JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
Cite This: J. Am. Chem. Soc. XXXX, XXX, XXX−XXX
pubs.acs.org/JACS

S_N2''-Selective and Enantioselective Substitution with Unsaturated Organoboron Compounds and Catalyzed by a Sulfonate-Containing NHC-Cu Complex

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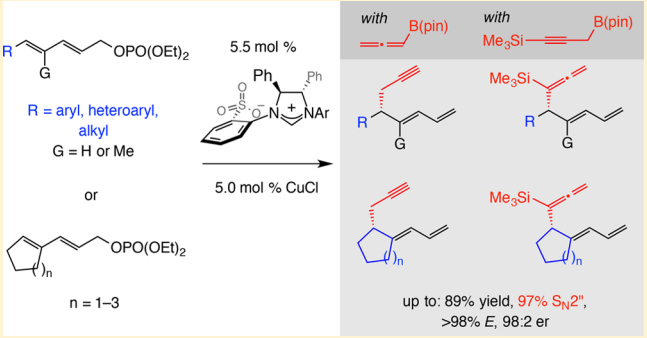
Supporting Information

ABSTRACT: The first broadly applicable strategy for S_N2''-selective and enantioselective catalytic substitution is disclosed. Transformations are promoted by 5.0 mol% of a sulfonate-containing NHC-Cu complex (NHC = N-heterocyclic carbene), and are carried out in the presence of commercially available allenyl-B(pin) (pin = pinacolato) or a readily accessible silyl-protected propargyl-B(pin). Acyclic, or aryl-, heteroaryl-, and alkyl-substituted penta-2,4-dienyl phosphates, as well as those bearing either only 1,2-disubstituted olefins or a 1,2-disubstituted and a trisubstituted alkene were found to be suitable starting materials. Cyclic dienyl phosphates may also serve as substrates. The products containing, in addition to a 1,3-dienyl group, a readily functionalizable propargyl moiety (from reactions with allenyl-B(pin)) were obtained in 51−82% yield, 84−97% S_N2'' selectivity, 89:11−97:3 *E*:*Z* ratio, and 86:14−98:2 enantiomeric ratio (er). Reactions with a silyl-protected propargyl-B(pin) compound led to the formation of the corresponding silyl-allenyl products in 53−89% yield, 69−96% S_N2'' selectivity, 98:2 to >98:2 *E*:*Z* ratio, and 94:6−98:2 er. Insight regarding several of the unique mechanistic attributes of the catalytic process was obtained on the basis of kinetic isotope effect measurements and DFT studies. These investigations indicate that cationic π-allyl-Cu complexes are likely intermediates, clarifying the role of the *s-cis* and *s-trans* conformers of the intermediate organocopper species and their impact on *E*:*Z* selectivity and enantioselectivity. The utility of the approach is demonstrated by chemoselective functionalization of various product types, through which the propargyl, allenyl, or 1,3-dienyl sites within the products have been converted catalytically and chemoselectively to several useful derivatives.



1. INTRODUCTION

Catalytic enantioselective allylic substitutions, transform an alkenyl substrate to a new unsaturated compound that bears an allylic stereogenic center and are widely used in organic synthesis (Scheme 1a).[1] The majority of these S_N2'-selective reactions allow for the addition of a methyl or a simple alkyl group.[1,2] Strategies for incorporation of a readily modifiable alkenyl,[3] allyl,[4] allenyl,[5] alkynyl,[6] or a propargyl[7] have been introduced only recently. In contrast, catalytic S_N2''-selective and enantioselective substitutions, regardless of the moiety being introduced, are relatively uncommon.[8−10] The one case of which we are aware involves reaction of a "soft" nucleophile (derived from $CH(NHAc)(CO_2Et)_2$) with a 2-bromo-1,3,5-triene to generate a vinylallene (up to 90.5:9.5 enantiomeric ratio (er)).[11]

We envisioned that it might be possible to develop catalytic enantioselective S_N2'' additions by exploiting a key isomerization (akin to a 3,3′-reductive elimination) that was recently used in designing 1,6-conjugate additions.[12] We imagined a process (Scheme 1b) through which a dienyl phosphate and commercially available allenyl-B(pin) **1**[13] (pin = pinacolato) would participate in an S_N2''- and enantioselective substitution via **I**, and **II**[7] (vs allene-containing derivatives by S_N2' and S_N2 pathways). The propargyl and the 1,3-dienyl groups would render the expected products of considerable utility, especially when containing a stereochemically defined trisubstituted alkene. Equally useful compounds containing an easily alterable silyl-substituted allenyl moiety could be similarly generated through the use of **2**, a readily accessible organoboron species[14,15] (Scheme 1b). Such 1,5-additions (i.e., S_N2''-selective) would be mechanistically distinct from the more widely utilized S_N2'-selective substitutions largely due to involvement of organocopper intermediates that contain an *extended* π system (cf. **II**, Scheme 1b). Involvement of the derived *s-cis* and *s-trans* conformers would pose key questions vis-à-vis their relative rates of interconversion and reaction, factors that impact *E*:*Z* selectivity and/or enantioselectivity. Also, S_N2''-selective substitutions would be mechanistically dissimilar to 1,6-conjugate additions[12] in that C−C bond formation would be occurring within an intermediate that

Received: October 9, 2018

DOI: 10.1021/jacs.8b10885
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 1. Relevant Previous Advances

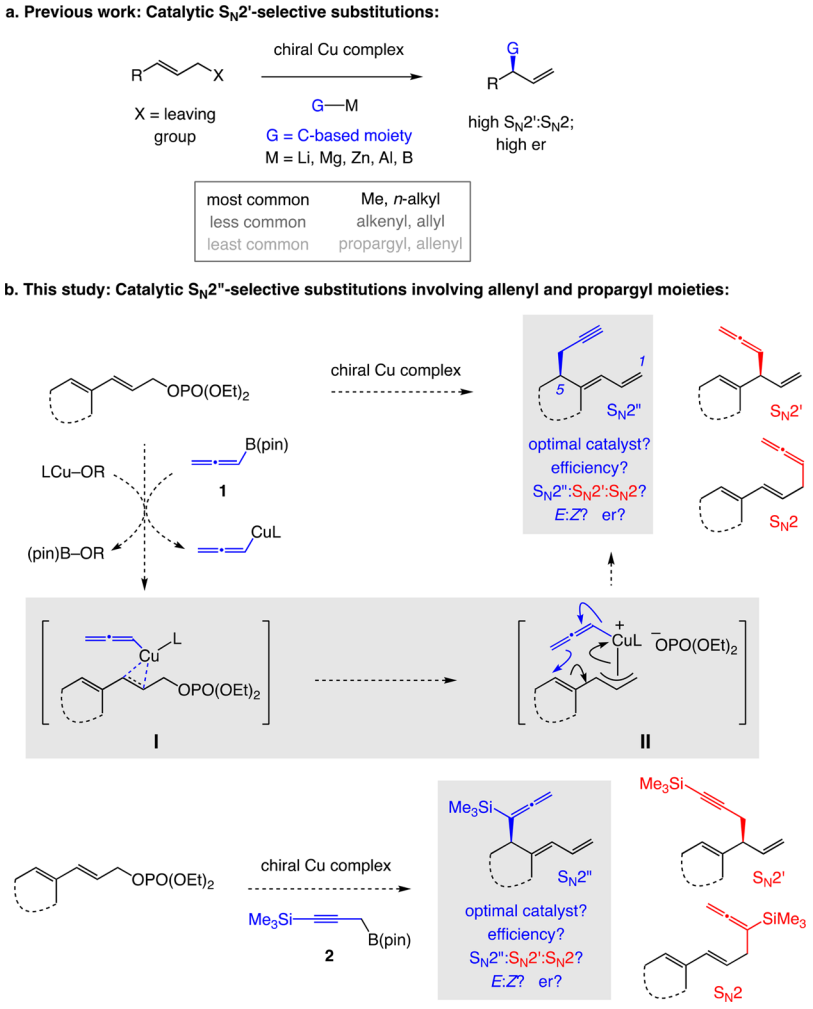
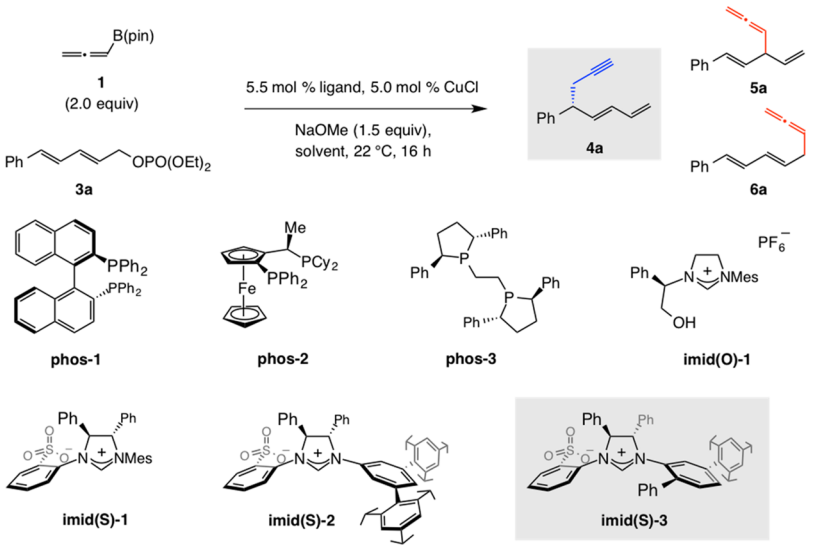


