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Site- and Enantioselective Formation of Allene-Bearing Tertiary or Quaternary Carbon Stereogenic Centers through NHC−Cu-Catalyzed Allylic Substitution

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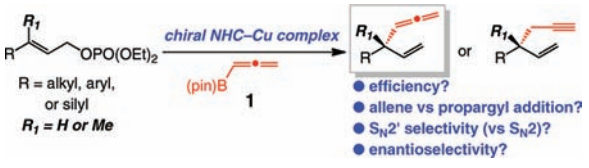
Supporting Information

ABSTRACT: Catalytic enantioselective allylic substitutions that result in addition of an allenyl group (<2% propargyl addition) and formation of tertiary or quaternary C−C bonds are described. Commercially available allenylboronic acid pinacol ester is used. Reactions are promoted by a 5.0−10 mol % loading of sulfonate-bearing chiral bidentate N-heterocyclic carbene (NHC) complexes of copper, which exhibit the unique ability to furnish chiral products arising from the S_N2' mode of addition. Allenyl-containing products are generated in up to 95% yield, >98% S_N2' selectivity, and 99:1 enantiomeric ratio (er). Site-selective NHC−Cu-catalyzed hydroboration of enantiomerically enriched allenes and conversion to the corresponding β-vinyl ketones demonstrates the method's utility.

Allenes are of significant utility in chemical synthesis.[1] Efficient protocols for preparing enantiomerically enriched allene-containing molecules can therefore be of substantial value; such procedures, however, are uncommon.[2] We have developed methods for enantioselective allylic substitution (EAS) reactions,[3] through which alkylmetals (i.e., Zn ,[4] Mg ,[5] or Al alkyls[6]) or vinyl-,[7] aryl-, heteroaryl-,[8] and alkynylaluminums[9] can be utilized to generate tertiary or quaternary carbon stereogenic centers.[10] We recently set out to explore whether the chiral NHC−Cu complexes[11] used to promote the aforementioned reactions with organometallic reagents[4−8] can catalyze additions with the commercially available and air-stable allenylboronic acid pinacol ester **1** (Scheme 1). We judged that

Scheme 1. [a]

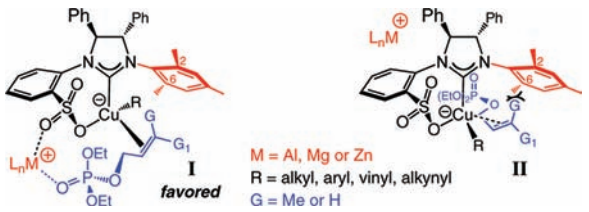


[a] B(pin) = pinacolatoboron.

the boron-based reagent would likely offer a more practical and functional group-tolerant alternative to a corresponding organometallic entity. Herein, we demonstrate that reactions of allylic phosphates bearing a di- or a trisubstituted alkene with allenylboron **1** proceed with exclusive addition of an allenyl unit (<2% propargyl addition). Transformations are performed with 10 mol % of sulfonate-bearing chiral bidentate NHC−Cu complexes, which exhibit the unique ability to promote site-selective addition of an allenyl group (77% to >98% S_N2'); the desired products are generated in 63−95% yield and 90.5:9.5−99:1 enantiomeric ratio (er).

The design of an efficient EAS with a boron-based reagent[12] raises a number of questions that are distinct from those pertaining to reactions with organometallics (e.g., a vinylmetal or an allenylmetal). One issue relates to the significance of Lewis acidic metal salts. For example, our studies indicate that in Cu-catalyzed allylic substitutions of trisubstituted allylic phosphates,[7c] the equatorial Lewis basic sulfonate oxygen can be involved in a metal chelate with the phosphate unit (**I**, Scheme 2);[5] the reactivity might be accordingly enhanced,

Scheme 2. Reaction Modes with Organometallic Reagents



allowing reactions to be performed at lower temperatures (e.g., −50 °C), leading to an improvement in enantioselectivity. Although in **I** and **II**, the bound substrate is orientated such that there is proper alignment of the Cu−R σ bond with the LUMO of the allylic phosphate, Lewis acid activation in **I** together with unfavorable steric interactions in **II** result in the former delivering the major isomer. Lewis acidic metal activation and organization is absent with an organoboron.

