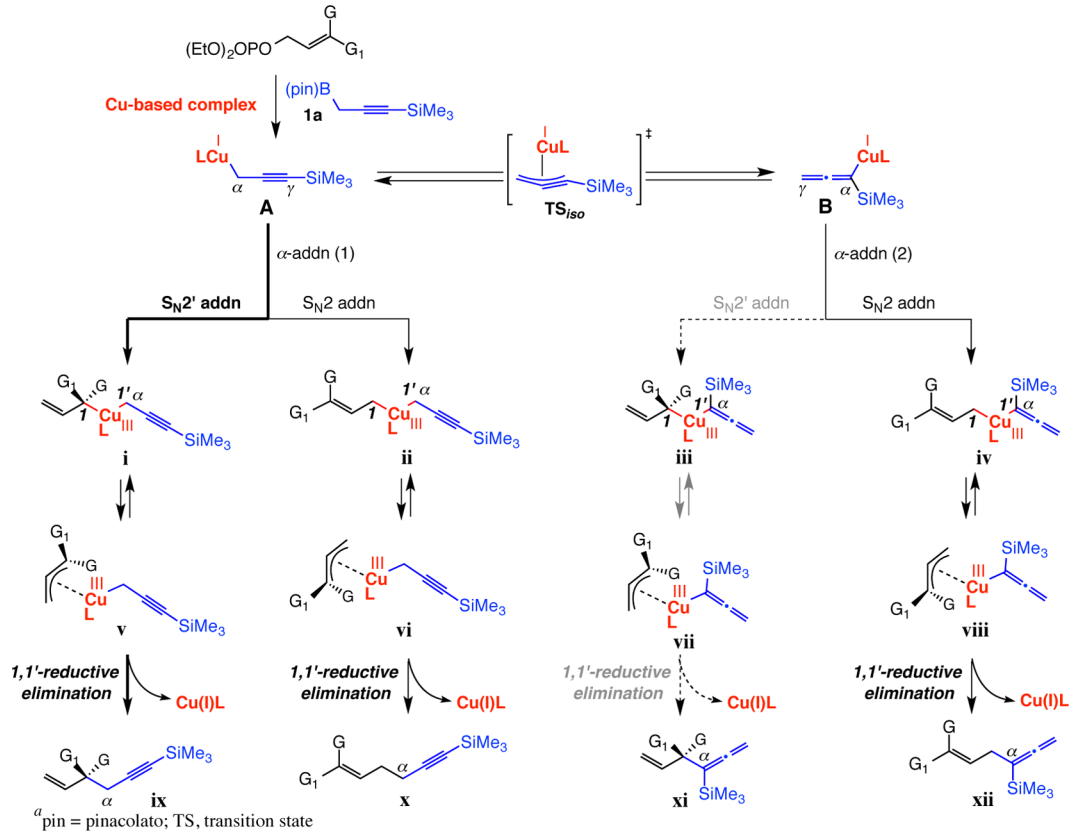
promoting highly branched and enantioselective transformations, in promoting EAS reactions, we performed extensive density functional theory (DFT) calculations. Several salient features of our studies merit discussion before analysis of the results of theoretical investigations.

5.2.1. Experimental Data on Which Investigations Are Based. Our mechanistic proposals rely on a number of different substrate and nucleophile classes that have been shown to generate tertiary[9,10b] (cf. Table 2, Schemes 2 and 3) and/or quaternary[6a,9,10a] carbon stereogenic centers (cf. Table 5) with high enantio- and S_N2'-selectivity (Scheme 8). The profiles that have evolved from the current as well as former studies suggest that in EAS reactions catalyzed by NHC−Cu complexes derived from ligands that contain a sizable 3,5-disubstituted *N*-aryl moiety (e.g., **9a**,**b**) the nucleophilic component adds to a disubstituted allyl phosphate preferentially from the *si* face. In contrast, in transformations that give all−carbon quaternary stereogenic centers, C−C bond formation typically favors addition to the *re* face with catalysts originating from imidazolinium salts such as **9c** or **9e**−**g**, (Scheme 8) where the symmetrical *N*-aryl group has substituents at ortho and/or para sites. One of our goals was to provide a rationale for such trends in site selectivity.

5.2.2. Key Structural Attributes of the Sulfonate-Containing Chiral NHC Complexes (Monodentate or Bidentate?). Although we have previously suggested that sulfonate-containing NHC−Cu complexes may be serving as bidentate catalysts,[9,10b,45] more recent investigations, outlined below, indicate otherwise. Our initial reasoning for considering bidentate complexes was largely based on X-ray crystal structures that we had secured for Al- and Zn-based carbenes **37** and **38** (Scheme 9), respectively.[45] The reservation regarding the latter hypothesis arose because of the significantly higher Lewis acidity of Al(III) and Zn(II) versus a Cu(I) complex; that in Cu−C bonds the highest occupied molecular orbital (HOMO) is located at the transition metal center and Cu−alkyl compounds are significantly more nucleophilic than alkylzinc species deepened this concern.[46] We have examined

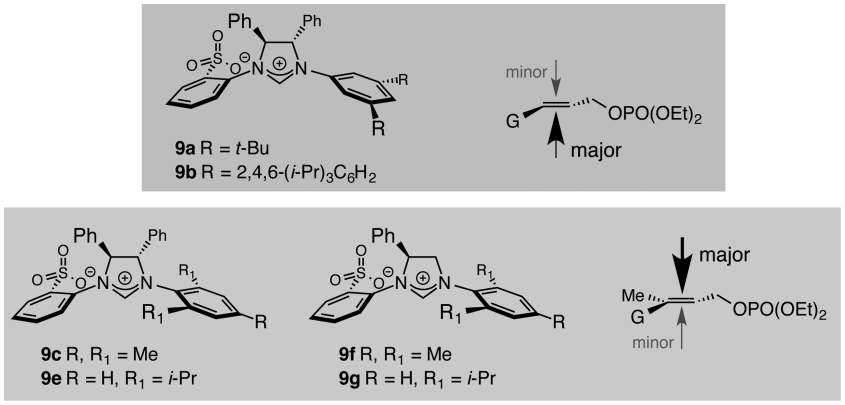
DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

Scheme 7. Catalytic EAS Involving a Propargyl Unit: Overview of Key Mechanistic Issues[a]



[a]pin = pinacolato; TS, transition state.