Table 1. Examination of Different Types of Cu-Based Complexes[a]



entry	ligand	solvent	conv (%)[b]	S_N2'':S_N2':S_N2 (**4a**:**5a**:**6a**)[b]	*E*:*Z* (**4a**)[b]	yield **4a** (%)[c]	er[d]
1	–	thf	>95	95:<2:5	81:19	71	–
2	**phos-1**	thf	87	88:<2:12	79:21	55	50:50
3	**phos-2**	thf	>95	92:<2:8	81:19	65	50:50
4	**phos-3**	thf	79	93:<2:7	83:17	58	50:50
5	**imid(O)-1**	thf	>95	90:<2:10	80:20	82	50:50

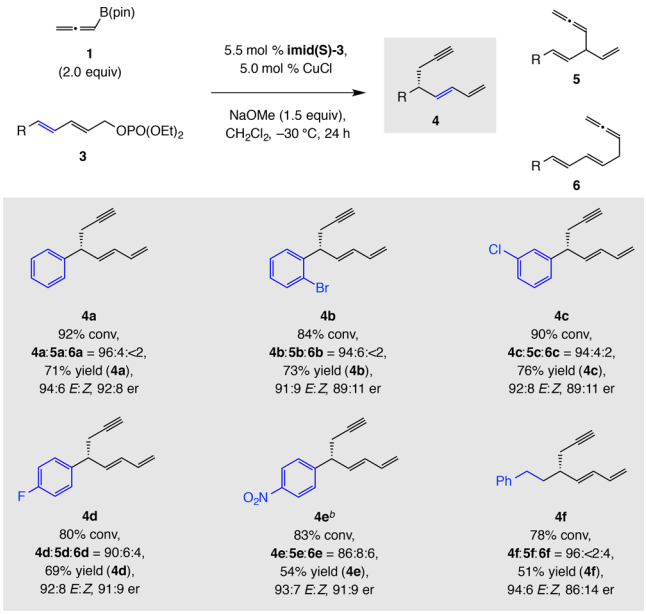
DOI: 10.1021/jacs.8b10885
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. continued

entry	ligand	solvent	conv (%)[b]	S_N2'':S_N2':S_N2 (**4a**:**5a**:**6a**)[b]	*E*:*Z* (**4a**)[b]	yield **4a** (%)[c]	er[d]
6	**imid(S)-1**	thf	>98	80:18:2	86:14	76	39:61
7	**imid(S)-2**	thf	>95	86:10:4	93:7	69	85:15
8	**imid(S)-3**	thf	>95	74:19:7	85:15	72	73:27
9	**imid(S)-2**	CH_2Cl_2	>98	93:4:3	95:5	75	85:15
10	**imid(S)-3**	CH_2Cl_2	>98	88:7:5	90:10	75	90:10

[a]Performed under N_2 atm. [b]Conversion and S_N2'':S_N2':S_N2 ratios were determined by analysis of ^{1}H NMR spectra of unpurified mixtures; conv (±2%) refers to disappearance of the **3a**. [c]Yields are for isolated and purified **4a** (*E* and *Z* isomers; ±5%). [d]Enantioselectivity was determined by HPLC or GC (±1%). See the Supporting Information for experimental and analytical details. Abbreviations: Mes, 2,4,6-$(Me)_3C_6H_2$.

Scheme 2. S_N2''-Selective and Enantioselective Substitutions with Dialkenyl Phosphates That Contain Only Disubstituted Alkenes[a]



[a]Reactions were carried out under N_2 atm. Conversion was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%) and correspond to *E* and *Z* olefin mixtures. Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more. [b]Performed with 7.5 mol % **imid(S)-3** and 7.5 mol% CuCl. See the Supporting Information for details.

no longer carries an electron-withdrawing moiety. One must therefore contend with less substituted π systems, which are conformationally more flexible and electronically less activated.

2. RESULTS AND DISCUSSION

2.1. Catalytic S_N2''-Selective and Enantioselective Substitutions Involving an Allenyl-B(pin) Reagent.

2.1.1. Identification of an Effective Catalyst. To explore feasibility, we chose to examine the reaction of **1** with dienyl phosphate **3a** in the presence of 5.5 mol% of a ligand and 5.0 mol% CuCl in thf and at room temperature (22 °C). Representative data regarding the different types of Cu complexes are shown in Table 1.[16] Without a ligand (entry 1), the reaction was efficient and highly S_N2''-selective (>95% conv, 95% S_N2''), but **4a** was formed as an 81:19 mixture of *E* and *Z* alkene isomers.

We then probed the effectiveness of a number of different chiral bisphosphine ligands. The transformations carried out with **phos-1**–**3** (Table 1, entries 2–4) were similarly efficient and regioselective (88–93% S_N2'') as when there was no ligand present (entry 1), and the product was again generated in up to 83:17 *E*:*Z* ratio without any enantioselectivity.