The second problem is that the allenylcuprate[13] (cf. complexes in Scheme 2) might not be efficiently generated with a substantially less nucleophilic organoboron (vs an organometallic). We surmised that the presence of a metal alkoxide, such as NaOMe,[14] should allow the NHC−Cu−allene to be formed by transmetalation via the allenylboronate (eq 1).[15]

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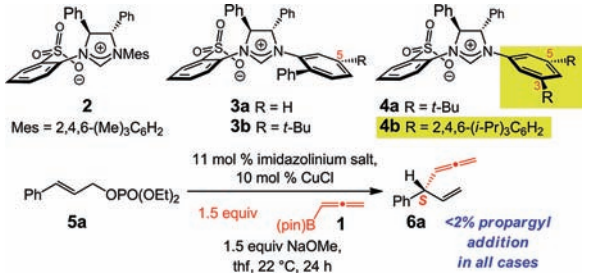
The third potential complication is whether C–C bond formation can occur selectively at the C3 position (propargyl addition) or C1 position (allenyl addition; cf. cuprate in eq 1).[16] Such issues did not concern the previously reported reactions with vinylmetals.[7] In this connection, during recent studies regarding allyl additions to imines,[17] we established that the corresponding NHC–Cu–allyls collapse readily to the derived π-allyl complexes, resulting in a nonselective mode of reaction at the two termini.

With **5a** serving as the substrate, we first examined the ability of the NHC–Cu complex derived from sulfonate **2** to promote the desired addition. As the data in entry 1 of Table 1 illustrate,

Table 1. Evaluation of Chiral NHC Complexes[a]

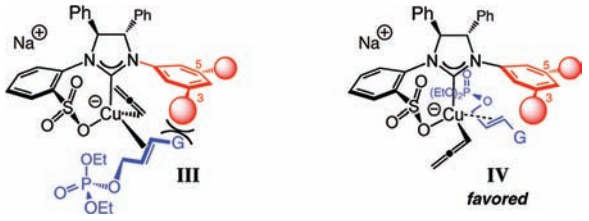


entry	imide salt	conv (%)[b]	$S_N2':S_N2$[b]	er[c]; config.[d]
1	**2**	67	>98:2	34:66; *R*
2	**3a**	82	90:10	45:55; *R*
3	**3b**	83	>98:2	26:74; *R*
4	**4a**	92	98:2	83:17; *S*
5	**4b**	***>98***	***96:4***	***95.5:4.5; S***

[a]Reactions were performed under N_2. [b]Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures and based on consumption of the substrate. [c]Determined by GLC analysis. [d]Configuration of the major enantiomer; see the SI for details.

the reaction proceeded with complete group- and site selectivity (<2% propargyl[18] and <2% S_N2 addition); <2% conversion was observed without the Cu salt. The enantioselectivity was low, however (34:66 er); presumably, in the absence of a metal chelate between the catalyst and substrate and without a third alkene substituent, reaction via complexes otherwise represented as **I** and **II** (Scheme 2) become competitive. Among the catalysts probed subsequently, the findings related to **3a** and **3b** were particularly informative (Table 1, entries 2 and 3). We realized that the presence of a *t*-Bu at C5 of the NAr moiety leads to a more favorable formation of (*R*)-**6a**, likely by disfavoring **IV** versus **III** (Scheme 3). Follow-up examination of molecular models suggested that substitution at C3 and C5 of the NAr can exert a significant effect on the association of the alkene substrate with the NHC–Cu complex. We also noted that a group at C3 blocks substrate coordination more effectively (see **III** in Scheme 3) relative to the ability of a C5 substituent to impede the same in **IV**; we attributed this partly to the lack of the methyls at C2 and C6 (cf. **I** and **II**, Scheme 2) allowing the NAr to be oriented such that the group at C3 more effectively hinders substrate approach in **III**. Such considerations led us to discover that the Cu complex derived from

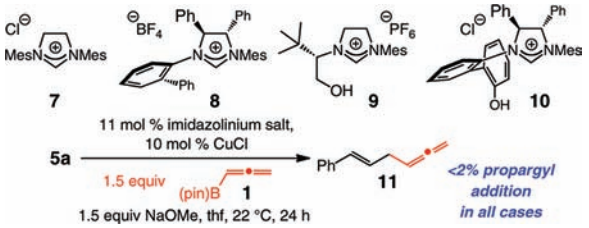
Scheme 3.



