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Article

Copper-Catalyzed Coupling of Alkyl Vicinal Bis(boronic Esters) to an Array of Electrophiles

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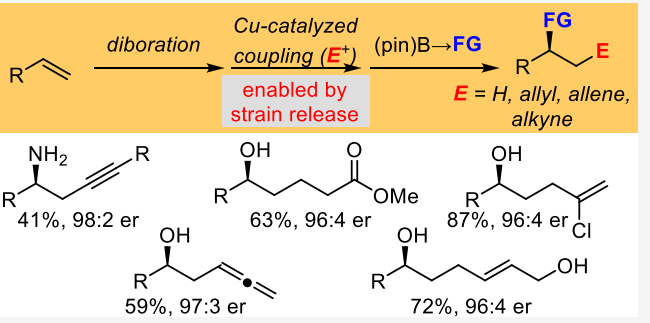
ABSTRACT: A neighboring boronate group in the substrate provides a dramatic rate acceleration in transmetalation to copper and thereby enables organoboronic esters to participate in unprecedented site-selective cross-couplings. This cross-coupling operates under practical experimental conditions and allows for coupling between vicinal bis(boronic esters) and allyl, alkynyl, and propargyl electrophiles as well as a simple proton. Because the reactive substrates are vicinal bis(boronic esters), the cross-coupling described herein provides an expedient new method for the construction of boron-containing reaction products from alkenes. Mechanistic experiments suggest that chelated cyclic ate complexes may play a role in the transmetalation.



INTRODUCTION

Catalytic enantioselective difunctionalization of non-activated alkenes, especially simple α-olefins, is a pressing problem in contemporary organic synthesis.[1] One strategy that addresses this challenge is to conduct catalytic asymmetric alkene diboration[2,3] and then subject the vicinal bimetallic intermediate to subsequent transformation (Scheme 1a). For example, by subjecting the vicinal diboron intermediate to regioselective Pd-catalyzed Suzuki−Miyaura coupling[3a,4] or carbenoid-based homologation,[5] extension of the carbon chain can be accomplished and the remaining secondary boronic ester may be transformed separately (Scheme 1b). A significant limitation of this strategy has been that the Pd-catalyzed coupling of alkyl boronic esters only applies to C(sp^2) electrophiles and this severely limits the reaction scope. To engage alkyl electrophiles in Suzuki−Miyaura reactions, palladium,[6] copper,[7] nickel,[8] and iron[9] catalysts have been employed; however, these processes generally require trialkylborane derivatives for productive reaction. While copper catalysis can extend to alkylboronic esters,[7c,d] until recently, this process was similarly limited to C(sp^2) electrophiles.[10] Recent studies in our laboratory showed that upon activation with *t*-butyllithium, copper catalysts can facilitate coupling between alkylboronic esters and a range of non-C(sp^2) electrophiles (Scheme 1c). Herein, we demonstrate that using simple alkoxide activation, 1,2-bis(boronic esters) exhibit remarkable reactivity in Cu-catalyzed reactions and undergo regioselective coupling with carbon-based electrophiles (Scheme 1d). This overall process enables useful strategies to convert alkenes to a broad array of chiral, enantiomerically enriched reaction products.

RESULTS AND DISCUSSION

To extend the range of enantiomerically enriched reaction products available from terminal alkenes via diboration, we considered catalytic site-selective reaction of vicinal diboronates with non-C(sp^2)-derived electrophiles. Expanding the scope of metal-catalyzed cross-couplings that operate with alkylboronic esters faces two inherent challenges with respect to reactivity. First, relative to boronic acids and trialkylboranes, alkylboronic esters have diminished Lewis acidity and therefore a reduced capacity to form reactive four-coordinate "ate" complexes that are often required for transmetalation with metal-based catalysts.[11] Second, relative to aryl and alkenyl boron congeners, the diminished *s* character at the reacting sp^3-hybridized carbon of *alkyl* boronic esters makes the carbon atom less able to support the transient buildup of charge during transmetalation, and this effect retards reaction rates.[12] In spite of the general poor reactivity of alkylboronic esters in metal-catalyzed coupling reactions, the enhanced reactivity of vicinal bis(boronates) in Pd catalyzed reactions[4b] prompted an investigation into these substrates with other metal salts. As shown in Table 1, when vicinal bis(boronate) **1** was treated with allyl bromide in the presence of 20 mol % of various metal salts and lithium methoxide at 60 °C for 16 h, little reactivity was observed for Ni(II), Co(II), Mn(II), and Fe(II) salts