Scheme 8. General Enantioselectivity Trends in EAS Reactions Promoted by Sulfonate-Containing Chiral NHC−Cu Complexes

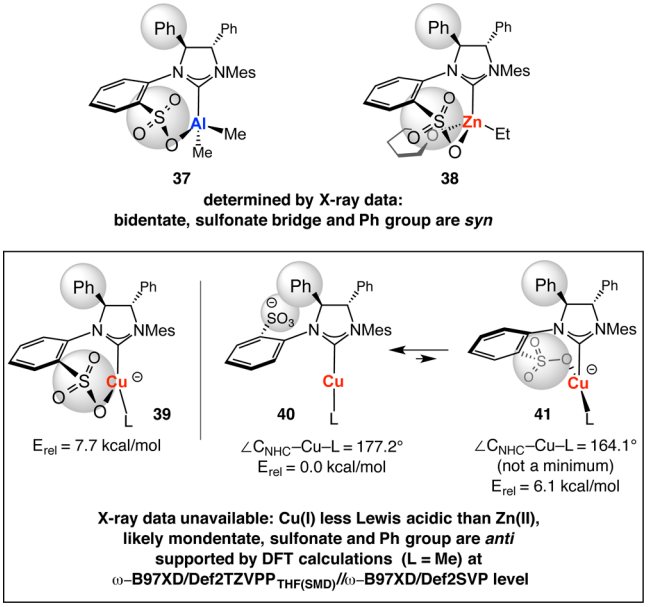


the energetics of anionic NHC−Cu(I)−Me species with a syn (**39**) or an anti (**40** and **41**) sulfonate group (Scheme 9; L = Me; DFT calculations).[47] We find that bidentate complex **39** is disfavored (by 7.7 kcal/mol) compared to monodentate **40**. According to DFT calculations, as the sulfonate group approaches the Cu center, at the distance of 2.3 Å where a Cu−O bond may be formed, the energy of the complex (**41**) is raised by 6.1 kcal/mol. While such ground-state effects may not be a reliable indicator of principles that govern transition state structures, based on additional supporting arguments shown below (section 5.2.3), we chose to focus on catalytic cycles that involve NHC−Cu systems where the transition metal and the sulfonate group are unassociated. A consequence of the above analysis is the stereochemical identity of the organometallic complexes involved. As described previously, to minimize steric repulsion between the ortho C−H bond and the nearby phenyl group of the NHC, in bidentate species **37** and **38** the sulfonate and the NHC phenyl units are oriented in a syn fashion.[45] Without internal chelation, as exemplified by Ag-based complexes such as **10b** (cf. Table 1), steric factors probably favor the anti relationship between the latter two moieties (cf. **40**, Scheme 9).[48]

5.2.3. Importance of Square Planar NHC−Cu(III) d^8 Complexes. The EAS transformations likely proceed through different Cu(I) and Cu(III) complexes.[49] One possibility, illustrated in Scheme 10 (path 1), is that the initially generated NHC−Cu(I) species **I** might be in equilibrium with the more nucleophilic cuprate complex **II**, which then reacts with the

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

Scheme 9. Bidentate versus Monodentate NHC–Metal Complexes



allylic phosphate (oxidative insertion) to afford square planar species **III**; reductive elimination would deliver the EAS product. The issue here, as mentioned above, is the likelihood of whether the sulfonate is able to establish reasonably effective coordination with the Cu(I) center. Alternatively (path 2, Scheme 10), association of **I** with the allylic phosphate, may afford Cu–alkene complex **IV**. Formation of square planar Cu(III) complex **V** would ensue, giving rise to the final product.

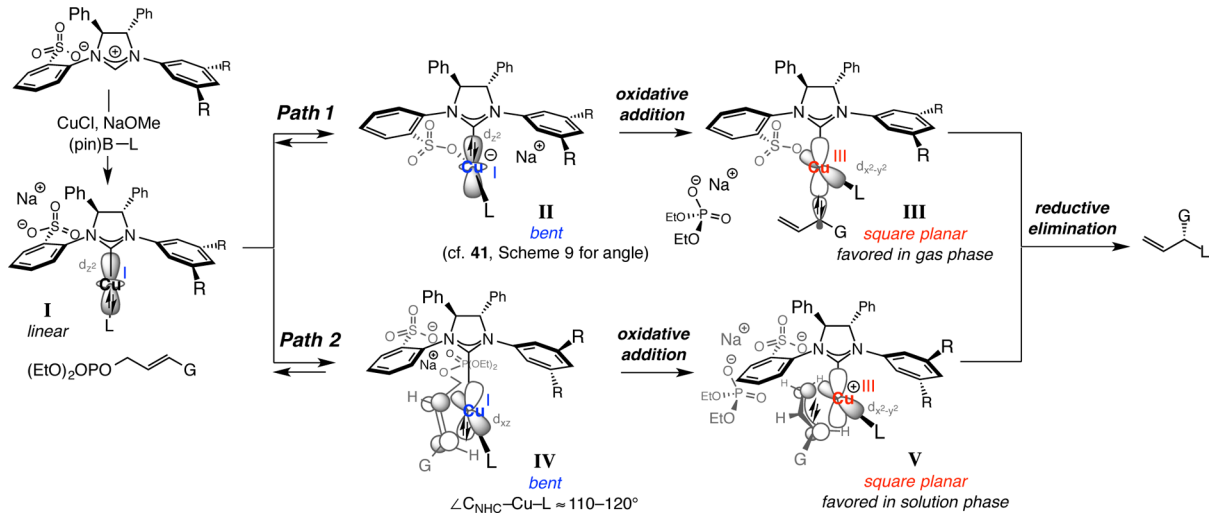
The crucial point here is regardless of which step is turnover-limiting (oxidative addition or reductive elimination), the transition states of either transformation probably resembles a square planar Cu(III) species. That is, since a d^8 Cu(III) complex is higher in energy than a d^{10} Cu(I) system,[50] according to the Hammond postulate,[51] the corresponding transition states that lead to their formation (i.e., in the case of oxidation addition; **II** → **III** or **IV** → **V**) or are involved in their further transformation (i.e., reductive elimination **III** or **V** → product) also resemble a square planar Cu(III) entity. Reaction through path 2 may provide a larger degree of stereocontrol because the formation of a Cu–π complex can afford a structurally more rigid system (cf. **IV** and **V**). When modeled (DFT) in the solution phase (Scheme 10)[47] intermediate **V**, which displays a greater degree of charge separation, is significantly more stabilized than complex **III**.

