Asymmetric Catalysis

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Copper-Catalyzed Enantioselective Allylboration of Alkynes: Synthesis of Highly Versatile Multifunctional Building Blocks

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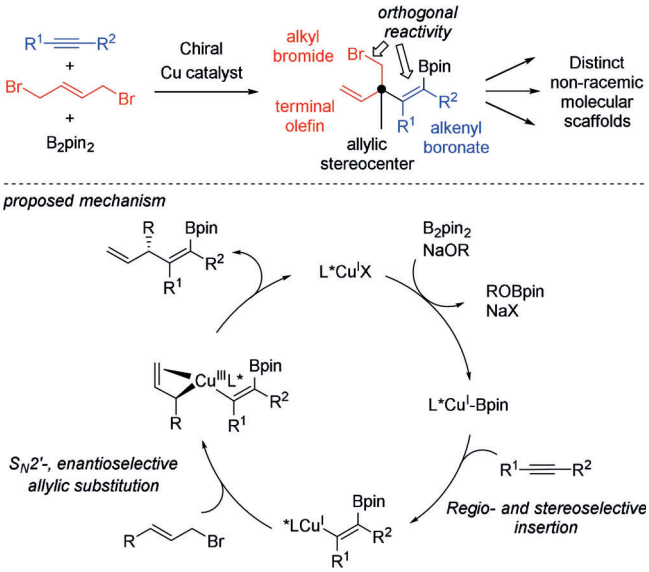
Abstract: *The first copper-catalyzed enantioselective allylboration of alkynes is reported. The method employs a multitasking chiral NHC-Cu catalyst and provides access to densely functionalized molecules from simple starting materials with excellent levels of chemo-, regio-, and enantioselectivity. These multifunctional products display highly versatile reactivity as shown by the synthesis of a variety of non-racemic molecular scaffolds. DFT calculations were conducted to gain insight into the high selectivity levels of this catalytic process.*

Synthetic methods that enable the catalytic and enantioselective assembly of complex organic molecules from simple and readily available materials are highly sought after. In particular, asymmetric multicomponent reactions that provide efficient access to chiral, densely functionalized building blocks capable of undergoing a variety of chemical transformations still represent a formidable challenge and are particularly valuable in the quest to accelerate the drug discovery process by diversity-oriented synthesis.[1] In recent years, the copper-catalyzed carboboration of alkynes has provided efficient processes for the construction of synthetically useful alkenyl boronates.[2] Despite important advances in this field, and in contrast to other borylative couplings using allenes[3] or alkenes,[4] a catalytic asymmetric multicomponent carboboration of alkynes has remained elusive.[5–7] Given the diverse reactivity of alkenyl boronates,[8] a catalytic enantioselective transformation that stereoselectively provides a scaffold bearing this reactive motif together with other orthogonal functional groups would represent a highly versatile synthetic tool. We thus envisioned a catalytic process in which a chiral copper catalyst efficiently promotes a regio- and stereoselective Cu–Bpin addition to an alkyne, while avoiding competing Cu–Bpin allylation.[9] The resulting alkenyl copper complex should then undergo a regio- (formal S_N2' selectivity) and enantioselective allylic substitution (Scheme 1). Such a highly selective multitasking catalyst would facilitate the formation of a chiral multifunctional 1,4-diene featuring an alkenyl boronate, an allylic stereocenter, a terminal olefin, and additional functionality (e.g., an alkyl bromide) coming from the allylic substrate. Moreover, this transformation would constitute a significant contribution to the field of asymmetric allylic substitution where the incorporation of alkenyl groups has been typically associated with the stoichiometric use of alkenyl metal reagents, which have to be prepared a priori; in addition, in some cases, their relatively high reactivity can compromise the functional group tolerance of the reaction.[10–12]



Scheme 1. Copper-catalyzed enantioselective allylboration of alkynes.

Herein, we report a copper-catalyzed enantioselective coupling of alkynes, B_2pin_2, and allylic bromides using a chiral NHC-Cu catalyst. This multicomponent reaction provides chiral densely functionalized 1,4-dienes with excellent levels of chemo-, regio-, and enantioselectivity under mild conditions. A distinctive feature of this strategy is the high synthetic versatility of the multifunctional products, which can be easily converted into a variety of non-racemic structures.