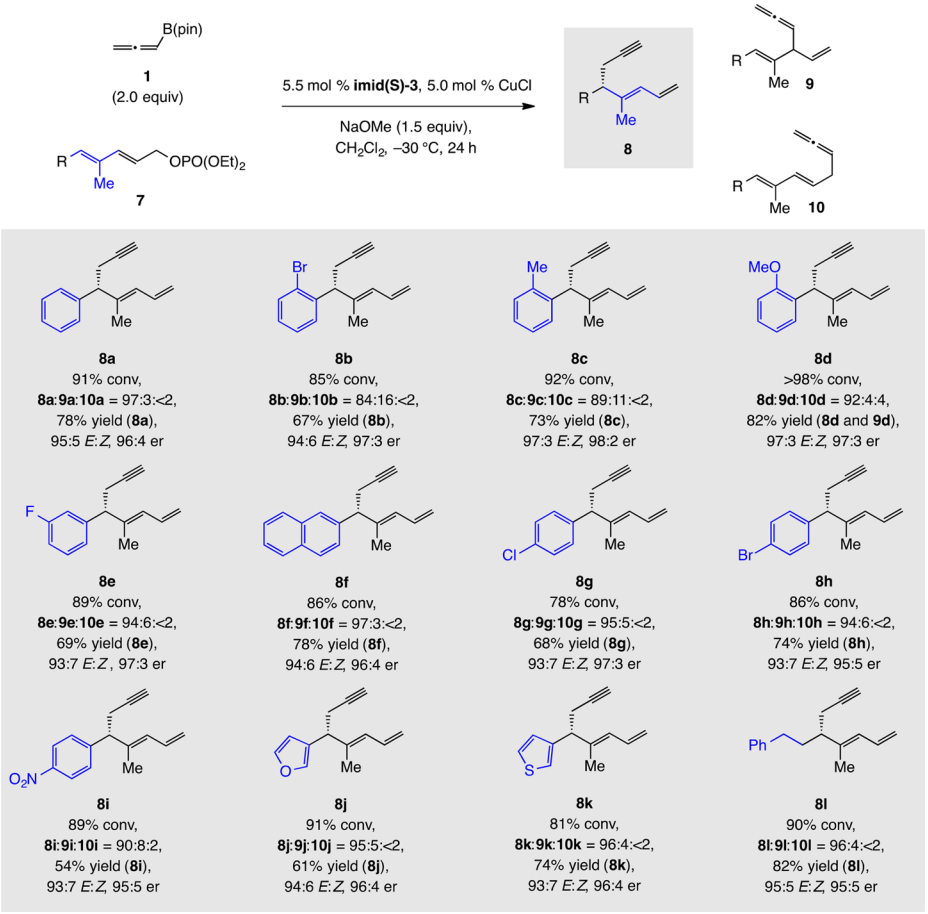
Particularly disconcerting was that with **imid(O)-1**, optimal for enantioselective 1,6-conjugate additions with the same allenyl-B(pin) compound,[12] **4a** was generated in 80:20 *E*:*Z* selectivity and in the racemic form (entry 5). Enantioselectivity was first detected when sulfonate-containing imidazolinium salt **imid(S)-1**[17] was utilized (39:61 er, entry 6). The low er was accompanied by an improvement in the *E*:*Z* ratio (86:14), which came at the expense of diminished regioselectivity (80:18:2 S_N2'':S_N2':S_N2). We then examined **imid(S)-2**, which bears a 3,5-disubstituted NAr unit (vs a 2,4,6-trisubstituted NAr group), and is the precursor to a catalyst proved to be optimal in several previous studies[2,3e,5,7,18] (entry 7). There was a modest increase in S_N2'' selectivity, a larger increase in *E* selectivity (93:7 *E*:*Z*), and an even greater boost in er (85:15). In the reaction involving **imid(S)-3**, containing an NAr group with C2 and C5 substituents (entry 8), selectivity suffered in comparison to **imid(S)-2** (74% S_N2'', 85% *E*, 73:27 er). Finally, we evaluated the performance of the NHC-Cu complexes derived from **imid(S)-2** and **imid(S)-3** in a similarly polar but non-coordinating solvent (CH_2Cl_2; entries 9–10), leading us to establish that under the latter conditions, **imid(S)-3** is overall the most effective chiral ligand (88% S_N2'', 90% *E*, 90:10 er; entry 10).

2.1.2. Further Optimization and Exploration of the Scope. We subsequently found that results could be improved when the reaction was carried out with **imid(S)-3** at −30 °C in CH_2Cl_2: **4a** was isolated in 71% yield, 96% S_N2'' selectivity, 92:8 er, and 94:6 *E*:*Z* selectivity (Scheme 2). Transformations with substrates with an *o*-, *m*-, or *p*-substituted aryl halide delivered **4b**–**d** in 69–76% yield, 90–94% S_N2'' selectivity, 91–92% *E* selectivity, and 89:11–91:9 er (Scheme 2). Reaction of *p*-nitro-substituted dienyl phosphate afforded **4e** with comparable regio- and stereoselectivity, but higher catalyst loading (7.5 mol%) was needed for >80% conversion. Synthesis of alkyl-substituted **4f** was similarly regio- and stereoselective, but the yield was lower (51%) probably due to diminished electrophilicity of the alkyl-substituted substrate. In every instance that a comparative experiment was carried out, transformations were less enantioselective with **imid(S)-2** (e.g., 82% and 50% yield, >98:<2:<2 and 95:5:<2 S_N2'':S_N2':S_N2, 97% and 95% *E*, 89:11 and 80:20 er for **4a** and **4f**, Scheme 2, respectively).

While the reactions in Scheme 2 were highly S_N2'' selective, and *E*:*Z* ratios ranged from 91:9 to 94:6, we were concerned about the moderate enantioselectivity, which dipped to as low as 86:14 er. These considerations led us to investigate processes where C–C bond formation takes place at a trisubstituted alkene; our hope was that the additional substituent would translate to more effective differentiation between the competing transition states (Scheme 3). We found such

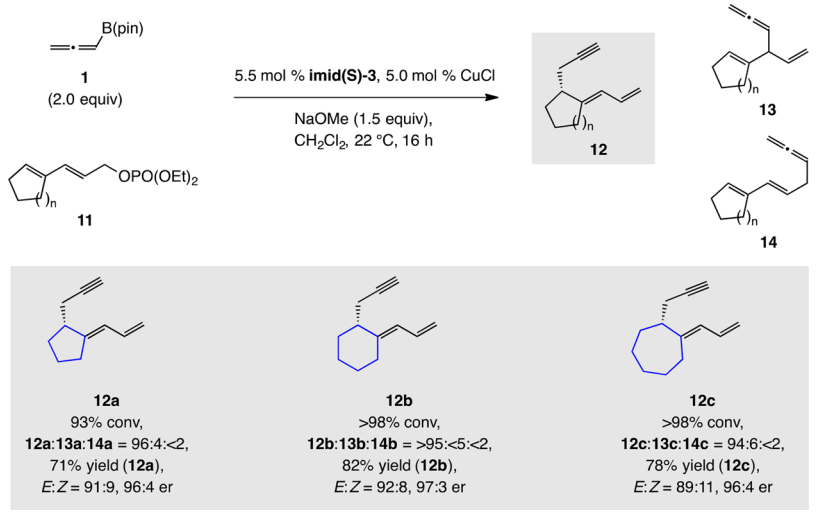
DOI: 10.1021/jacs.8b10885
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Scheme 3. S_N2''-Selective and Enantioselective Substitutions with Dialkenyl Phosphates That Contain a Trisubstituted Alkene[a]



[a]Reactions were carried out under N_2 atm. Conversion was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more. See the Supporting Information for details.