5.2.4. DFT Calculation Method Used. Computations have been performed with Gaussian09 at the ω–B97XD/Def2TZVPP$_{\text{DCM or THF(SMD)}}$//$\omega$–B97XD/LANL2DZ or Def2SVP level of theory.[47,52] We opted for a computational approach that not only considers the findings of this investigation but those reported previously with the same class of catalysts as well.[6a,9,10] Due to the relative complexity resulting from the possible presence of charged species in solution as well as conformational flexibility of the Cu complexes (i.e., the associated high entropy-dependent free energy component), prediction of energy differences associated with stereoselectivity (~2–3 kcal/mol) by DFT is nontrivial. We thus assume that the computational errors are on a similar scale as the energy difference that leads to high selectivity.

5.3. Role of the Sulfonate Group on High S_N2' (Branched) Selectivity.[53] Two roles may be envisioned for the sulfonate group (Scheme 10). (1) It serves as a Lewis basic unit that coordinates to the Cu center, elevating the energy (nucleophilicity) of the transition metal's filled d_{z^2} orbital (path 1, Scheme 10). Such a scenario is akin to enhancement of the oxidation rate of Pd– or Pt–alkyl bonds by a weakly coordinating sulfonate group that has been proposed to be involved in the corresponding oxidative addition [Pt(II) → Pt(IV)] and reductive elimination steps [Pt(IV) → Pt(II)].[54] (2) The weakly Lewis basic group, together with Cu–alkene association, might function as a chelating[55]/directing group by interacting with the cationic counterion (i.e., Na^+ in path 2, Scheme 10).

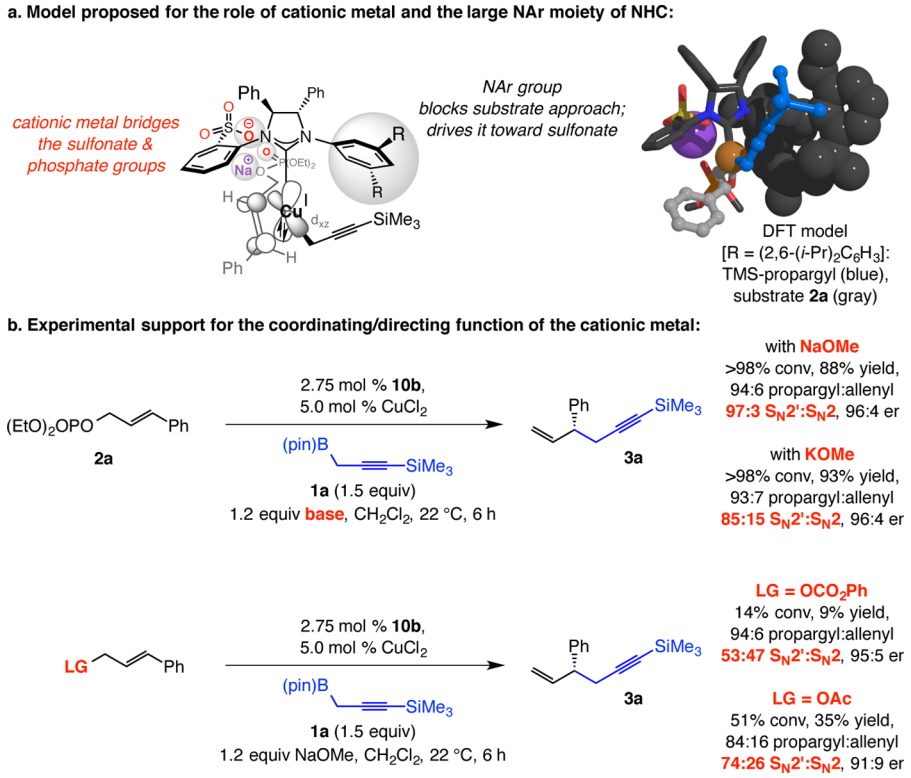
On the basis of the findings and considerations described above (Schemes 8–10), a stereochemical model may be proposed (Scheme 11a). The substrate (**2a**) might approach the sizable and conformationally flexible 3,5-disubstituted aryl group within the Cu complex derived from **9b** or **10b** such that the substrate's alkene substituent points away from the larger moieties of the chiral ligand. The phosphate group would then be placed in the rear so that it can participate in a bridging

Scheme 10. Possible EAS Pathways Involving Bent Cu(I) and Square Planar Cu(III) Complexes as Intermediates



DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948–8964

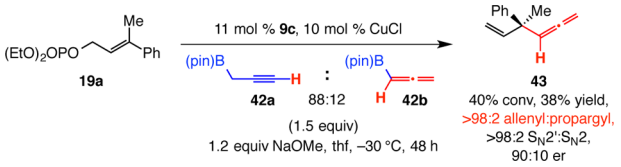
Scheme 11. On the Role of the Cationic Metal and Leaving Group on Site Selectivity[a]



[a]Conversion levels (allylic phosphate consumption) and group selectivities were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification; site selectivities (±2%) were determined by analysis of 400 MHz ^{1}H NMR spectra of purified products. Yields (±5%) are the lowest obtained after a minimum of three runs and are for products after purification (includes inseparable linear product **21**). Enantioselectivities (±1%) were determined by HPLC or GC analysis. See the Supporting Information for all experimental and analytical details.

interaction with the sulfonate by means of the sodium counterion; this scenario, which provides a rationale for why sulfonate-containing NHC−Cu complexes predominantly afford branched product isomers (S_N2' vs S_N2 mode), would necessitate that the sulfonate unit is anti to the proximal phenyl unit of the NHC ligand (Scheme 11a). These considerations underline the significance of the identity of the metal alkoxide and the nature of the leaving group. The experiments shown in Scheme 11b support this contention. Site selectivity suffers when KOMe is used instead of NaOMe (85:15 vs 97:3 $S_N2':S_N2$).[56] (Control experiments indicate that C−C bond formation is not promoted by the metal alkoxides.) Further, with electrophilic components that contain a less Lewis basic moiety, substantial amounts of the achiral linear isomer were generated: an allylic benzoate and acetate afforded branched/linear preferences of 53:47 and 74:26, respectively. It therefore appears that the higher Lewis acidity of cationic sodium (vs potassium) engenders a more robust bridging interaction between the sulfonate group of the NHC−Cu complex and the allylic phosphate. Moreover, as illustrated by the data in Scheme 11b, site selectivity is impacted by the leaving group involved.