At the outset of our studies, we focused on creating an enantioselective variant of the coupling of alkynes, diboron compounds, and 1,4-dihalo-2-butenes that we had recently published.[5c] After surveying the performance of several chiral ligands in the reaction between phenylacetylene (**1**), 1,4-dibromo-2-butene (**2**), and B_2pin_2,[13] we found that the Cu complex derived from the sulfonate-bearing NHC ligand **L**[14] afforded **3** as a single isomer in 88% yield, with an excellent 97:3 enantiomeric ratio and complete levels of regioselectivity (β-borylation and S_N2' allylation >99%; Table 1, entry 1). Catalysts derived from other NHCs, phosphines, or Quinox-type ligands were much less efficient. Further investigations

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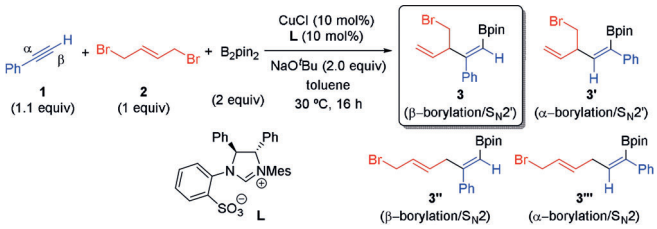
Table 1: Optimization studies.

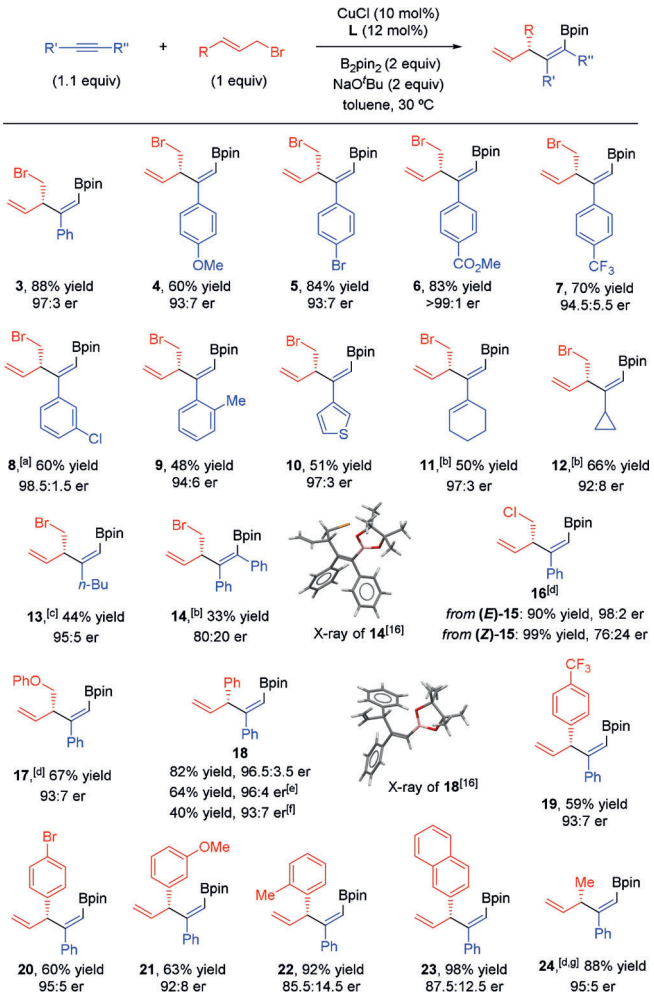


Entry	Variation from the "standard" conditions[a]	Conv. [%][b]	Yield [%][c]	er[d]
1	None	>99	88	97:3
2	without slow addition of **2**	>99	49	97:3
3	hexane instead of toluene	60	60	95:5
4	THF instead of toluene	85	31	92:8
5	LiO^{t}Bu instead of NaO^{t}Bu	94	35	90:10
6	KO^{t}Bu instead of NaO^{t}Bu	>99	55	97:3