Scheme 4. S_N2''-Selective and Enantioselective Substitutions with Allenyl-B(pin) and Involving Cyclic Substrates[a]

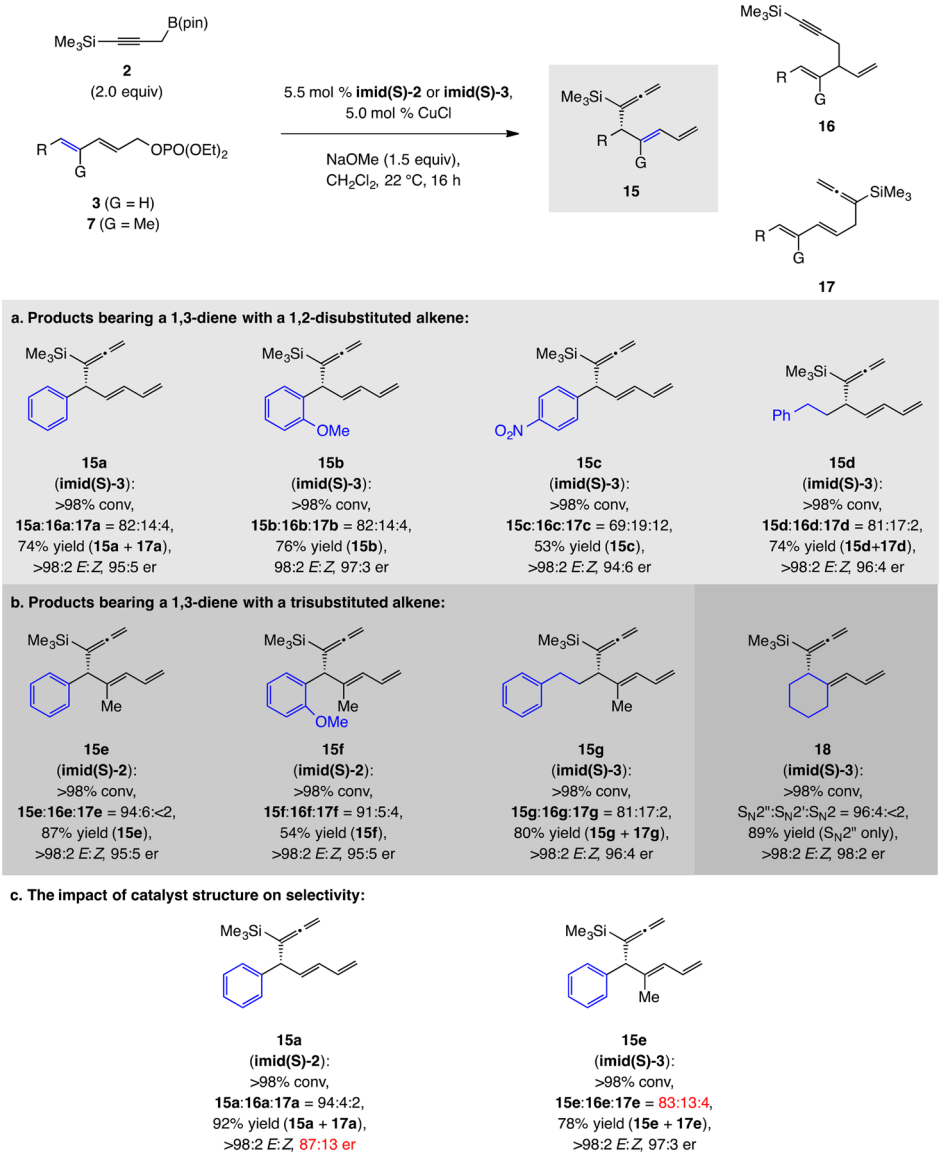


[a]Reactions were carried out under N_2 atm. Conversion was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more. See the Supporting Information for details.

an approach attractive for two additional reasons: (1) the relative difficulty of accessing the more highly substituted olefins stereoselectively by alternative catalytic methods,[19] and (2) the possible application to synthesis of fasicularin[20] (see Scheme 11).

DOI: 10.1021/jacs.8b10885
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 5. S_N2''-Selective and Enantioselective Substitutions Leading to Transfer of a Silyl-Substituted Allenyl Moiety[a]



[a]Reactions were carried out under N_2 atm. Conversion was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more. See the Supporting Information for details.

In the event, reactions with the more substituted dienyl phosphates **8a–l** (Scheme 3) proceeded from 78% to >98% conversion under the same conditions as before (Scheme 2).[21] Not only were the S_N2'' selectivities equally high (84–97%), products were obtained with better *E* selectivity (93:7–97:3 vs 91:9–94:6 in Scheme 2) and er (95:5–98:2 vs 86:14–92:8, Scheme 2). We were unable to obtain the pure S_N2'' addition product in just one instance (**8d**). An assortment of aryl-substituted substrates (**8a–i**, Scheme 3), regardless of the position and electronic attributes of their substituent, heteroaryl-containing dienyl phosphates (**8j,k**), and one bearing an aliphatic moiety (**8l**), reacted efficiently and selectively.

Cyclic phosphates afforded products with similarly high yields and selectivities. Dienynes **12a–c** (Scheme 4) were obtained in 71–82% yield, with a strong preference for the S_N2'' mode of addition (94 to >95%), and in 96:4–97:3 er. In the case of cyclic dienes *E* selectivity was slightly lower (89:11–92:8 *E*:*Z*); this could be improved at lower temperature, but at the expense of product yield (e.g., for **12b** at −30 °C for 24 h: 90% conv, 61% yield, >95:<5:<2 $S_N2'':S_N2':S_N2$ selectivity, 94:6 *E*:*Z*, and 98:2 er).

2.2. Catalytic S_N2''- and Enantioselective Substitutions with a Propargyl-B(pin) Reagent. With silyl-substituted propargyl-B(pin) compound **2** as the reagent (Scheme 5), processes involving dienyl allylic phosphates with only 1,2-disubstituted alkenes (Scheme 5a) or those containing a trisubstituted olefin (Scheme 5b) proceeded to completion under similar conditions as before (Schemes 2–4). Acyclic aryl- (cf. **15a–c,e,f**) and alkyl-substituted (cf. **15d,g**) dienyl phosphates and the corresponding cyclic systems (cf. **18**) proved to be effective substrates.

Several additional points merit note: (1) Transformations with phosphates that contain only disubstituted alkenes (Scheme 5a) were generally more enantioselective than those

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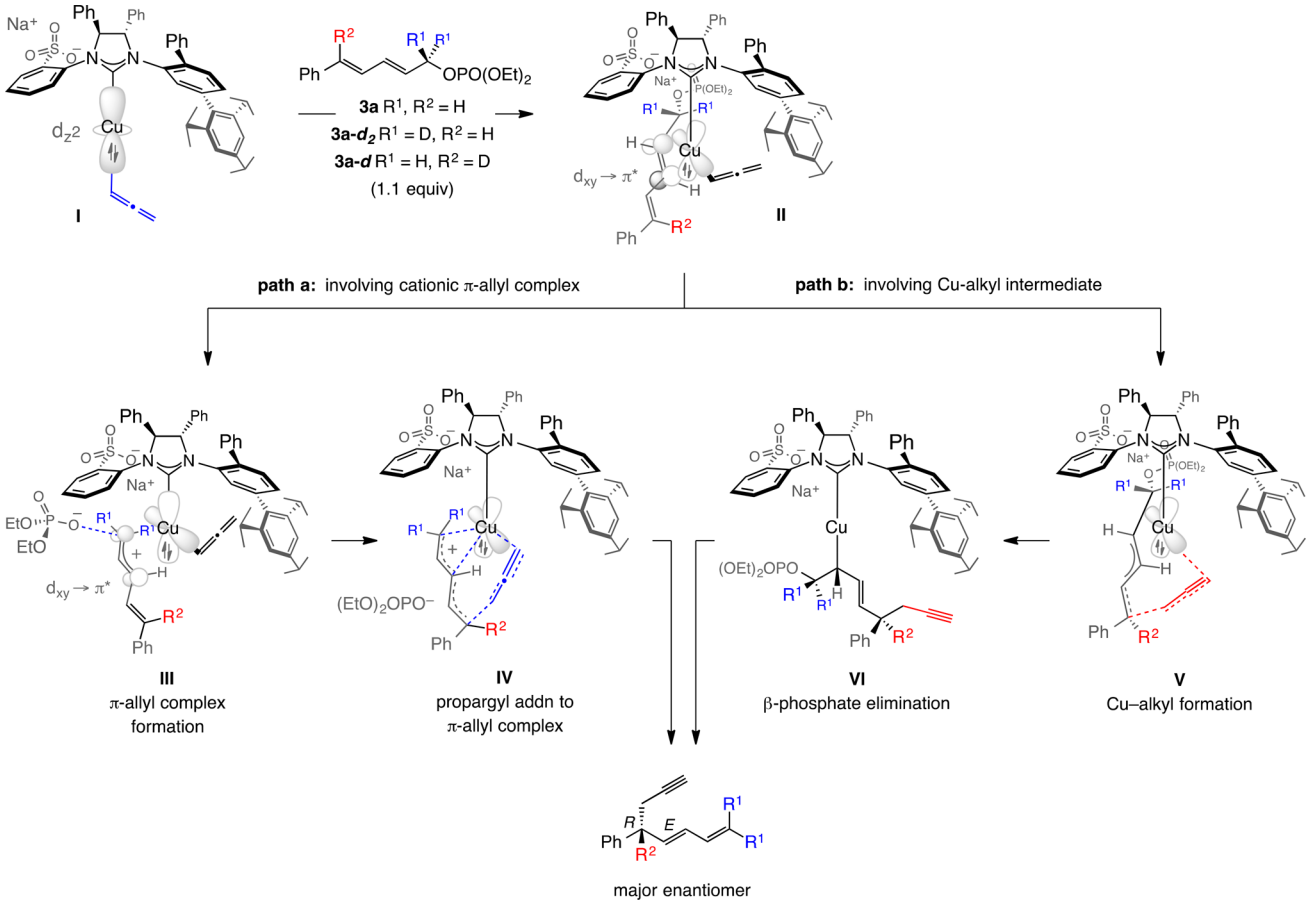
Scheme 6. Mechanistic Analysis on the Basis of Deuterium-Labeling Experiments