The free energy surface of a truncated model system corresponding to the EAS reaction that affords **3a** (cf. entry 1, Table 2), obtained through DFT calculations[47] at the ω−B97XD/Def2TZVPP$_{DCM(SMD)}$//ω−B97XD/LANL2DZ level, is exhibited in Figure 2. The low-energy transition state $\mathbf{TS_{iso}}$ (11.3 kcal/mol) for interconversion of the linear Cu(I)−propargyl (**A**) and the related allenyl species (**B**) suggests the involvement of Curtin−Hammett kinetics, consistent with complex **B** being −0.9 kcal/mol more stable than **A** and none of the chiral S_N2' addition products being generated through intermediacy of **B** (i.e., <2% **4** formed in the studies summarized in Table 2). The significance of the large trimethylsilyl group in providing sufficient quantities of complex **A** has been previously reported[44] and is confirmed by the transformation shown in eq 1; reaction with the propargyl−B(pin)/allenyl−B(pin) reagent mixture (**42a**:**42b**, 88:12[19f]) that lacks the silyl unit is less efficient and produces the allenyl product **43** exclusively.



(1)

In agreement with the higher reactivity (nucleophilicity) of propargyl complex **A** is the most favorable transition state for oxidative addition $\mathbf{OATs_{A,major}}$ (9.7 kcal/mol; OAts = oxidative addition transition state) through which structurally well-defined planar olefin π complex $\mathbf{PC_{A,major}}$ (0.6 kcal/mol; PC = π complex) is transformed to the cationic square planar π-allyl intermediate $\mathbf{PA_{A,major}}$ (4.8 kcal/mol; π-allyl).

The properly situated sodium cation, counterion to the sulfonate, can stabilize the developing negative charge on the leaving phosphate anion. In the pathway leading to the minor enantiomer through the complex labeled $\mathbf{OATs_{A,minor}}$ (13.7 kcal/mol), the presence of the substrate's substituent (Ph)

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

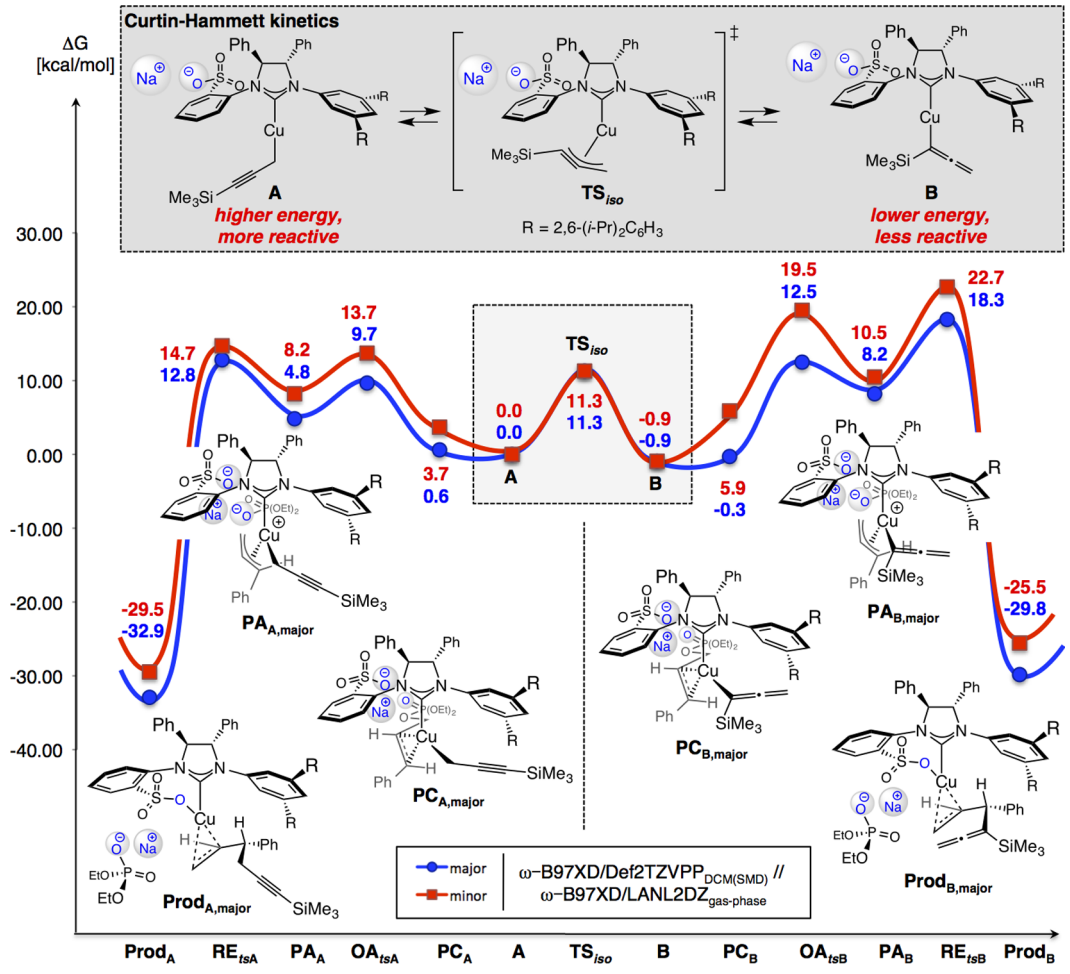


Figure 2. Energy profile regarding the origin of high site and group transfer selectivity (high S_N2':S_N2 and propargyl/allenyl addition) derived from DFT calculations. Abbreviations: RE, reductive elimination; TS, transition state; OA, oxidative addition; PA, π-allyl; PC, π complex.