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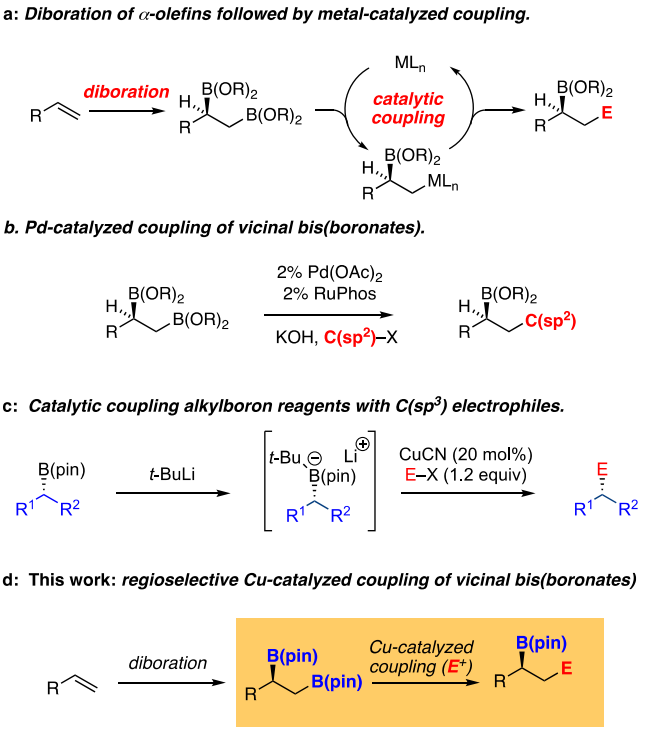
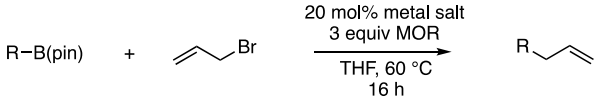
Scheme 1. Issues in Diboration of Alkenes and Subsequent Coupling



(entries 1−7). However, when CuBr was employed, the allylation product **2** was produced in 85% yield (entry 8) and as a single regioisomer. While the reaction with CuI was slightly inferior to that of CuBr (entries 8, 9), when CuCN was employed as the catalyst, the reaction was notably enhanced, achieving complete conversion in 16 h (entry 10). Examination of reactions employing lower loadings of CuCN showed that diminished amounts of catalyst could still deliver the product, but optimal yields were obtained with 20 mol % catalyst (entries 11−14). Analysis of other metal alkoxides (entries 15−17) revealed $LiOCH_3$ to be optimal, and analysis of ligands did not reveal a clear advantage of including NHC or phosphine-based structures. In contrast to the reaction of the vicinal diboronate **1**, attempted reaction of monoboronate **3** with allyl bromide did not provide any detectable amounts of coupling product (**4**) after 16 h at 60 °C (entry 21). Thus, the non-participating secondary boronate in **1** exerts a significant accelerating effect on the reaction. As shown in Table 1, the activating boronate group can be either primary (**5**, entry 22), secondary (**1**), or tertiary (**7**, entry 23) and still provide substrate activation. That this activating effect requires precise positioning between the activating and reacting boronates is exemplified by the lack of reactivity exhibited with 1,3-diboronate **9** (entry 24); with an extra atom between the two boronates, reactivity is significantly diminished.

Because the enantioselective transformation of terminal alkenes is a critical challenge in organic synthesis,[13] we considered that olefin diboration, followed by the above-described coupling, would provide a useful route from terminal alkenes to a broad range of functionalized products. Of note, relative to the use of Pd-based catalysts in cross-coupling reactions, Cu complexes can engage a broader array of electrophiles,[14] and this catalyst was subjected to a more detailed study of substrate scope. Also noteworthy is that in

Table 1. Metal-Catalyzed Coupling of Alkylboronic Esters with Allyl Bromide[a]



entry	copper salt	MOR	yield (%)[c]
			
1	$Ni(acac)_2$	LiOMe	< 5
2	$NiCl_2$	LiOMe	< 5
3	$Co(OAc)_2$	LiOMe	< 5
4	CoCl2	LiOMe	< 5
5	$MnCl_2$	LiOMe	< 5
6	$FeCl_2$	LiOMe	< 5
7	$Fe(acac)_2$	LiOMe	< 5
8	CuBr	LiOMe	85
9	CuI	LiOMe	81
10	CuCN	LiOMe	> 95
11	CuCN (10%)	LiOMe	63
12	CuCN (5%)	LiOMe	42
13	CuCN (2%)	LiOMe	31
14	CuCN (1%)	LiOMe	11
15	CuCN	NaOMe	50
16	CuCN	KOMe	53
17	CuCN	LiOtBu	63
18[b]	$CuCN/PPh_3$	LiOMe	78
19[b]	$CuCN/PBu_3$	LiOMe	65
20[b]	CuCN/iMes	LiOMe	92
			
21	CuCN	LiOMe	< 5
			
22	CuCN	LiOMe	> 95
			
23	CuCN	LiOMe	53
			
24	CuCN	LiOMe	6

[a]Reactions were carried out with 0.20 mmol of substrate and 0.30 mmol of allyl bromide. [b]Experiment employed 24 mol % of added ligand. [c]Yield determined by ^1H NMR versus an internal standard.

relation to other methods for alkene carboboration,[15] the diboration/Cu-catalyzed coupling provides complementary regioselectivity.