4a, bearing a 3,5-di-*tert*-butylphenyl group (Table 1, entry 4), promoted the formation of **6a** efficiently and with 83:17 er. As implied by the proposed model, the *S* isomer is generated predominantly with **4a** (vs 74% *R* with **3b**; entry 3). With the larger triisopropylphenyl groups at C3 and C5 (**4b**), the enantioselectivity improved to 95.5:4.5 er (entry 5), presumably since **III** was further disfavored.

Additional studies led us to discover that high S_N2' selectivity is a unique attribute of sulfonate-bearing NHC–Cu catalysts. In strong contrast to EAS with sulfonate-containing imidazolinium salts **2**–**4** (Table 2), reactions with monodentate salts **7** and **8**

Table 2. Control of Site Selectivity[a]



entry	imide salt	conv(%);[b] yield (%)[e]	$S_N2':S_N2$[b]	er[c]; config.[d]
1	**7**	79; 68	***<2:>98***	n.a.[f]
2	**8**	74; 68	***<2:>98***	n.a.[f]
3	**9**	71; 65	***5:95***	36:64; *R*
4	**10**	76; 66	***<2:>98***	n.a.[f]

[a–d]See footnotes *a*–*d* of Table 1. [e]Yield of purified product. [f]n.a. = not applicable.

and the bidentate variants **9** and **10** delivered achiral **11** with exceptional but *opposite* sense of site selectivity (≥95% S_N2). Complexes derived from bidentate sulfonate complexes (cf. Table 1) favor S_N2' addition likely because of the stronger (vs allenyl–Cu) association of the more electron-rich cuprates with the alkene of the substrate (more appreciable Cu→π* back-bonding). Allenyl–Cu complexes derived from monodentate **7** or **8** are probably more prone (vs cuprate) to displace the phosphate directly (S_N2),[19] a process that could involve chelation of the more Lewis acidic and less hindered Cu center (vs a cuprate) with the Lewis basic phosphate.[20] Moreover, the alkoxy–Cu or phenoxy–Cu bonds in complexes derived from **9** and **10** can undergo cleavage,[12c] yielding a monodentate NHC–Cu–allene.[20] Such intramolecular transmetalation is less likely through the poorly Lewis basic oxygen of a sulfonate ligand.[21] The ability to preserve their cuprate character appears to be another special attribute of sulfonate-bearing NHC–Cu complexes, translating into a unique preference for S_N2' selectivity.

A range of aryl-substituted allylic phosphates can be used to generate allene-substituted tertiary C–C bonds in 64–92% yield, 77% to >98% S_N2' selectivity, and 95:5–99:1 er (Table 3).

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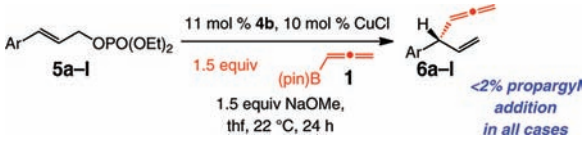
Table 3. Additions to Aryl Containing Substrates[a]



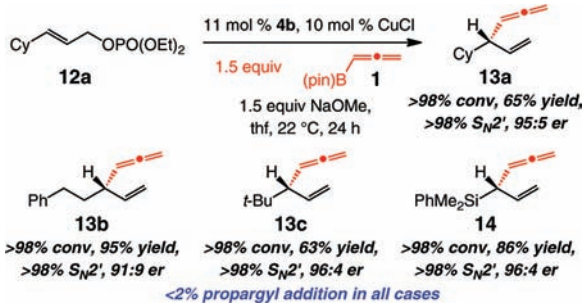
entry	Ar	conv (%);[b] yield (%)[c]	$S_N2':S_N2$[b]	er[d]
1	Ph, **5a**	>98; 79	96:4	95.5:4.5
2	*o*-FC_6H_4, **5b**	>98; 79	94:6	96:4
3	*o*-BrC_6H_4, **5c**	>98; 80	88:12	96:4
4	*o*-$CF_3C_6H_4$, **5d**	>98; 67	77:23	96:4
5	*o*-MeC_6H_4, **5e**	>98; 68	>98:2	95:5
6	*o*-$MeOC_6H_4$, **5f**	>98; 79	>98:2	96.5:3.5
7	*m*-BrC_6H_4, **5g**	>98; 92	97:3	98.5:1.5
8	*m*-$CF_3C_6H_4$, **5h**	>98; 65	91:9	98:2
9	*m*-MeC_6H_4, **5i**	>98; 71	>98:2	97:3
10	2-naphthyl, **5j**	>98; 88	98:2	99:1
11	*p*-ClC_6H_4, **5k**	>98; 64	93:7	96:4
12	*p*-$O_2NC_6H_4$, **5l**	>98; 69	85:15	97:3