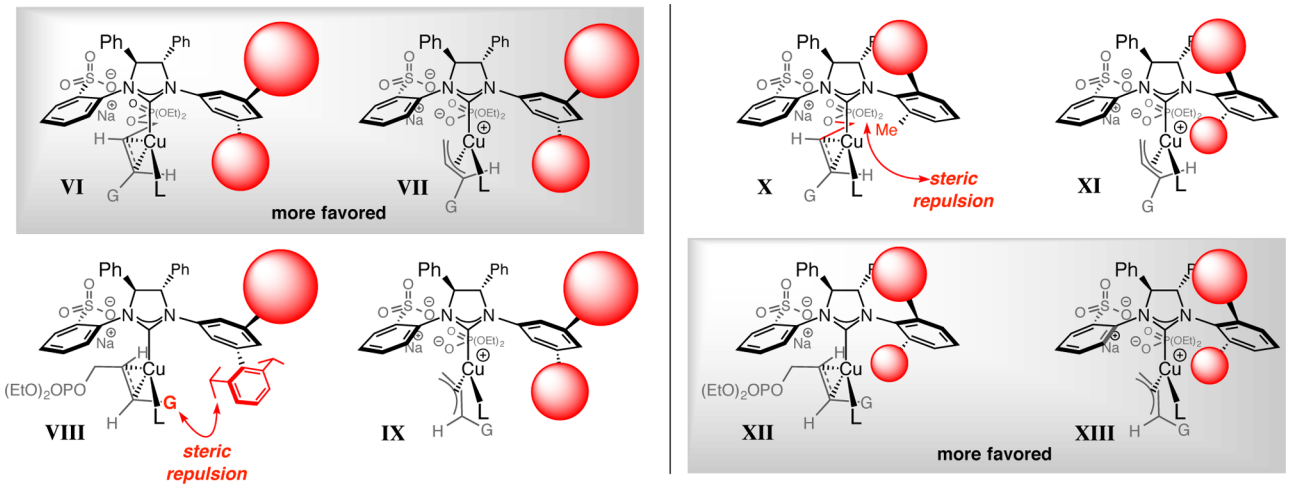
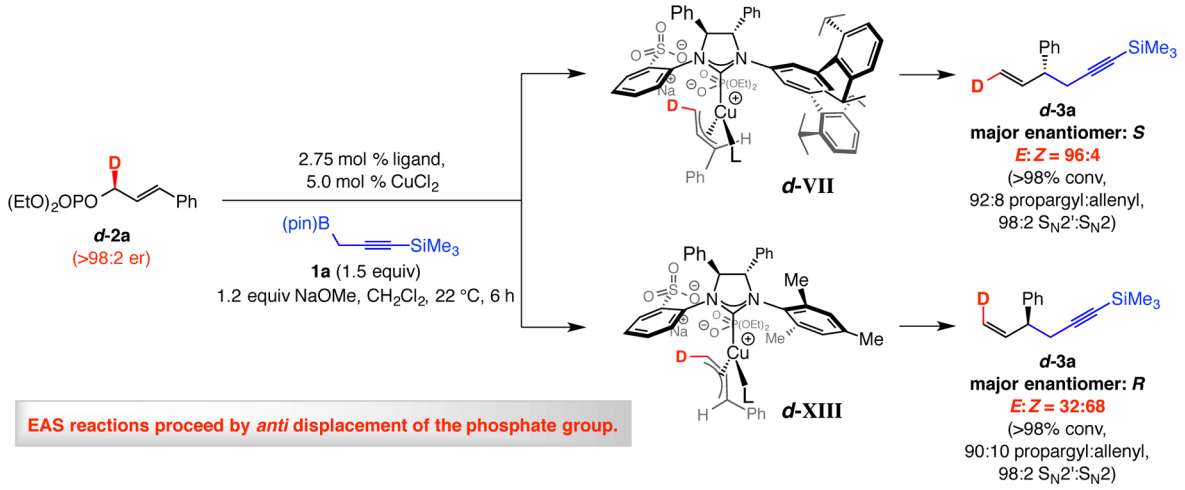


Figure 3. Stereochemical models accounting for different stereochemical outcomes with sulfonate-containing NHC–Cu complexes that contain a 3,5-disubstituted *N*-aryl moiety (e.g., derived from **9a**,**b** or **10a**,**b**; **VI**–**IX**) and those that bear a 2,6-disubstituted variant of the same moiety (e.g., derived from **9c**, **9e**–**g**; **X**–**XIII**). Abbreviations: L, alkenyl, alkynyl, allenyl, or propargyl group; G, substituent.

engenders repulsive steric interaction with the large *N*-aryl moiety of the Cu complex. As already mentioned, because of the size and mobility of the system it would be difficult to reach a reliable conclusion based on DFT calculations as to whether the oxidative addition or the reductive elimination step is turnover-limiting. Additionally, complications due to conformational complexity are exacerbated by the loosely associated $Na^+O_2P(OMe)_2^-$ salt (cf. **PA$_A$** → **Prod$_A$**, Figure 2). Nonetheless, our investigations indicate that the pathways leading to allenyl addition are energetically more costly. (Animations that

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948–8964

Scheme 12. Regarding the Stereochemistry of Phosphate Displacement



illustrate the proposed mechanistic picture are provided as part of the Supporting Information.)

5.4. Stereochemical Models: Scope and Relevance to EAS Reactions with Other Types of Sulfonate-Containing NHC–Cu Complexes. Given the uncertainty of the computed energies, the suggested mechanistic model would benefit from support in the form of applicability to EAS reactions promoted by additional classes of NHC–Cu systems and/or those that involve other types of organoboron reagents. In this context, we have been able to determine that the formerly reported enantioselectivities of alkenyl,[10] allenyl,[9] and alkynyl[6a] additions correlate favorably with the structure/selectivity pattern outlined above.

On the basis of the results of DFT calculations,[47] we propose that the presence of two sizable meta substituents within the 3,5-disubstituted *N*-aryl groups of the NHC–Cu catalysts derived from **9a,b** or **10a,b** are responsible for the observed enantioselectivities (**VI**–**IX**, Figure 3). Moreover, EAS promoted by sulfonate-bearing NHC–Cu complexes **9c**, **9e**–**g**, and **10c**, which carry an *N*-aryl unit with substituents at its C2 and C6 sites, should favor the opposite sense of stereochemical induction (**X**–**XIII**), consistent with the experimental findings presented here (cf. entry 8, Table 1) and in former disclosures.[6,9,10]

As discussed earlier, the principal stereochemistry-determining factors are tied to the structural preferences associated with a d^8 configuration in Cu(III) species and an appreciable tendency toward square planar structures (cf. Scheme 10). Analysis of the models illustrated in Figure 3 demonstrates that, because of the absence of ortho substituents in the *N*-aryl moiety of the Cu complex derived from imidazolinium salt **9b**, reaction through the mode of addition represented by **VI** is less energetically costly than the steric repulsion that would otherwise arise between the substrate substituent (G) and the sizable meta substituent in **VIII** (Figure 3). The lower enantioselectivities when quaternary carbon stereogenic centers are formed (cf. Tables 2 and 4) can be rationalized based on an opposing but less severe steric interaction between the trisubstituted alkene's methyl group and the *N*-aryl's meta substituents in **VI** and **VII**. With ortho-substituted *N*-aryl units in ligands **9c** and **9e**–**g** the steric pressure on the allylic carbon of the substrate increases, rendering modes of addition **XII**–**XIII** more preferable (vs **X**–**XI**; Figure 3). The present stereochemical model accounts for the opposite sense of enantioselectivity observed for reactions promoted by the two classes of sulfonate-containing NHC–Cu complexes (e.g., entries 7 and 8, Table 1).