With optimal reaction conditions as shown in Figure 1a, we examined the scope of the copper-catalyzed coupling with allyl bromide (Figure 1b). It was found that the Cu-catalyzed coupling reaction occurs with a range of terminal vicinal bis(boronic esters). Boron reagents derived from simple aliphatic alkenes and those bearing aromatic rings, silyl ethers, or protected nitrogen-based functional groups are appropriate substrates for cross-coupling and furnish allylation products in good yield. Because a broad range of α-olefins participate in carbohydrate-catalyzed enantioselective diboration,[2f,g] a se-

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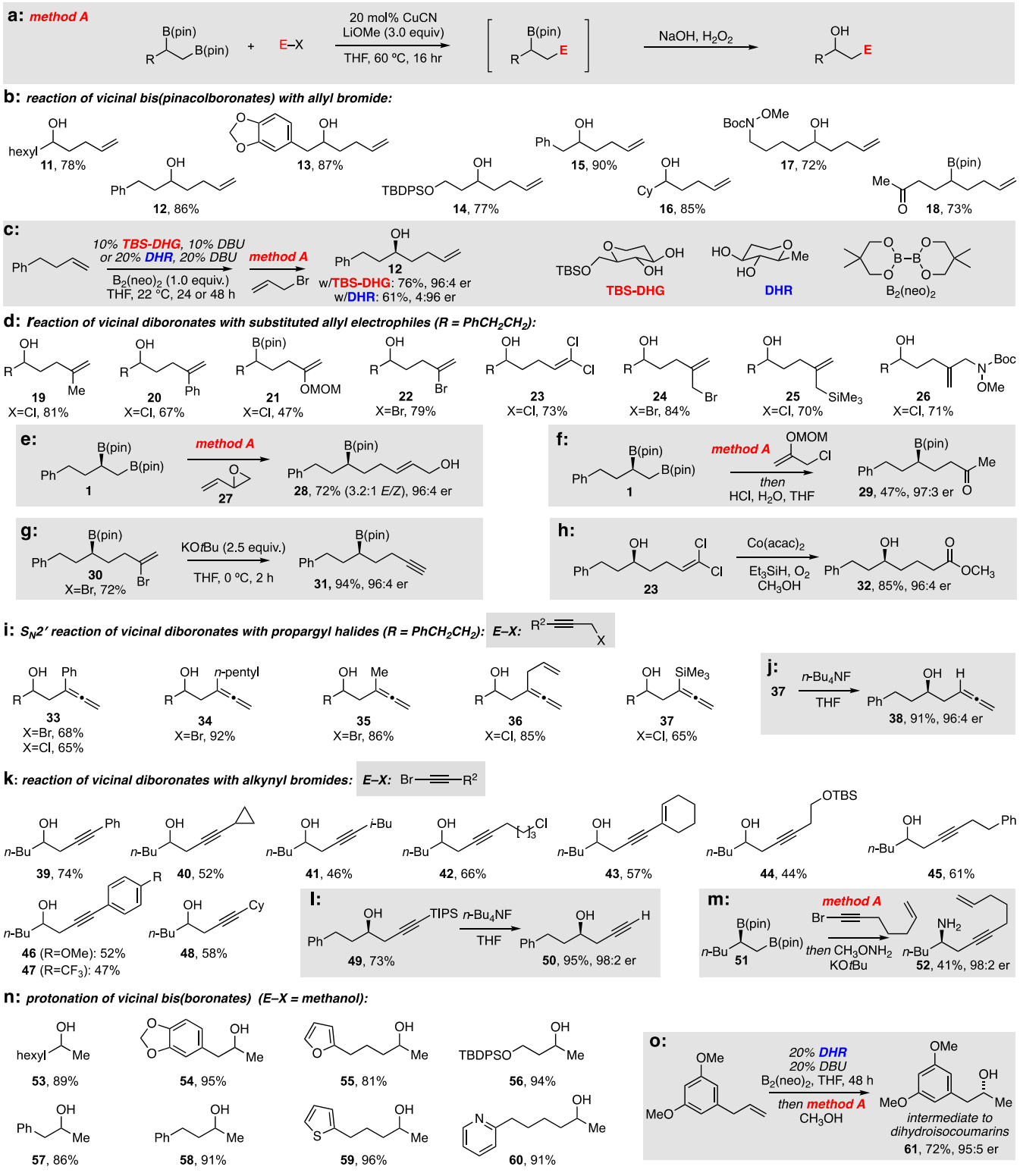