[a]Reactions were performed under N_2. [b]Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures; conversion refers to consumption of the substrate. [c]Yields of isolated and purified allenyl addition products. [d]Determined by GLC analysis; see the SI for details.

Substrates with an electron-withdrawing (entries 2–4, 7, 8, 11, and 12) or an electron-donating (entries 5, 6, and 9) group as well as those that carry a sterically demanding aryl unit (entries 5 and 10) undergo EAS to furnish the desired products site- and enantioselectively. Analysis of the data in Table 3 indicates that an electron-deficient substituent at the more influential ortho or para position within a substrate can lead to diminution of the site-selectivity (up to 23% S_N2 product; entries 1 and 5 vs entries 3, 4, 8, and 12).[22]

Allylic phosphates that contain an alkyl group (including a sterically demanding *t*-Bu) or a silyl group can be used in highly site- and enantioselective allene additions; the examples presented in Scheme 4 are illustrative. Similar to the reactions

Scheme 4. [a]

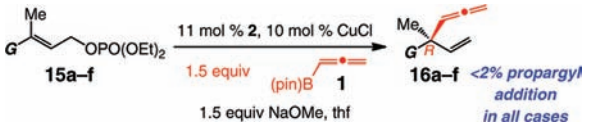


[a]Reactions were performed under the conditions in Table 2. The relatively low yields of **13a** and **13c** were due to volatility.

shown in Table 3, none of the alternative propargyl addition products were detected. Unlike the reactions of aryl-substituted substrates, there was complete S_N2' selectivity in all instances.

The catalytic EAS can be performed with trisubstituted allylic phosphates to generate all-carbon quaternary stereogenic centers in up to 83% yield, >98% S_N2' selectivity, and 98:2 er (Table 4).[10] Reactions with substrates carrying an ortho substituent must be performed at 22 °C (Table 4, entries 2–3,

Table 4. Additions to Trisubstituted Alkenes[a]



entry	*G*	temp (°C); time (h)	conv (%);[b] yield (%)[c]	$S_N2':S_N2$[b]	er[d]
1	Ph, **15a**	−30; 48	89; 74	>98:2	93.5:6.5
2	*o*-BrC_6H_4, **15b**	22; 24	>98; 79	91:9	98:2
3	*o*-$MeOC_6H_4$, **15c**	22; 24	>98;83	>98:2	95.5:4.5
4	*m*-BrC_6H_4, **15d**	−30; 48	82; 72	>98:2	90.5:9.5
5	*p*-ClC_6H_4, **15e**	−30; 48	85; 77	>98:2	91:9
6	Cy, **15f**	−30; 48	>98; 72	>98:2	94:6

[a–d]See footnotes *a*–*d* of Table 3.

vs −30 °C for Table 4, entries 1 and 4–6); otherwise <5% conversion was observed after 24 h. Unlike the reactions of disubstituted allylic phosphates, when **4b** was employed to prepare the Cu-based catalyst, low enantioselectivity was observed (33:67 er; 94% S_N2').[23] When imidazolinium salt **2** was used, **16a** was formed in 93.5:6.5 er (Table 4, entry 1). It is plausible that the alkene's methyl substituent induces an unfavorable steric interaction with the catalyst's NAr unit in the complex corresponding to **IV** (Scheme 3), rendering it a less favored mode of reaction. Similar repulsive forces are present in **II** (*G* = Me) but not in **I** (Scheme 2), which accounts for the observed level and sense of enantioselectivity when the NHC–Cu complex derived from **2** served as the catalyst [93.5% (*R*)-**16a** vs 67% (*S*)-**16a** with **4b**]. When the reactions were performed at reduced temperatures to improve the enantioselectivity, the reactivity suffered (e.g., 89% conv. to **16a** in 48 h at −30 °C), which might be partly due to the absence of the activating effect of a Lewis acidic metal salt (see Scheme 2).