[a] **1** (0.22 mmol), **2** (0.2 mmol, added by syringe pump over 5 h), B_2pin_2 (0.4 mmol), CuCl (10 mol%), **L** (10 mol%), NaO^{t}Bu (0.4 mmol), toluene (1.5 mL) at 30 °C. [b] Conversion (consumption of **2**) determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Yield of isolated **3**. Selectivity: **3**/**3′**/**3″**/**3‴** >99:<1:<1:<1. [d] Determined by SFC analysis on a chiral stationary phase.

revealed that slow addition of **2**, the solvent, and the metal alkoxide also play an important role in the reaction outcome (Table 1, entries 2–6), with NaO^{t}Bu in toluene being the best combination.

Having established optimized conditions for the asymmetric allylboration of alkynes, we set out to explore the scope of the reaction (Scheme 2). The Cu/**L** catalyst proved to be remarkably effective with a range of aryl alkynes. Products **3**–**9** were obtained in good yields with excellent regio- and enantioselectivity regardless of the electronic properties and position of the substituent on the aromatic ring (60–88% yield, >99% β-borylation, >99% S_N2', 93:7 to >99:1 er). Functional groups such as ether, ester, halogen, and trifluoromethyl groups were well tolerated. Similarly, terminal alkynes bearing heteroaromatic (**10**), alkenyl (**11**), or cyclopropyl (**12**) groups provided the corresponding products in good yields with excellent levels of selectivity. The reaction with 1-hexyne suffered from a slightly lower site selectivity (β/α-borylation 78:22), although **13** was still obtained as a pure product with perfect S_N2' selectivity and high er. Importantly, allylic alkynylation[15] was never observed with terminal alkynes. The use of internal alkynes was illustrated with diphenylacetylene, which turned out to be less reactive, leading to incomplete conversion. Although **14** was only obtained with 80:20 er, it is important to note that, to the best of our knowledge, this represents the first example of an enantioselective alkenyl allylation using a tetrasubstituted alkenyl nucleophile. Gratifyingly, we observed that this new method can be extended to other types of allylic substrates. (*E*)-1,4-Dichloro-2-butene (**15**) was equally efficient for this transformation and gave rise to the chloro-substituted product **16** in 90% yield and 98:2 er. Importantly, the use of (*Z*)-**15** afforded **16** in very good yield but with only 76:24 er, thus showing that the enantioselectivity of the reaction is influenced by the *E*/*Z* configuration of the allylic starting material. A bifunctional allylic substrate in the form of a phenyl ether was also well tolerated and provided product **17** with perfect site selectivity and 93:7 er. Cinnamyl-type substrates also proved to be efficient partners for this transformation, providing the corresponding products **18**–**23** in good yields and with high enantioselectivities except for allylic bromides bearing sterically demanding substituents. Remarkably, the S_N2' selectivity was as high as that obtained with 1,4-dihalo-2-butenes, despite the absence of a coordinating unit in the allyl substrate.[17] Cinnamyl phosphate and chloride could also be used for the asymmetric allylboration of phenylacetylene (**18**), although they proved to be less efficient than cinnamyl bromide. We also investigated the asymmetric allylboration with crotyl bromide, which has been scarcely used in catalytic asymmetric allylic substitution reactions involving organometallic nucleophiles likely because of the challenging enantiotopic differentiation caused by the small size of the



Scheme 2. Scope of the copper-catalyzed enantioselective allylboration of alkynes.[16] For the exact reaction conditions, see Table 1, entry 1. Selectivity >99% unless otherwise noted. [a] At 40 °C. [b] At 50 °C. [c] β-borylation/α-borylation 78:22. [d] Slow addition of the allyl bromide was not required. [e] Diethyl cinnamyl phosphate used instead of cinnamyl bromide. [f] Cinnamyl chloride used instead of cinnamyl bromide. [g] S_N2'/S_N2 94:6.

methyl substituent.[18] To our delight, the reaction of crotyl bromide with phenylacetylene and B_2pin_2 afforded methyl-substituted product **24** in 88% yield with very high regioselectivity (S_N2'/S_N2 94:6) and enantioselectivity (95:5 er), further highlighting the efficiency of the catalytic system.