Figure 1. Scope of the Cu-catalyzed cross-coupling of vicinal bis(boronates) and organic electrophiles. Yields are of isolated material after purification by column chromatography. Enantiomer ratio (er) determined by chiral HPLC or SFC analysis. The oxidation step was omitted for compounds **21**, **29**, and **30**. A loading of 30 mol % CuCN was employed for section k.

quential single-flask diboration/Cu-catalyzed allyl coupling was probed (Figure 1c). When pseudoenantiomeric TBS-DHG and DHR catalysts (derived from glucose and rhamnose, respectively) were employed, either enantiomer of chiral alcohol **12** was produced from 4-phenyl-1-butene in an efficient and selective single-flask reaction. In addition to allyl bromide, coupling with functionalized allyl electrophiles was also found to be efficient and provides a practical route to a collection of other useful chemical building blocks (Figure 1d). Important observations are that alkyl, aryl, alkoxy, halo, and other valuable functional groups can be incorporated in the electrophile and high-yielding reactions result (**19**–**26**). A

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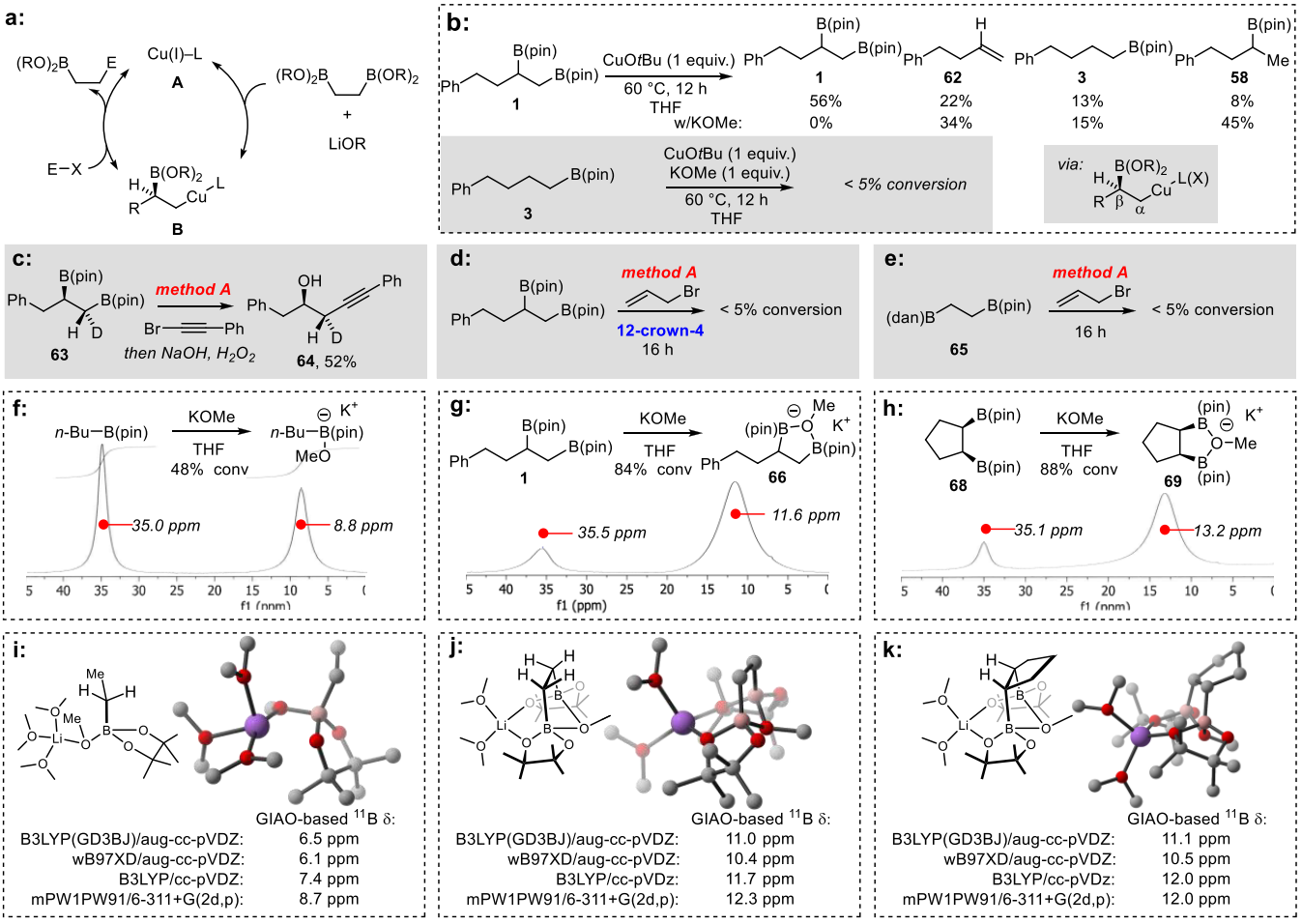