To secure additional support for the suggested mechanistic scenario, we designed the deuterium-labeling experiments presented in Scheme 12. The EAS reaction performed with enantiomerically enriched (>98:2 er) and isotopically labeled allylic phosphate *d*-**2a** furnished enyne (*E*)-*d*-**3a** with 96:4 *E*:*Z* selectivity when imidazolinium ligand, containing a 3,5-disubstituted *N*-aryl moiety **10b**, was used as the catalyst precursor; this observation is consistent with the high enantioselectivity obtained with **2a** (97:3 er; cf. Table 1, entry 7). Further, the diastereoselectivity with which enyne (*Z*)-*d*-**3a** was generated (32:68 *E*:*Z*) through EAS promoted by NHC–Cu complex originating from *N*-Mes-substituted ligand **10c** is congruent with the original alteration of the sense (reversal vs **10b**) and level of enantioselectivity (31:69 er; Table 1, entry 8). These data lend credence to the proposal that the phosphate group is displaced with anti stereochemistry (vs the incipient Cu–C bond) in processes that occur via square planar cationic Cu(III) π-allyl species represented by *d*-**VII** and *d*-**XIII**.[57] Furthermore, the high stereoselectivities observed (Scheme 12) indicate that π-allyl isomerization does not compete with the reductive elimination process. These results are in contrast to the frequently occurring π-allyl isomerizations at Cu(I) species that provide the basis for Curtin–Hammett kinetics, such as was discussed for complexes **A** and **B** (cf. Scheme 7 and Figure 2).

■ CONCLUSION

We disclose the first examples of allylic substitution reactions that culminate in the addition of a propargyl unit; depending on the catalyst employed, achiral linear or chiral, branched products can be obtained with high selectivity. When transformations were performed in the presence of a Cu complex that contains an enantiomerically pure sulfonate-containing ligand, not only was exceptional site selectivity observed, enantioselectivity levels of 83:17–99:1 er were achieved as well. We demonstrate that additions can be carried out with di- or trisubstituted alkene substrates: 1,5-enynes that contain an allylic tertiary or all-carbon quaternary stereogenic center may be generated.

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948–8964

The EAS products are structurally distinct from those produced by related previously disclosed protocols (e.g., reactions that lead to incorporation of an alkenyl, allenyl, alkynyl, or allyl moiety). From the point of view of chemical synthesis, a notable aspect of the catalytic method is that it contains readily differentiable alkynyl and alkenyl sites; the acetylene unit can be transformed, among other possibilities, to a *Z*-alkenyl halide or an *E*-alkenyl−B(pin) moiety. These are secondary products accessed by reactions that occur with complete chemoselectivity (<2% at the alkenyl site) but may not be as concisely and/or efficiently synthesized directly or through functionalization of compounds formed by an alternative EAS process (e.g., difficulty in chemoselective modification of a 1,5-diene derived from enantioselective allyl−allyl coupling). We show that the aforementioned attributes can be exploited in the use of sequential EAS reactions as the means to prepare reasonably complex acyclic polyenes that possess remote stereogenic centers (1,5). The linear fragment of plakinic acid A was prepared through NHC−Cu-catalyzed group-, site-, and enantioselective propargyl addition, followed by an NHC−Cu-catalyzed proto-boryl addition to the (desilylated) alkyne and a second NHC−Cu-catalyzed EAS involving the alkenyl−B(pin) residue.

A variety of mechanistic questions have been addressed; these studies also pertain to a number of previously reported catalytic EAS protocols. Unlike former EAS methods promoted by Cu-based complexes, much of the complications arise from the possibility of either dissymmetric unsaturated hydrocarbon fragment to participate in the C−C bond forming process by involvement of two different carbon sites. We show that, according to DFT calculations, it is not reactions via the lower energy copper−allenyl species that leads to the observed products; rather, the predominant reaction route involves the more reactive isomeric propargylmetal species (Curtin−Hammett kinetics). A central issue relates to the strong dependence of ligand structure on the tendency of the derived Cu complex to promote the formation of branched (S_N2' process) or linear products (S_N2 mode of reaction). We provide support for a chelating/directing role of the sulfonate group through a cationic mediator (Na^+); this leads to the generation of Cu(III) π-allyl intermediates that can undergo reductive elimination to generate 1,5-enyne products preferentially. Experimental support for the involvement of Cu(III) π-allyl intermediates has been provided in the form of deuterium labeling experiments; we illustrate that the O−C bond is ruptured anti to the incipient Cu−C bond during the oxidative addition process (i.e., on the opposite side of the allyl fragment).

The advances detailed in this report, the ones corresponding to issues of reaction development as well as those that further our mechanistic understanding, are expected to enhance the utility of this already important class of C−C bond forming transformations as well as pave the way for upcoming efforts in reaction and catalyst design.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details for all reactions and analytic details for all enantiomerically enriched products and tables of electronic and free energies and geometries of computed structures for two model systems with imidazolinium salts **9b** and **9g** at various levels of theory as well as graphical representation of the potential energy surfaces. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05805.

■ AUTHOR INFORMATION

Corresponding Author

*amir.hoveyda@bc.edu

Author Contributions

Y.S. and B.J. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Professor Richard R. Schrock on the occasion of his seventieth birthday. Financial support was provided by the NIGMS (GM-47480). We thank Kashif Khan and Tyler Mann for helpful advice regarding the catalytic cross-metathesis reactions and Kevin McGrath and Fang Gao for additional informative discussions.

■ REFERENCES

(1) For reviews on catalytic EAS reactions with "hard" C-based nucleophilic reagents, see: (a) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779−1785. (b) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435−4439. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796−2823. (d) Baslé, O.; Denicourt-Nowicki, A.; Crévisy, C.; Mauduit, M. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A., Krause, N., Woodward, S., Eds.; Wiley−VCH: Weinheim, Germany, 2014; pp 85−125.

(2) For representative studies performed in these laboratories on EAS reactions promoted by NHC-based chiral complexes and with alkyl-based organometallic reagents, see: (a) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 15604−15605. (b) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554−4558. (c) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860−3864.

(3) The manuscripts were identified by means of Scifinder, Web of Science and Google Scholar search engines. For a complete list of the manuscripts indicated in the analysis in Figure 1, see the Supporting Information.

(4) (a) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446−447. (b) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419−423. With a related investigation involving aryl- or heteroarylaluminum reagents, (c) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8370−8374.

(5) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961−10963.

(6) (a) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778−4781. (b) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7694−7699. For a more recent related study, see: (c) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7532. (d) Harada, A.; Makida, Y.; Sato, H.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 13932−13939.

(7) Hall, D. G., Ed. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Wiley−VCH: Weinheim, Germany, 2005.

(8) For NHC−Cu-catalyzed EAS processes performed with arylboronic acid neopentyl glycol esters, see: Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656−8659.

(9) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490−1493.