with allenyl-B(pin) (compare to data in Scheme 2). (2) Particularly with **imid(S)-3**, S_N2'' selectivities were lower for reactions with silyl-protected propargyl-B(pin) reagent (**2**; 69–96% vs 84–97%). This difference might arise from increased steric pressure for C–C bond formation in the proximity of a larger substituent when the silyl-containing organoboron compound is involved. (3) In general, while S_N2'' selectivities were lower with **imid(S)-3** and dienylphosphates containing disubstituted alkenes (Scheme 5a), the er was higher; formation of **15a** with **imid(S)-2** (Scheme 5c) is a case in point (94% vs 82% S_N2'' and 87:13 vs 95:5 er with **imid(S)-2** and **imid(S)-3**, respectively). Thus, if product yield happens to be more critical than its enantiomeric purity, then **imid(S)-2** might be the more suitable catalyst precursor. (4) The situation is more straightforward with substrates that contain a trisubstituted olefin (Scheme 5b). As the data for **15e** indicate (Scheme 5c), although enantioselectivity was similar (95:5 and 97:3 er for **imid(S)-2** and **imid(S)-3**, respectively), S_N2'' selectivity was higher with **imid(S)-2** (94% vs 83% for **imid(S)-3**).

2.3. Mechanistic Investigations. We have previously shown that sulfonate-bearing NHC-Cu complexes are especially effective in promoting allylic substitutions with high S_N2' selectivity and enantioselectivity.[2,3a–e,5,6a,b,7] The catalyst's ability to accommodate a metal bridge between its sulfonate moiety and the electrophile's phosphate unit appears to be central to high regio- and stereocontrol.[2,7,22] Nonetheless, as noted earlier, the S_N2''-selective substitutions are mechanistically distinct, mainly because of the involvement of stereoisomeric organocopper complexes that contain an extended π system. The associated *s-cis* and *s-trans* conformers and the relative rates of their interconversion (vs C–C bond formation) and/or reactivity can impact *E*:*Z* selectivity and/or enantioselectivity. Mindful of such issues and considering the data presented above, we set out to establish the identity of the stereochemistry-determining step and, with the support of DFT studies, to gather insight regarding the origins of the stereoselectivity differences.

2.3.1. Identifying the Stereochemistry-Determining Step. We evaluated two mechanistic possibilities, which typically involve *anti* displacement[23–25] of the leaving group, and are commonly invoked in allylic substitution processes (Scheme 6).[26] One route (**path a**) entails the formation of π-allyl complex **III** by initial cleavage of the C–O^{phosphate} bond, followed by the collapse of the relatively high-energy π-allyl intermediate **IV** and formation of a C–C bond.[27] Alternatively, the C–C bond generation in **path b** might occur prior to elimination of the phosphate moiety from the Cu-alkyl species (**II** → **V** → **VI**).

Based on the results of competition experiments involving equal amounts of labeled (i.e., **3a-d_2** and **3a-*d***) and non-labeled substrate (**3a**) we were able to identify the more likely sequence of events (Scheme 7). Through the reaction with **3a-d_2** (R^1 = D, R^2 = H, Scheme 7a) we measured a secondary kinetic isotope effect of 1.11 ± 0.01, which suggested that there is $sp^3 \rightarrow sp^2$ hybridization change at the carbon bearing the phosphate group during the stereochemistry-determining step. When **3a-*d*** (R^1 = H, R^2 = D, Scheme 7b) was used, we did not detect any secondary kinetic isotope effect (0.99 ± 0.01), implying that C–C bond formation probably is energetically more favorable and occurs at a subsequent stage (**IV** → product).[28]