Figure 2. Mechanistic aspects of the Cu-catalyzed coupling reaction. (a) General catalytic cycle of reaction of vicinal bis(boronates). (b) Stoichiometric reaction of substrates with CuOtBu shows a rate enhancement for reaction of bis(boronates) versus monoboronates. (c) Reaction of the labeled substrate indicates the coupling proceeds with retention of configuration at carbon. (d) Inhibition of the coupling by 12-crown-4 suggests that the lithium ion is required for the reaction. (e) Substrate activation does not occur when the adjacent boronate is a less Lewis acidic diazaborole. (f–h) Treatment of organoboronic esters with potassium methoxide relative to boron suggests the intermediacy of internally chelated borates. (i–k) GIAO-DFT-based chemical shift calculations are consistent with the assignment of cyclic chelated ate complexes. Methods/basis sets are for the calculation of isotropic shielding constants; geometry optimizations were by B3LYP(D3)/6-311G(d), B3LYP/cc-pVDZ, or M06-2x/6-31+G(dp). See Supporting Information for details.

few allylation reactions merit special mention: vinyl epoxide **27** (Figure 1e) serves as an effective electrophile and allows for direct conversion of enantiomerically enriched vicinal bis(boronate) **1** to boron-containing allylic alcohol **28** with preservation of enantiomeric purity. Moreover, synthesis of difficult-to-access chiral γ-boryl carbonyls, compounds that represent dissonant oxidation patterns[16] in organic molecules, is accessible by hydrolysis of an enol ether-containing allylation product (**1** → **29**, Figure 1f). Single-step transformation of products **30**[17] and **23**[18] readily provides enantiomerically enriched compounds with remote alkyne and ester functional groups (Figure 1g,h). That molecules **28**–**32** can now be easily accessed from simple alkenes in an enantioselective fashion is likely to be of value for chemical synthesis.

In addition to allylic halides, the Cu-catalyzed coupling of vicinal bis(boronates) extends to other electrophile classes. Substituted primary propargylic halides undergo cross-coupling in an S_N2' fashion providing substituted allenes **33**–**37** in good yield (Figure 1i). Of note, the silicon group in allene **37** is readily removed upon fluoride treatment, and this gives a route to homoallenic alcohols such as **38** (Figure 1j) that are not easily prepared by other methods.[19] Alkynyl bromides also undergo coupling with vicinal bis(boronates) under Cu catalysis, and this provides a route to versatile homopropargylic boronic esters (Figure 1k). The products delivered from this reaction (**39**–**48**) indicate a useful level of substrate tolerance with alkyl, aryl, and alkenyl containing alkynes participating, as well as halide and silyl ether functional groups. Notably, the simple terminal alkyne derivative **50** is readily available by efficient desilylation of **49** (Figure 1l). Also of note, the boronate that remains after alkyne coupling can be subject to stereospecific amination,[20] which provides access to homopropargylic amines (**52**, Figure 1m).

When electrophiles bearing aliphatic ketone, ester, amide, or nitrile functional groups were subjected to Cu-catalyzed coupling conditions, protodeboronation of the primary boronate occurred, suggesting that the organocopper intermediate is moderately basic and may remove the acidic proton adjacent to the carbonyl of these functional groups. While this feature currently places a limitation on the electrophile scope, the protodeboronation itself, when conducted after enantioselective diboration, provides a high-yielding enantioselective