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

(10) (a) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6613−6617. (b) Gao, F.; Carr, J. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 2149−2161.
(11) Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026−6029.
(12) For a recent case of catalytic EAS with organolithium reagents, see: Pérez, M.; Fañanás-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. *Nat. Chem.* **2011**, *3*, 377−381.
(13) For a review regarding catalytic EAS with Grignard reagents, see: (a) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824−2852. For a recent example, see: (b) Hornillos, V.; Pérez, M.; Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2013**, *135*, 2140−2143.
(14) For a review regarding catalytic enantioselective propargyl addition reactions, see: Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914−1937.
(15) (a) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716−9719. (b) Ref 13b. (c) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 3006−3009. For examples involving an alkenyl−B(pin)-containing allylcopper reagent, see: (d) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367−374.
(16) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 8770−8773.
(17) Hoffmann, R. W.; Brinkmann, H.; Frenking, G. *Chem. Ber.* **1990**, *123*, 2387−2394.
(18) (a) Fandrick, D. R.; Reeves, J. T.; Song, J. J. International Patent WO 2010/141328 A2, 2010. (b) Fandrick, D. R.; Roschangar, F.; Kim, C.; Hahm, B. J.; Cha, M. H.; Kim, H. Y.; Yoo, G.; Kim, T.; Reeves, J. T.; Song, J. J.; Tan, Z.; Qu, B.; Haddad, N.; Shen, S.; Grinberg, N.; Lee, H.; Yee, N.; Senanayake, C. H. *Org. Process Res. Dev.* **2012**, *16*, 1131−1140.
(19) (a) Fandrick, D. R.; Reeves, J. T.; Tan, Z.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5458−5461. (b) Flegeau, E. F.; Schneider, U.; Kobayashi, S. *Chem.—Eur. J.* **2009**, *15*, 12247−12254. (c) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 7600−7601. (d) Fandrick, D. R.; Johnson, C. S.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 748−751. (e) Fandrick, K. R.; Fandrick, D. R.; Reeves, J. T.; Gao, J.; Ma, S.; Li, W.; Lee, H.; Grinberg, N.; Lu, B.; Senanayake, C. H. *J. Am. Chem. Soc.* **2011**, *133*, 10332−10335. (f) Fandrick, D. R.; Saha, J.; Fandrick, K. R.; Sanyal, S.; Ogikubo, J.; Lee, H.; Roschangar, F.; Song, J. J.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 5616−5619. (g) Reddy, L. R. *Chem. Commun.* **2012**, *48*, 9189−9191. (h) Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Rodriguez, S.; Qu, B.; Kim, S.; Niemeier, O.; Li, Z.; Byrne, D.; Campbell, S.; Chitroda, A.; DeCroos, P.; Fachinger, T.; Fuchs, V.; Gonnella, N. C.; Grinberg, N.; Haddad, N.; Jäger, B.; Lee, H.; Lorenz, J. C.; Ma, S.; Narayanan, B. A.; Nummy, L. J.; Premasiri, A.; Roschangar, F.; Sarvestani, M.; Shen, S.; Spinelli, E.; Sun, X.; Varsolona, R. J.; Yee, N.; Brenner, M.; Senanayake, C. H. *J. Org. Chem.* **2013**, *78*, 3616−3635.
(20) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358−7362.
(21) Control experiments indicate that Ag−NHC complexes do not promote the EAS process. For catalytic transformations promoted by Ag-based complexes and involving organoboron reagents (thus involving Ag/B exchange processes), see: (a) Wisniewska, H. M.; Jarvo, E. R. *Chem. Sci.* **2011**, *2*, 807−810. (b) Kohn, B. L.; Ichiishi, N.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 4414−4417.
(22) Transformations are equally selective when performed in THF but require 24 h to reach completion (vs 6 h in CH_2Cl_2). However, the Cu(II) salt is preferred due to its somewhat lower cost.
(23) For an example where the presence of a pyridyl group leads to deactivation of a Cu-based complex, see: Meng, F.; Jang, H.; Jung, B.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 5046−5051.
(24) For recent reviews on catalytic enantioselective methods for formation of all-carbon quaternary stereogenic centers, see: (a) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593−4623. (b) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181−191.
(25) Unlike EAS reactions that afford a tertiary carbon center, those that generate a quaternary carbon deliver lower site- and enantioselectivity when performed in CH_2Cl_2 (vs THF). For example, under otherwise identical conditions as shown in Table 4 but with CH_2Cl_2 as the solvent, **17a** was obtained in 74% yield with 73:27 S_N2'/S_N2 selectivity and 87:13 er (vs 84% yield, 94:6 S_N2'/S_N2 selectivity, and 92:8 er).
(26) As far as we are aware, with one exception, all reported examples of site-selective functionalization of 1,5-dienes that are derived from enantioselective allyl−allyl coupling reactions involve substrates that carry an allylic quaternary carbon stereogenic center (i.e., one olefin is significantly more sterically encumbered); see ref 15a. The exception is a noncatalytic hydroboration (with 9-BBN), which takes place with 9:1 site selectivity; see: Hamilton, J. Y.; Hauser, N.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10759−10762.
(27) (a) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859−860. (b) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747−751. Converting a 1,5-diene compound (derived from allyl−allyl cross-coupling) to a monosubstituted allene would be substantially more complicated. Firstly, it is improbable that high levels of chemoselectivity would be achievable. Secondly, in the event that high chemoselectivity could somehow be attained, one procedure calls for formation of the derived dibromocyclopropane, followed by treatment with *n*-BuLi at −10 °C, see: (c) Moore, W. R.; Ward, H. R. *J. Org. Chem.* **1962**, *27*, 4179−4181.) These harsh conditions do not tolerate a variety of important functional groups, and moreover, we have found this latter procedure to be generally unreliable and low yielding. The only alternative would then be to convert the alkene to an alkyne through conversion to the corresponding aldehyde, subsequent treatment with $TMSCHN_2$, and then a Crabbé reaction. (d) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, *1994*, 107−108. Not only is such an approach more cumbersome, it is doubtful that one of the two α-alkene moieties can be selectivity converted to an aldehyde by oxidative cleavage.
(28) For recent examples, see: site- and stereoselective hydroamination reactions catalyzed by Au- or Rh-based complexes, (a) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314−3317. (b) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066−9073. (c) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 10876−10879. Site- and stereoselective silylboron additions, (d) Ohmura, T.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2006**, *128*, 13682−13683. Site- and stereoselective diboron additions catalyzed by phosphine−Pd complexes, (e) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766−8773. Site- and stereoselective cross-coupling with arylboronic acids catalyzed by phosphine−Pd complexes, (f) Yoshida, M.; Matsuda, K.; Shoji, Y.; Gotou, T.; Ihara, M.; Shishido, K. *Org. Lett.* **2008**, *10*, 5183−5186. (g) Yoshida, M.; Shoji, Y.; Shishido, K. *Org. Lett.* **2009**, *11*, 1441−1443. Site- and stereoselective protoboration reactions promoted by NHC− or phosphine−Cu complexes, (h) Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. *Org. Lett.* **2013**, *15*, 1414−1417. (i) Yuan, W.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 1867−1872. Site-, diastereo-, and enantioselective Cu−B(pin) addition/addition to aldehydes and ketones catalyzed by phosphine−Cu complexes, (j) ref 23. Conversion to propargyl bromides and heterocyclic derivatives, (k) ref 17. (l) Wu, H.; Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 3780−3783. Stereoselective [2 + 2 + 2] cycloadditions catalyzed by phosphine−Rh complexes, (m) Noucti, N. N.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 8424−8427. Site- and stereoselective cross-coupling with arylboronic acids promoted by NHC−Cu complexes, (n) Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 3475−3479. (o) Li, C.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 862−865. For a review on the use of