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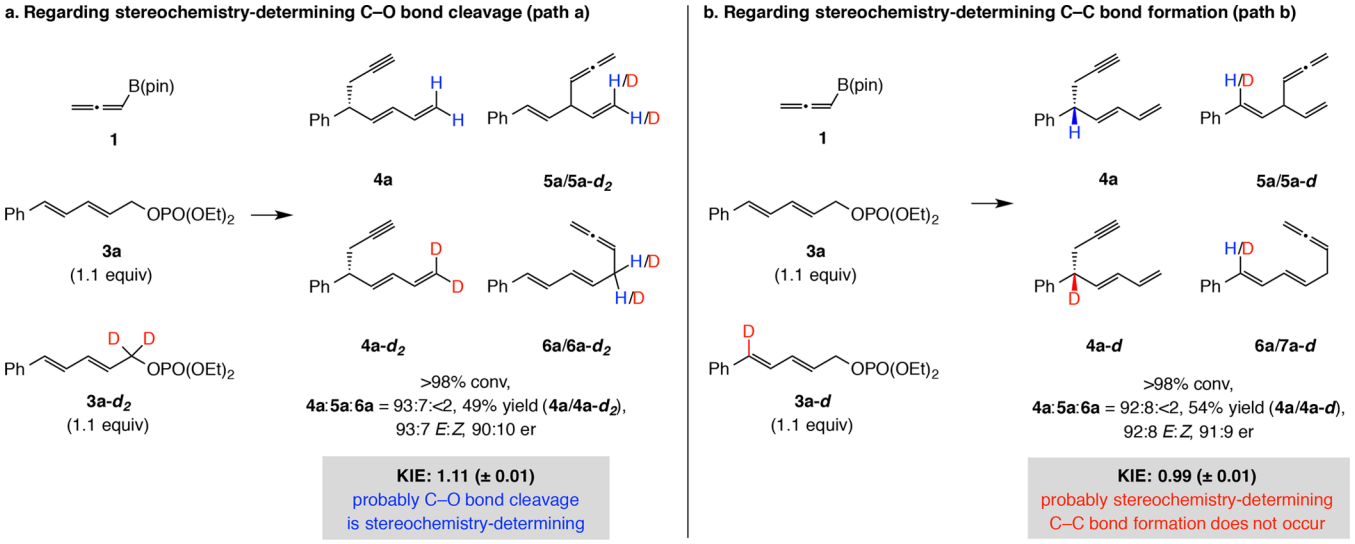
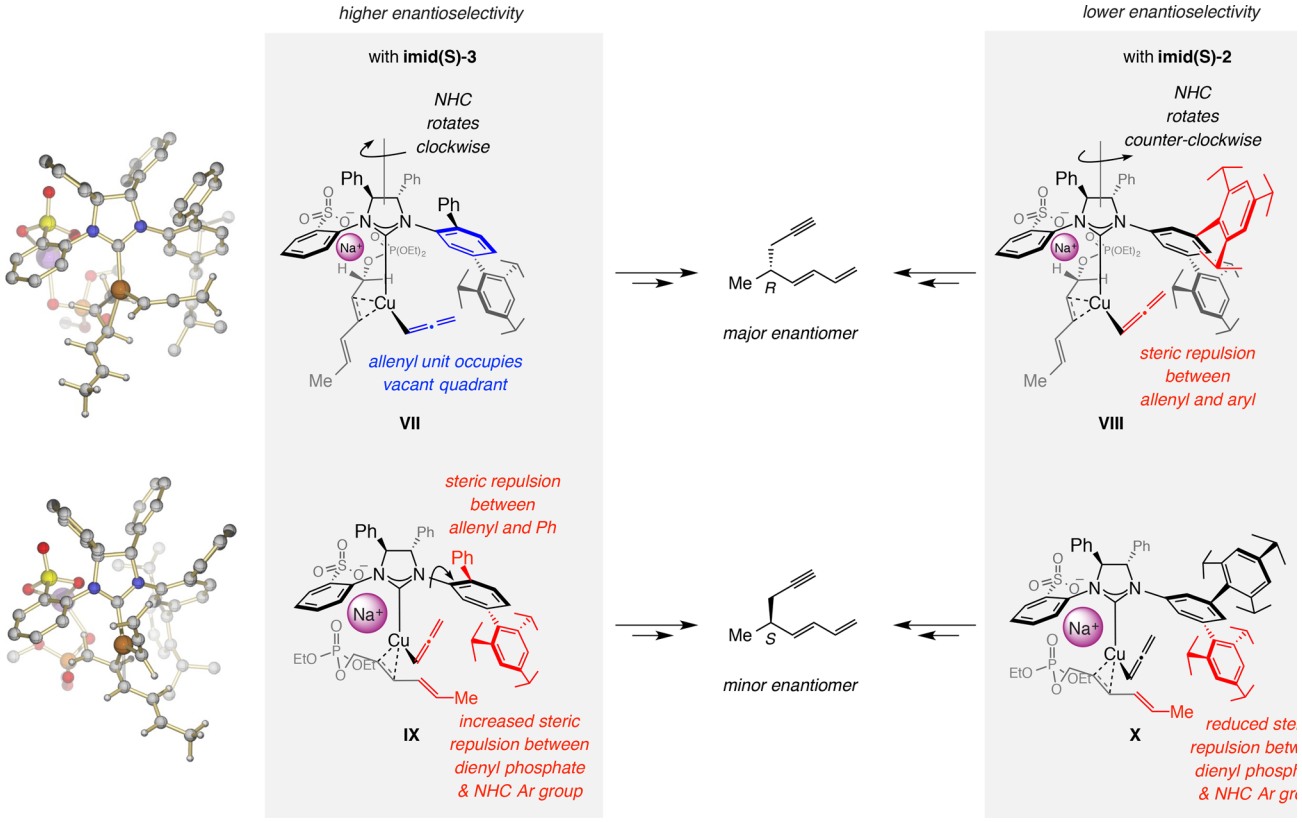
Scheme 7. Kinetic Isotope Effect Measurements[a]



[a]Conditions: 5.5 mol% **imid(S)-3**, 5.0 mol% CuCl, 1.5 equiv NaOMe, CH_2Cl_2, −30 °C, 24 h. See the Supporting Information for details.

Scheme 8. Mechanistic Model: Origin of Enantioselectivity



2.3.2. Regarding the Enantioselectivity Variations. The results of DFT calculations (Scheme 8) allow us to formulate a rationale as to why reactions were more enantioselective with the Cu-based complex derived from **imid(S)-3** compared to when **imid(S)-2** was used (90:10 vs 85:15 er, respectively). Comparison of the transition states leading to the *E* isomer of the major enantiomer in processes involving **imid(S)-3** (cf. **VII**) and **imid(S)-2** (cf. **VIII**) reveals that the NHC ligands possess distinct conformational preferences (see top panel, Scheme 8). This may be appreciated more easily if while holding the position of the allenyl ligand constant, the NHC ligands derived from **imid(S)-3** and **imid(S)-2** are rotated in a clockwise and counterclockwise manner, respectively. In **VII** and **VIII** the dienyl phosphate can approach the allenyl-Cu complex so that its phosphate unit can establish the key sodium cation bridge with the NHC ligand's sulfonate group.[7] In the lowest energy conformer of **VII**, the allenyl moiety can therefore be placed within the vacant quadrant. Because there is no large meta substituent in the Cu complex derived from **imid(S)-3**, there is little steric repulsion between the ligand's NAr moiety

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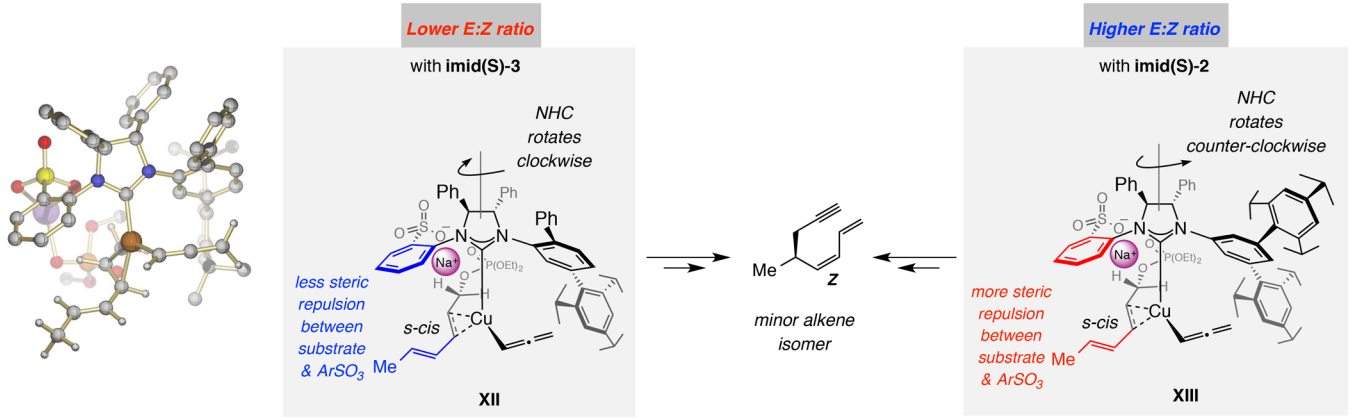
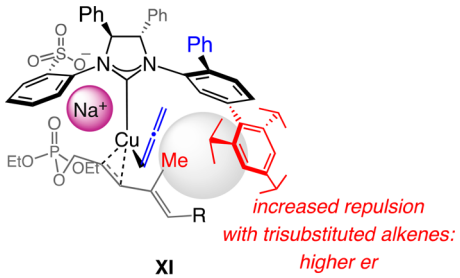
Scheme 9. Mechanistic Model: Differences in *E* Selectivity as a Function of NHC Ligand[a]



[a]See the Supporting Information for details.