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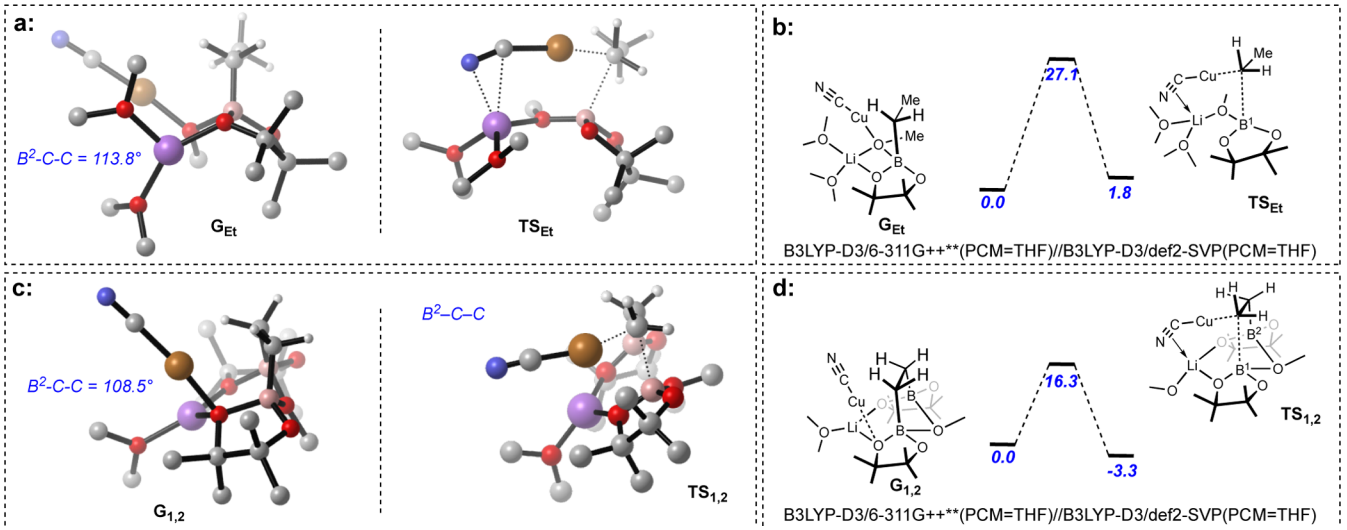

Figure 3. DFT Calculations. (a) Ground state and transition state structures for the reaction of methoxide-activated EtB(pin) B3LYP-D3/Def2SVP//B3LYP-D3/6-311++G** with PCM (THF) solvent model. (b) Calculated barrier for transmetalation of methoxide-activated EtB(pin). (c) Ground state and transition state structures for the reaction of methoxide-activated vicinal diboronate **5**. (d) Calculated barrier for transmetalation of methoxide-activated vicinal diboronate **5**.

contra-steric hydroboration of α-olefins (Figure 1n). Production of compounds **53**−**60** with high levels of regio- and enantioselectivity by hydroboration of 1-alkenes[21] would be a challenge with other methods, but are readily provided by this Cu-catalyzed protonation process. Moreover, a single-flask diboration/protonation sequence can be conducted, and it provides useful yields and selectivity for the synthesis of compound **61** (Figure 1o), which is an intermediate in several syntheses of dihydroisocoumarin natural products.[22]

The transformations in Figure 1 are enabled by the presence of the non-reacting secondary pinacolato boronate group, and the requirements for this species to enhance the reaction rate warrant investigation. In terms of the general mechanism for catalysis, we presume transmetalation of the organic group from boron to copper is a requisite event. The observation that protodeboronation (Figure 1n) occurs efficiently in the absence of a redox-active electrophile suggests the operation of a catalytic cycle where oxidation of Cu(I) is not likely required for transmetalation with the vicinal bis(boronate). Thus, we consider that transmetalation might occur directly with CuCN, with a Cu(I) alkoxide,[23] an alkoxy-derived cuprate,[24] or related Cu(I) salts (**A**, Figure 2a) to give an intermediate such as **B**, prior to electrophilic trap that releases the copper salt and the product. To gain more insight into the nature of the transmetalation reaction, a series of experiments were undertaken. First, we examined the direct stoichiometric reaction between vicinal diboron reagent **1** and CuO*t*Bu (Figure 2b). Conversion of the diboron to alkene **62** and monoboronic ester **58** occurs slowly at 60 °C in the absence of alkoxide but is accelerated by the inclusion of 1 equivalent of KOMe (lithium methoxide is only partially soluble in THF and therefore was not employed in mechanistic studies). The products of this reaction are consistent with the intermediacy of an organocopper compound such as **B** (Figure 2a): compound **62** would arise from β-boryl elimination,[25] while compound **58** would arise from protonation of the organometallic intermediate by an adventitious proton source. In contrast, treatment of monoboron **3** with CuO*t*Bu and KOMe for 12 h at 60 °C did not result in consumption of the boronic ester reactant, highlighting the activating effect of a vicinal boronate group. To probe the stereochemical course of the transmetallation, diastereomerically enriched deuterium-labeled vicinal diboron **63** was subjected to the catalytic coupling reaction with bromoacetylene (Figure 2c). This reaction delivered **64** selectively, revealing that the reaction of the primary boronate proceeds with net retention of configuration at the carbon center, presumably by way of a stereoretentive transmetalation. The activating effect of the vicinal boronate on the transmetalation might arise by a number of different mechanisms. The experiments in Figure 2d suggest the cation plays a critical role (12-crown-4 is a lithium scavenger[26]), and the reaction in Figure 2e indicates that the activating boron group should be Lewis acidic in order to exert its effect [B(dan) is a weaker Lewis acid than B(pin)].