Two additional points merit a brief discussion: (1) Preliminary studies indicate that lower catalyst loadings can be used. For example, **6e** (Table 3, entry 5) and **16c** (Table 4, entry 3) were obtained in 70 and 78% yield (>98 and 95% conv.), 98% S_N2' selectivity, and 95:5 er (both cases) with 5.0 mol % **4b** and **2**, respectively.

(2) The availability of EAS products containing an allenyl-substituted stereogenic center offers new opportunities to synthesize a variety of useful enantiomerically enriched organic molecules that cannot be easily accessed by an alternative protocol; representative cases are shown in Scheme 5. NHC–Cu-catalyzed hydroboration of allenyl alkene **6f**, based on the conditions developed recently for transformations of aryl alkenes and terminal alkynes,[24] resulted in the formation of **17** and **18** in 84% yield with 9:1 selectivity. Oxidation of the mixture of **17** and **18** furnished enantiomerically enriched (96:4 er; Scheme 5) methyl ketone **19** in 86% yield (i.e., 70% overall yield from **6f**). Similarly, **21** was obtained in 78% overall yield (through a 4:1 mixture of vinylboronates); the aldehyde derived from ozonolysis of the terminal alkene in **21** was used to synthesize α-cuparenone (**22**).[25] The high chemoselectivity in the catalytic hydroborations in Scheme 5 are noteworthy; when **6f** or **20** was treated with a common hydroborating agent, such as 9-BBN, a range of products was generated from reaction at the alkene and allene sites. Moreover, the two-step procedure constitutes a method for the enantioselective formation of β-vinyl carbonyls. The latter is a significant feature of the present approach, since protocols that allow

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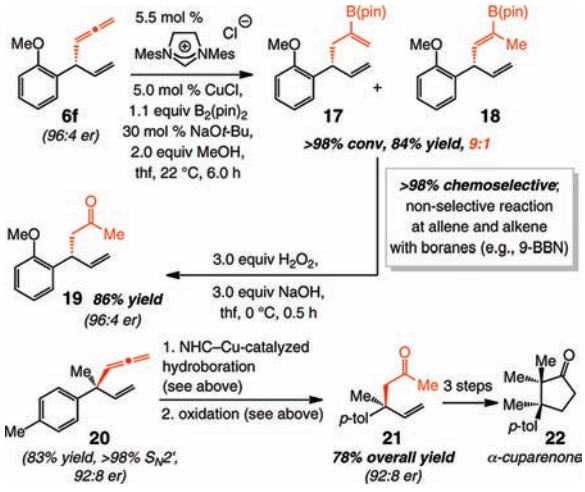
Scheme 5. Catalytic Hydroboration of Allenes



access to such entities by enantioselective conjugate addition of an unsubstituted vinyl unit to an enone or of an aryl or alkyl group to the corresponding dienone are scarce, particularly in cases where quaternary carbons are involved (e.g., **20**).[26] Catalytic EAS processes with enol-based reagents also remain undisclosed.

■ ASSOCIATED CONTENT

Supporting Information

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

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(20) See the Supporting Information (SI) for more details.

(21) In support of the proposal that a metal phenoxide (but not a metal sulfonate) is sufficiently Lewis basic to promote allene transfer from boron to Cu (cf. eq 1), we found that NaOPh (instead of NaOMe) can be used as the base in the EAS process, affording **11**. When NaO_2SOPh was used, <2% conversion was observed.

(22) For an analysis regarding the site selectivity patterns as a function of the electronic attributes of the substrate, see the SI.

(23) See the SI for the efficiency and selectivity observed for reaction of **15a** with different NHC–Cu catalysts.

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