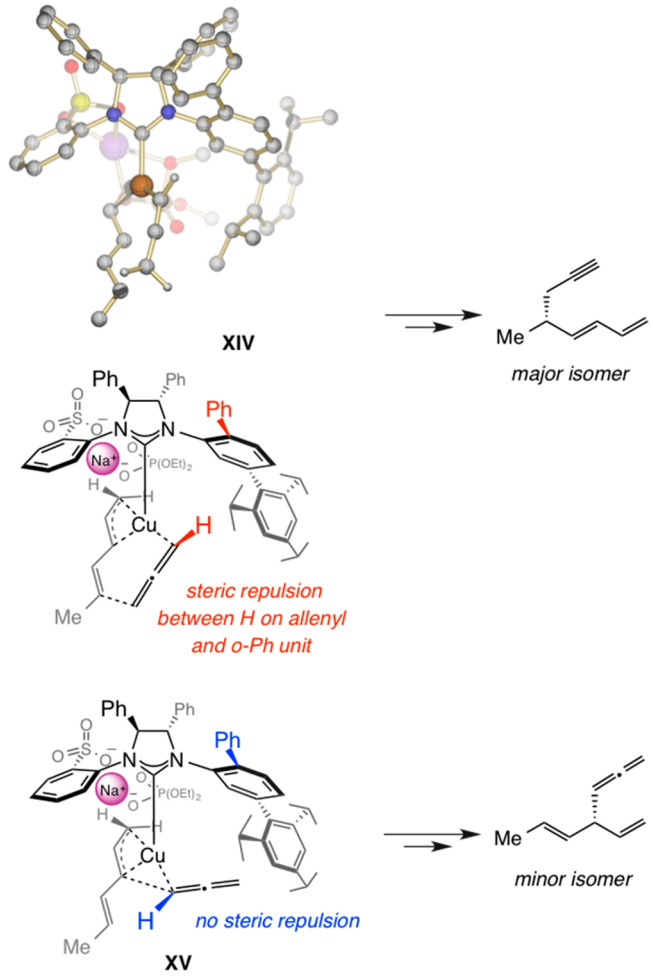
(highlighted in blue; **VII**) and the allenyl unit. The proximity of a triisopropylphenyl moiety and the allenyl group in **VIII** (in red), on the other hand, gives rise to steric pressure, which can be countered by counterclockwise rotation around the Cu−C^{NHC} bond. These factors impact the relative energies of the transition states leading to the minor product enantiomer (**IX** and **X**, lower panel, Scheme 8). In **IX** rotation around the N−C^{Ar} bond can help minimize the steric strain generated by the nearness of the ligand's *o*-phenyl substituent and the allenyl moiety. However, this conformational adjustment induces the corresponding *m*-triisopropylphenyl moiety to be positioned closer to the tail end of the dienyl phosphate, exacerbating an unfavorable interaction. Such considerations provide a basis for the higher energy of **IX** and the attendant increase in er. In **X**, the triisopropylphenyl group, which points to the rear of the complex, can move further away from the dienyl phosphate. Steric repulsion can thus be diminished and greater amounts of the minor enantiomer generated (i.e., lower er).

The proposed model offers an explanation for other enantioselectivity trends as well. For example, as shown in **XI**, the additional substituent of the trisubstituted alkene destabilizes the intermediates leading to the minor enantiomer and er values improve (compared to dienyl phosphates that have only disubstituted olefins; compare the data in Schemes 2 and 3).



2.3.3. Regarding the E Selectivity Variations. Another question arises: Why does the less enantioselective catalyst derived from **imid(S)-2** afford products with higher *E*/*Z* selectivity (95:5 vs 90:10 for **imid(S)-2** and **imid(S)-3**, respectively)? The answer hinges on the geometry of the extended π-allyl intermediate complex (cf. **III** and **IV**, Scheme 6), where an *s-trans* conformer likely leads to the *E*-alkene.

Scheme 10. Mechanistic Model: Variations in S_N2''/S_N2'



The conformational mobility of the NHC ligands discussed above (i.e., clockwise or counterclockwise rotation around the Cu−C^{NHC} bonds, Scheme 8) offers hints as to why *E* selectivities are higher with the complex derived from **imid(S)-2**. The **imid(S)-3**-derived NHC in **XII** (Scheme 9)—an *s-cis* conformer—can rotate (clockwise, as shown) without incurring significant steric pressure (see above). The sulfonate unit can therefore be placed, with little or no cost in energy, at a site that is more distal from the dienyl phosphate. The situation is

DOI: 10.1021/jacs.8b10885
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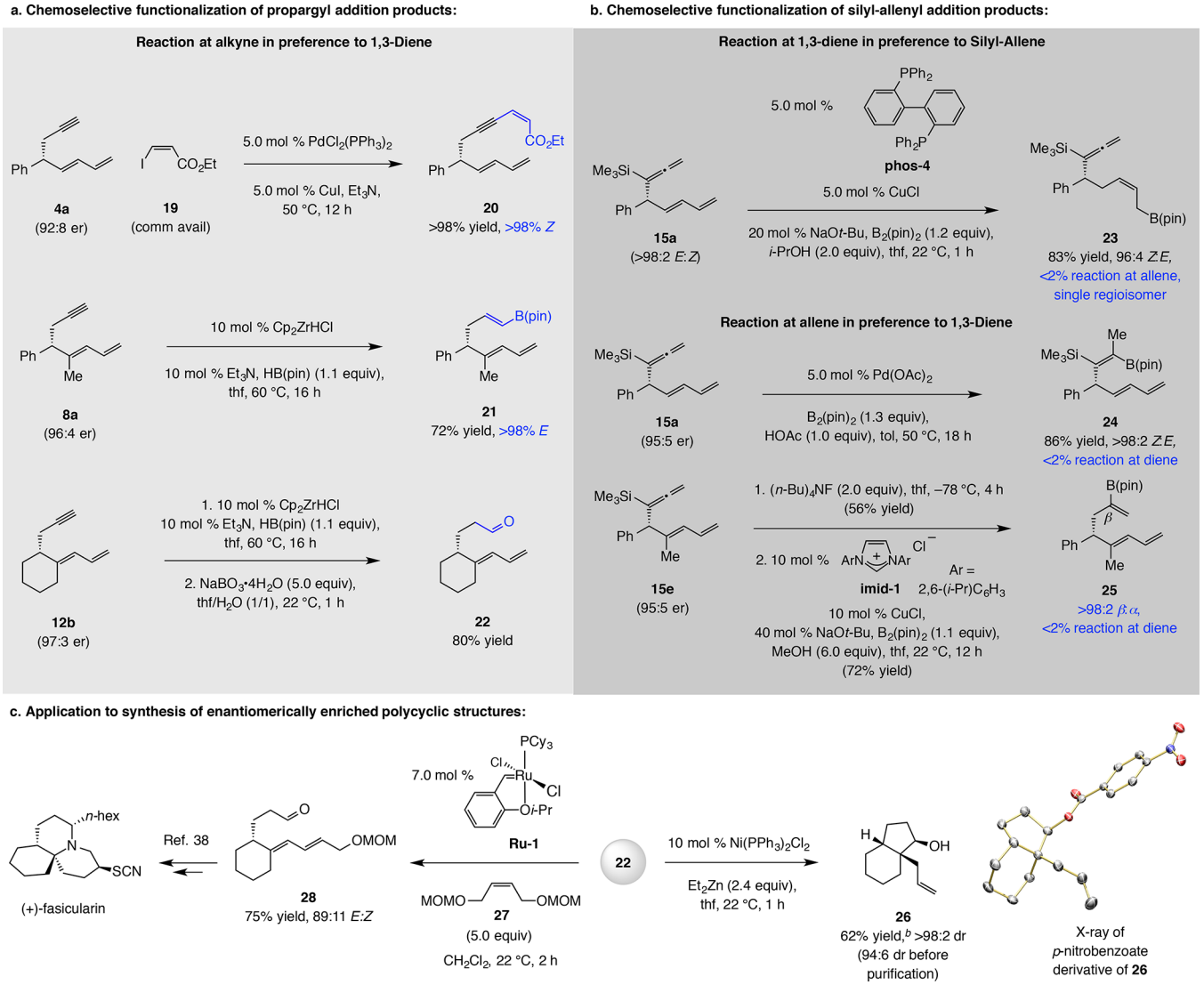
Scheme 11. Chemo- and Stereoselective Functionalization of Products and Demonstration of Utility[a]