The experiments mentioned above suggest that the mechanism for substrate activation may involve both boronate groups acting in concert when bonding to the metal alkoxide. To probe this, alkoxide complexation with several organoboron compounds was examined by ^{11}B NMR spectroscopy. For calibration, treatment of a *n*-BuB(pin) with 1 equivalent of KOMe resulted in partial conversion (48% conv) of the starting material (35.0 ppm) to a compound with an upfield shifted resonance (8.8 ppm), consistent with the formation of the derived four-coordinate organoboronate (Figure 2f). When the diboron **1** was treated with one equivalent of methoxide (0.5 equiv of alkoxide relative to total boron), 84% conversion of total three-coordinate boron to a new upfield resonance (11.6 ppm) was observed (Figure 2g), suggesting a bonding mode that involves both boron atoms of the substrate. The ^{11}B chemical shift of this species is consistent with that calculated for an internally-chelated four-coordinate complex (Figure 2j) using gauge-including atomic orbital DFT calculations (use of GIAO DFT also predicts the chemical shift of EtB(pin)·methoxide complex, Figure 2i).[27] Examination of other structures is in line with this bonding mode: the ^{11}B resonance for *cis*-1,2-diborylcyclopentane **68** (Figure 2h,k), a compound that should be predisposed to make internally chelated species (presumably for steric reasons, **68** does not undergo coupling),

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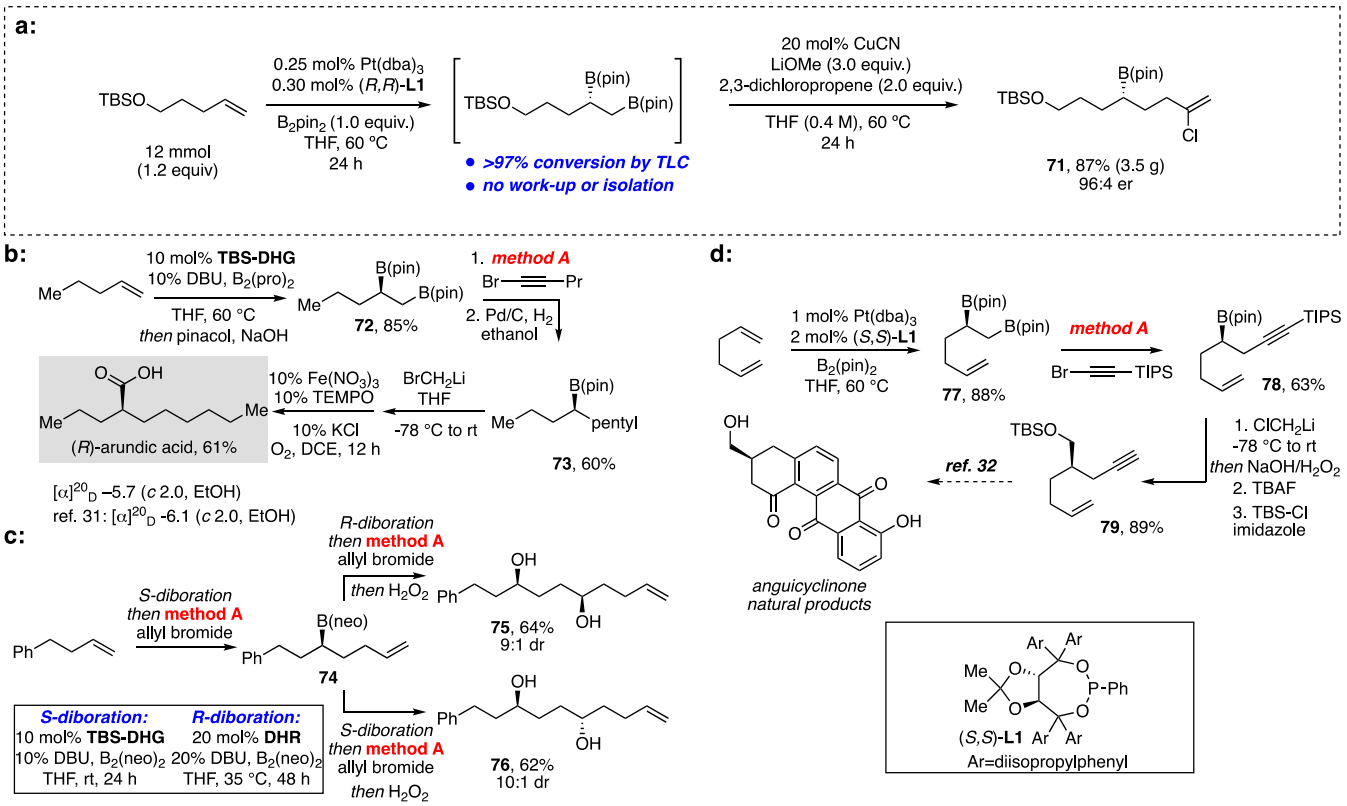