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964

allenes in chemical synthesis, see: (p) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074−3112.
(29) (a) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046−16047. (b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154−3157.
(30) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1897−1900.
(31) (a) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727−1730. (b) Sidera, M.; Costa, A. M.; Vilarrasa, J. *Org. Lett.* **2011**, *13*, 4934−4937.
(32) For representative C−C bond forming reactions that involve alkenyl iodide compounds, see: (a) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215−4217. (b) Kabir, M. S.; Lorenz, M.; Namjoshi, O. A.; Cook, J. M. *Org. Lett.* **2010**, *12*, 464−467. (c) LeClair, C. A.; Boxer, M. B.; Thomas, C. J.; Maloney, D. J. *Tetrahedron Lett.* **2010**, *51*, 6852−6855. (d) Krasovskiy, A.; Lipshutz, B. H. *Org. Lett.* **2011**, *13*, 3818−3821. (e) Krasovskiy, A.; Lipshutz, B. H. *Org. Lett.* **2011**, *13*, 3822−3825. (f) Carrillo, J.; Gómez, A.; Costa, A. M.; Fernández, P.; Isart, C.; Sidera, M.; Vilarrasa, J. *Tetrahedron Lett.* **2014**, *55*, 4623−4627.
(33) To the best of our knowledge, there are two examples of the use of a methyl-substituted electrophilic partner in an EAS reaction involving "hard" nucleophiles. See: (a) ref 14d; (b) ref 6d.
(34) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859−7871.
(35) (a) Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807−810. (b) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031−6034. (c) Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026−6029.
(36) For NHC−Cu-catalyzed EAS reactions involving alkenylboron reagents, see: (a) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656−8659. (b) Ref 10.
(37) (a) Phillipson, D. W.; Rinehart, K. L. *J. Am. Chem. Soc.* **1983**, *105*, 7735−7736. Structurally related natural products exhibit cytotoxic activity; see: (b) Davidson, B. S. *J. Org. Chem.* **1991**, *56*, 6722−6724.
(38) For a study regarding total synthesis of plakinic acid A, see: Dai, P.; Trullinger, T. K.; Liu, X.; Dussault, P. H. *J. Org. Chem.* **2006**, *71*, 2283−2292.
(39) For a comprehensive review on the use of molybdenum alkylidenes in chemical synthesis, see: Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633.
(40) For reviews on catalytic enyne metathesis reactions, see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (b) Fischmeister, C.; Bruneau, C. *Beilstein J. Org. Chem.* **2011**, *7*, 156−166 . .
(41) (a) Ref 9b. (b) Jang, H.; Jung, B.; Hoveyda, A. H. *Org. Lett.* **2014**, *16*, 4658−4661.
(42) The EAS reactions, regardless of the source of the Cu salt used (CuCl or $CuCl_2$), likely involves NHC−Cu(I) species. This hypothesis is supported by the nearly identical selectivities observed regardless of the copper halide used. See also ref 22.
(43) Fandrick, K. R.; Ogikubo, J.; Fandrick, D. R.; Patel, N. D.; Saha, J.; Lee, H.; Ma, S.; Grinberg, N.; Busacca, C. A.; Senanayake, C. H. *Org. Lett.* **2013**, *15*, 1214−1217.
(44) Mszar, N. W.; Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 3362−3365.
(45) Lee, Y.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 11625−11633.
(46) For detailed comparative molecular orbital analysis of cuprate and zincate complexes, see: Mori, S.; Hirai, A.; Nakamura, M.; Nakamura, E. *Tetrahedron* **2000**, *56*, 2805−2809.
(47) See the Supporting Information for details.
(48) Brown, K. M.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097−1100.
(49) For a review regarding general mechanistic aspects of nucleophilic Cu reactions, see: Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339−2372.
(50) Consistent with proposed energetic scenario, Cu(III) complexes have scarcely been isolated and require the presence of polyfluoroalkyl groups or a macrocyclic ligand structure (e.g., porphyrin) to survive. For representative examples, see ref 48.
(51) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334−338.
(52) For references suggesting the use of dispersion-corrected density functionals, see: (a) Zhao, Y.; Truhlar, D. G. *Org. Lett.* **2007**, *9*, 1967−1970. (b) Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615. (c) Torker, S.; Merki, D.; Chen, P. *J. Am. Chem. Soc.* **2008**, *130*, 4808−4814. (d) Minenkov, Y.; Occhipinti, G.; Singstad, A.; Jensen, V. R. *Dalton Trans.* **2012**, *41*, 5526−5541.
(53) For mechanistic investigations regarding linear/branched selectivity in allyic substitution and conjugate addition reactions, see: (a) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287−6293. (b) Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 4697−4706. (c) Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862−12863.
(54) (a) Vedernikov, A. N. *Acc. Chem. Res.* **2012**, *45*, 803−813. (b) For a related review regarding bimetallic oxidative palladium catalysis, see: Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2012**, *45*, 840−850.
(55) For the role of chelating interactions to control regioselectivity in allylic substitution reactions promoted by Cu, see: Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862−12863.
(56) The related experiment with LiOMe afforded <2% conversion due to low solubility of the salt.
(57) For previous investigations regarding the stereochemical attributes for displacement of a phosphate leaving group (syn vs anti relative to Cu), see: Takeda, M.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2014**, *79*, 2354−2367.

DOI: 10.1021/jacs.5b05805
J. Am. Chem. Soc. 2015, 137, 8948−8964