[a]Carried out under N_2 atm. Conversion (>98% in all cases) was determined by analysis of ^1H spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivities were determined by HPLC or GC analysis (±1%). Experiments were run in duplicate or more. [b]Samples contained 5−10% of the isomerized alkene. See the Supporting Information for details.

different for the *s-cis* conformer corresponding to **imid(S)-2** (**XIII**) where counterclockwise turning of the NHC ligand positions the sulfonate group nearer to the dienyl phosphate. This causes **XIII** to be higher in energy and lesser amounts of the *Z*-alkene to be generated (i.e., higher *E*:*Z* ratio).

DFT studies suggest that *s-cis* geometry is in all likelihood established during C−O bond cleavage (cf. Scheme 6). This implies that *s-cis* to *s-trans* isomerization in the cationic π-allyl intermediate is energetically more demanding than the C−C bond formation event.[26] Consequently, reaction via **XII** delivers the *Z* alkene of the *S* enantiomer, whereas transformation through **VII** leads to the *E*-alkene of the *R* enantiomer. This scenario is supported by the observation that hydrogenation of a derivative of **4a** (90:10 *E*:*Z*, 90:10 er (*E*), 92:8 er (*Z*)) afforded the alkane with diminished enantiomeric purity (79:21 er).[29]

2.3.4. Regarding the S_N2''/S_N2' Selectivity Variations. Another notable difference between the **imid(S)-2** and **imid(S)-3**-derived NHC ligands relates to the S_N2''/S_N2' ratios (see Scheme 5; e.g., 94:4 vs 82:14 for **15a** with **imid(S)-2** and **imid(S)-3**, respectively). We propose that in the transition state for C−C bond formation (**XIV**; Scheme 10) the allenyl nucleophile likely adopts a conformation that engenders steric repulsion between the nucleophile's Cα−H and phenyl moiety of the NHC ligand in **imid(S)-3**. This interaction can be avoided in **XV**, resulting in greater amounts of the S_N2' product isomer to be generated.

2.4. Utility. A notable attribute of the method is that it delivers products bearing a 1,3-diene and a terminal alkyne or a silyl-substituted allene. The transformations in Scheme 11 demonstrate several distinct ways by which further structural modifications may be implemented.

Catalytic coupling[30] of **4a** to commercially available *Z*-alkenyl iodide **19** afforded enyne **20** with complete retention of stereochemical identity in quantitative yield (Scheme 11a). Analogously, zirconocene-catalyzed hydroboration[31] of **8a** afforded alkenyl-B(pin) **21** in 72% yield and >98:2 *E*:*Z* selectivity (Scheme 11a). The same procedure followed by oxidative treatment furnished the corresponding aldehyde **22** in 80% yield.

DOI: 10.1021/jacs.8b10885
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

The transformations in Scheme 11b represent the type of chemoselective modification that is possible with a silyl-allenyl product. The 1,3-dienyl fragment in **15a** was selectively functionalized by bisphosphine-Cu-catalyzed regioselective 1,4-proto-boryl addition,[32] affording **23** in 83% yield, and 96:4 *Z*:*E* ratio. Only the primary C−B bond was formed, and none of the side product derived from reaction at the allenyl site was detected.[33]

The allenyl moiety could be modified chemoselectively as well, as represented by conversion of **15a** to tetrasubstituted alkenyl-B(pin) **24** by regio- and stereoselective hydroboration promoted by a Pd-based catalyst. This process, performed according to a method by Bäckvall and co-workers,[34] has the distinction of likely being directed by a dienyl unit (vs an alkene). Chemoselective catalytic cross-coupling involving the C−B bond might be used to access various tetrasubstituted alkenylsilane derivatives.[35] Another case relates to chemoselective NHC-Cu-catalyzed proto-boryl addition[5,36] to the monosubstituted allene derived from **15e**, affording **25** in 72% yield and >98% β selectivity.

Applicability is further highlighted by phosphine−Ni-catalyzed cyclization[37] of **22** to afford bicyclic alcohol **26** (Scheme 11c), which was obtained in 62% yield and 94:6 diastereomeric ratio (dr). The X-ray structure of the *p*-nitrobenzoate derivative of **26** confirmed the constitutional and stereochemical identity of the products. Cross-metathesis with **22** and alkene **27** was most effectively with complex **Ru-1**, affording **28** in 75% yield and 89% *E* selectivity. This latter product is an intermediate that was prepared in the racemic form in a reported total synthesis of fasicularin.[38]

3. CONCLUSIONS

The investigations described herein introduce methods that are notable for several reasons. These are the first examples of catalytic S_N2''-selective and enantioselective substitutions that allow for incorporation of versatile and easily modifiable propargyl or allenyl moieties. While there is just a single report corresponding to catalytic S_N2'-selective enantioselective allylic substitution of an allenyl unit[5] and one dealing with incorporation of a silyl-protected propargyl moiety,[7] to the best of our knowledge, there are none involving the addition of an unprotected propargyl group or a silyl-allenyl group. It has formerly been shown,[15c] and the findings presented here further substantiate, that different product types can be used for generation of valuable compounds. The present advances furnish access to a variety of useful, polyfunctional, and otherwise difficult-to-access organic molecule building blocks in high er.

A combination of deuterium labeling experiments (KIE) and DFT studies were used to establish that a cationic π-allyl-Cu intermediate is probably generated prior to C−C bond formation, and that the process likely does not involve migratory insertion of an alkene into a Cu−C bond (unlike a Cu−H or a Cu−B bond). The pre-activation of the electrophile before C−C bond formation, formerly proposed on the basis of computational studies,[7] provides new insight vis-à-vis the unique ability of sulfonate-containing NHC-Cu complexes to facilitate S_N2' and enantioselective allylic substitutions. Stereochemical models have been provided that shed light on the role of different conformational isomers of organocopper intermediates bearing an extended π system. These models provide a rationale for why a Cu-based catalyst with an NHC ligand that contains a 2,5-disubstituted NAr moiety delivers higher er, but with some diminution in *E* selectivity.

These studies underscore the need for development of chemoselective methods. With the emergence of increasingly sophisticated strategies, products with multiple functionalities are becoming more easily available. Without reliable protocols for site-selective modification of multiple reactive sites within a multifunctional molecule, however, the full potential of such advances can only be partially fulfilled.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b10885.

Experimental details for all reactions and analytic details for all products (PDF)

X-ray crystallographic data for *p*-nitrobezoate derivative of **26** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the NIH (GM-47480). We thank M. S. Mikus for assistance in obtaining the X-ray structure for *p*-nitrobezoate derivative of **26**. We are grateful to Dr. J. del Pozo and Dr. F. W. W. Hartrampf for helpful discussions.

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DOI: 10.1021/jacs.8b10885
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