To gather insight into the origin of the high levels of selectivity achieved in this new transformation, DFT calculations were performed using the formation of **24** as a model reaction (Figure 1).[13] We found that the most favored

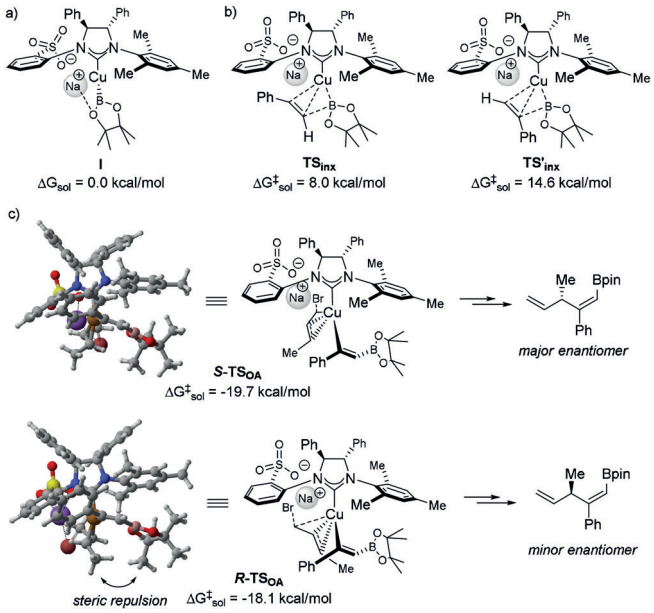
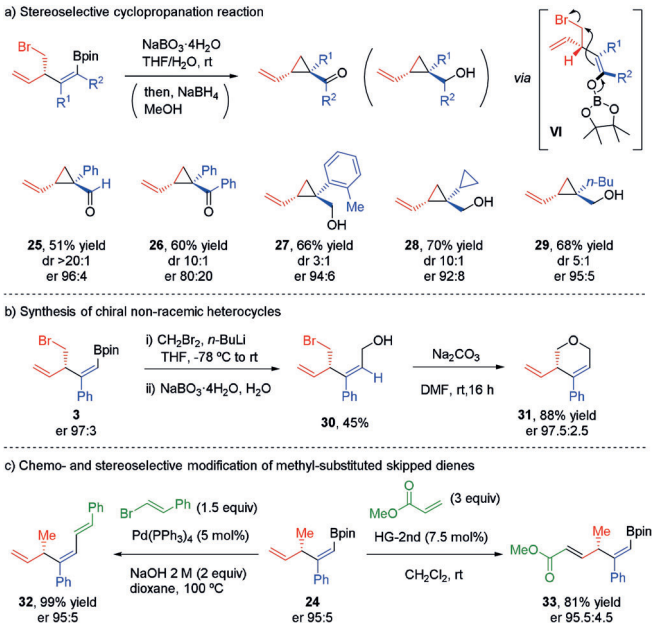


Figure 1. Optimized structures and energies calculated at the ωB97XD/Def2-TZVPP$_{tol(SMD)}$//ωB97XD/6-31G(d) level of theory for a) complex **I**, b) the transition states for the alkyne borylcupration step, and c) the stereochemistry-determining oxidative addition step. The energies given are relative to complex **I** combined with those of the relevant substrates.