Figure 4. Application of the Cu-catalyzed coupling reaction to targets of interest. (a) Preparative scale tandem diboration/copper-catalyzed coupling. (b) Synthesis of (*R*)-arundic acid by diboration, coupling, hydrogenation, homologation, and oxidation. (b) Construction of 1,4-dioxygenated motifs by two sequential diboration/coupling tandem reactions. (c) Construction of a precursor to anquicyclinones by alkyne coupling.

is converted to a structure with a similar upfield resonance (88% conv.; 13.2 ppm). While oxygen-bridged bis(boronic) esters have not been described in the literature, a recent report describes oxygen-bridged *ortho* phenylenediboronic acids,[28] and related 1,2-alkoxide complexes of Lewis acidic vicinal diborons also adopt this bonding mode.[29]

To learn about the origin of the enhanced reactivity of 1,2-diboronates, a preliminary series of DFT computational experiments was conducted to compare the reactive 1,2-diboronate with the less reactive monoboronate. As shown in Figure 3, conversion of ground state ate complexes derived from either EtB(pin) or a vicinal diboronate shows markedly different profiles in conversion to the transition state for transmetalation: the barrier for reaction of methoxide-activated EtB(pin) (Figure 3b) is nearly 10 kcal/mol higher than the barrier for reaction of the methoxide-activated cyclic chelate (Figure 3d). Part of this barrier can be traced to the differences in the starting material strain. For the ground state of the cyclic chelate, the B−C−C bond angles are measurably compressed relative to the unstrained acyclic compound $\mathbf{GS}_{\mathbf{Et}}$ (108.5° vs 113.8°) and relative to unstrained acyclic boronic esters (see Supporting Information for this analysis). Upon achieving the transition state for transmetalation of the vicinal organoboronate, the B−C−C angle for the remaining organoboronate is expanded to 118.2°, suggesting a significant relaxation of the cyclic structure. It also appears that reaction of the 1,2-diboron complex benefits from a developing interaction between the lithium atom and the cyano ligand as the transition state is approached, and this may be relevant also. Notably, Nakamura has detected a related CuCN−Li interaction during DFT studies of allylic substitution.[30]

The use of catalytic enantioselective diboration followed by vicinal diboronate cross-coupling may provide practical synthesis routes to medicinally relevant targets. To establish the practicality of the process, it was shown that on a multi-mmol scale, Pt-catalyzed enantioselective diboration[2c,d] could be accomplished with just 0.25 mol % Pt catalyst, and Cu-catalyzed coupling could enable single-pot transformation of an α-olefin to organoboronate **71** (Figure 4a). Not only does this process occur with excellent yield but the crude reaction mixture is remarkably clean, rendering product isolation straightforward. As shown in Figure 4b, this two-step synthesis strategy can be employed to address the synthesis of the therapeutic agent (*R*)-arundic acid (ONO-2506). Thus, enantioselective diboration of pentene, followed by Cu-catalyzed coupling to 1-bromopentyne, followed by hydrogenation, gives a simple route to secondary boronate **73**, which was easily converted to the astrocyte activation inhibitor ONO-2506[31] by homologation and oxidation. In an alternate forum, sequential diboration/allyl coupling reactions can be conducted with alternate enantioselectivity such that either diastereomer of 1,4-dioxygenated products **75** and **76** (Figure 4c) can be accessed in a stereoselective fashion. Given the importance of chiral 1,4-diols in bioactive materials and the challenge presented by preparing this dissonant oxidation pattern,[16] this strategy promises to be a useful tool for chemical synthesis. Lastly, compound **79** (Figure 4d) has proven to be a versatile intermediate in the synthesis of anguicyclinones[32] and is readily prepared by Pt-catalyzed asymmetric diboration of

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1,5-hexadiene and coupling with an alkynyl bromide to give **78**; subsequent homologation and protection furnishes the intermediate in short order.

CONCLUSIONS

The remarkable propensity for vicinal diboronates to participate in Cu-catalyzed coupling reactions opens up an array of new synthesis strategies for the construction of strategically functionalized chiral organoboronic esters from simple alkene precursors. While it can be anticipated that these processes will be useful for chemical synthesis, it is also expected that the unique reactivity of chelated ate complexes in transmetalation may enable other metal-catalyzed couplings for asymmetric synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c02817.

Procedures, characterization, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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