conformation for the Cu–Bpin complex **I** arises from a coordination of the Na cation to one oxygen atom of the pinacolato group (Figure 1a).[19,20] This situation favors coordination of the alkyne on the opposite side from the sulfonate group of NHC. Transition state $\mathbf{TS_{inx}}$ leading to the β-boryl-substituted alkenyl copper complex **III** was found to be 6.6 kcal mol^{-1} more favorable than $\mathbf{TS'_{inx}}$ associated with the α-borylation pathway (Figure 1b).[21] Based on our findings, a stereochemical model for the subsequent stereochemistry-determining oxidative addition step,[22,23] where the allyl bromide approaches the intermediate alkenyl copper complex so that a sodium cation bridge is established between the NHC's sulfonate group and the bromide unit,[20] may be proposed. Among the investigated modes of coordination,[13] the one featuring the allyl bromide opposite to the sizable NMes unit led to the most favorable pathways. As shown in Figure 1c, the relative energy of transition state $\mathbf{\textit{S}\text{-}TS_{OA}}$ (pathway to the major *S* enantiomer) is 1.6 kcal mol^{-1} lower than that of $\mathbf{\textit{R}\text{-}TS_{OA}}$, which is consistent with the observed 95:5 er. In the pathway leading to the minor enantiomer, the Me substituent in the allylic substrate would experience a repulsive interaction with the Bpin unit. The higher enantioselectivity observed in non-polar solvents (see Table 1, entries 1, 3, and 4), where stronger ion pairing would lead to a more rigid transition state, is in accordance with the key supramolecular interaction between the Na cation and the bromide. In this context, the lower er observed when LiO^{t}Bu was used (Table 1, entry 5) might arise from a less efficient interaction due to the smaller size of the Li cation.

An attractive feature of this new asymmetric allylboration reaction is the functional group diversity present in the products, which makes them highly versatile non-racemic building blocks (Scheme 3). Notably, treatment of bromo-



Scheme 3. Synthetic modifications of the products.

substituted dienyl boronates with sodium perborate resulted in a new stereoselective cyclopropanation reaction[24] for the asymmetric synthesis of functionalized vinylcyclopropanes, which are important structural motifs that are present in a range of natural products and pharmaceuticals,[25] and are also valuable synthetic intermediates.[26] Vinylcyclopropane carbaldehydes (or carbinols after reduction) **25**–**29**, bearing a newly generated all-carbon quaternary center next to the tertiary stereocenter, were formed with generally high diastereoselectivity, and without any reduction in enantiopurity. This process likely involves intramolecular trapping of the newly generated boron enolate **VI**, where the sizable OBpin unit would be placed *anti* to the vinyl group (Scheme 3a). Product **3** also serves as a useful precursor for the construction of non-racemic heterocycles. A homologation/oxidation/cyclization sequence afforded vinyl-substituted dihydropyran **31** in good yield and with total stereochemical retention (Scheme 3b). Moreover, the presence of both a terminal olefin and an alkenyl boronate offers the possibility of chemo- and stereoselective modification of both termini of the skipped diene skeleton. Thus, methyl-substi-

tuted skipped diene **24** could be selectively modified by Suzuki cross-coupling (**32**) or cross-metathesis (**33**; Scheme 3c). This strategy represents a versatile tool to access structurally diverse chiral skipped dienes bearing a methyl-substituted central stereogenic carbon atom, which are common structural motifs in a range of biologically active compounds.[27]

In summary, we have developed the first copper-catalyzed enantioselective allylboration of alkynes. The method provides densely functionalized molecules from simple starting materials with excellent levels of chemo-, regio-, and enantioselectivity. Key to achieving this selectivity is the use of a catalyst featuring a sulfonate-bearing chiral NHC ligand capable of establishing substrate–cation bridging interactions in different catalytic steps, as suggested by DFT calculations. We have shown that these multifunctional products display very diverse reactivity, which makes them very attractive building blocks for asymmetric chemical synthesis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · boron · copper · diversity-oriented synthesis · multicomponent reactions

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Communications

Asymmetric Catalysis

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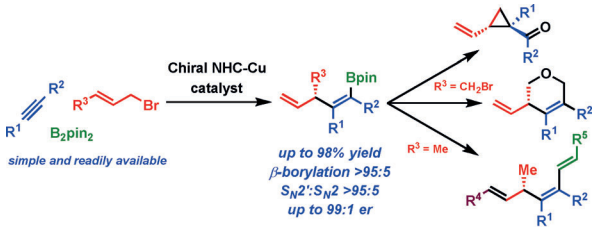
Copper-Catalyzed Enantioselective Allylboration of Alkynes: Synthesis of Highly Versatile Multifunctional Building Blocks



Complexity from simplicity: A copper-catalyzed enantioselective alkyne allylboration provides access to non-racemic densely functionalized molecules from simple starting materials with remarkable chemo-, regio-, and enantioselectivity. These multifunctional products are easily converted into a variety of important molecular scaffolds.

