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Letter

Asymmetric Access to Boryl-Substituted Vicinal Aminoalcohols through Cu-Catalyzed Reductive Coupling

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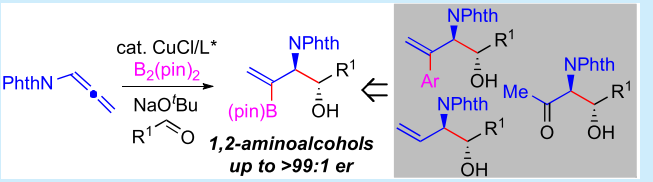
ABSTRACT: Herein, we report the development of a Cu-catalyzed enantioselective borylative aminoallylation of aldehydes using a N-substituted allene to access boryl-substituted 1,2-aminoalcohol synthons for diversification to chiral heteroatom-rich organic compounds. The reported reaction provides access to several different substitution patterns of chiral 1,2-aminoalcohol products from the same readily available starting materials with high diastereo- and enantioselectivity.



The chiral 1,2-aminoalcohol motif is an important architectural feature found in a variety of biologically active complex natural products and pharmaceutical candidates.[1] Accordingly, asymmetric installation of this functional unit is an important endeavor in organic synthesis.[2] While many techniques rely on the chemical forging of a carbon–heteroatom bond,[2a] methodologies whereby the vicinal substitution is installed through direct coupling of the carbon atoms bearing the heteroatom functional groups are less established[2b] and typically employ umpolung,[3] α-amino-anions,[4] or radical processes.[5] Moreover, biologically significant 1,2-aminoalcohols are often found to have additional polar N or O heteroatom functional groups throughout the carbon framework (Figure 1A).[1,2,6] Therefore, to access such heteroatom-rich compounds, strategies for the introduction of these additional functionalities must be an integral part of the overall retrosynthetic plan. Along these lines, carbonyl aminoallylation by N-substituted organometallic reagent **2** represents a useful strategy for gaining asymmetric access to **1** bearing a pendant alkene that can serve as a useful handle for further derivatization (Figure 1B).[7]

With current modern trends allowing for generation of substituted allylic organometallic reagents in a catalytic fashion from unsaturated hydrocarbons,[8] catalytic asymmetric access to **1** through reductive coupling methods has recently emerged (Figure 1C).[7] Notably, the Krische group[7a] applied his pioneering hydrogen autotransfer technique for the coupling of **3** and an *N*-phthaloyl allene to afford *anti*-aminoalcohol precursor **5** with high enantioselectivities under Ir catalysis. Additionally, our group reported a Cu-catalyzed enantioselective[7e] variant using ketone electrophiles with allenamides to produce *syn*-aminoalcohol surrogate **8** and also demonstrated this process under chiral auxiliary control.[7g−j] *anti*-1,2-Aminoalcohols can also be obtained when using acyclic allenamides.[7f] Finally, the Malcolmson group[9] has introduced 2-aza-triene

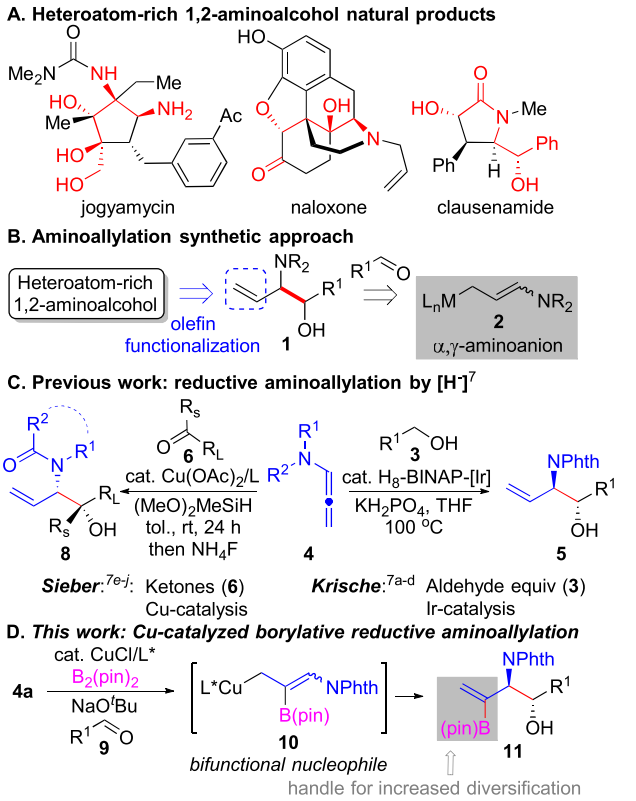


Figure 1. Reductive coupling approaches to heteroarom-rich organic compounds through aminoallylation.

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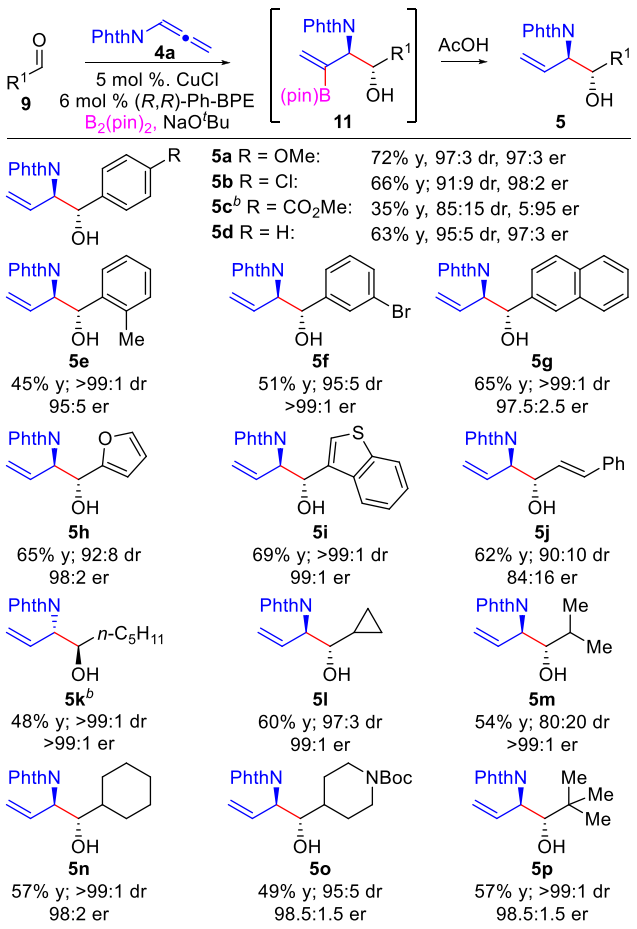
reagents for the Cu-catalyzed enantioselective aminoallylation of imines.

In the course of our development of Cu-catalyzed asymmetric reductive coupling reactions of ketones and allenamides utilizing silane reductants,[7e−j,10] we reasoned that application of a diboron reductant [e.g., $B_2(pin)_2$] in these reactions may offer significant benefits in the context of accessing heteroatom-rich organic architectures (Figure 1D).[11] We reasoned that borylcupration[12] of **4a** should be a viable pathway for accessing bifunctional nucleophilic α,γ-amino-anion **10**, ultimately leading to boryl-substituted aminoalcohol surrogate **11** in a straightforward manner. Due to the vast array of chemistries suitable to process the C−B bond into a variety of functionalities, **11** represents a highly valuable intermediate for the asymmetric synthesis of complex 1,2-aminoalcohol-containing chiral architectures. Herein, we describe our studies toward developing a Cu-catalyzed enantioselective borylative aminoallylation reaction of aldehydes.[13,14]

Initial investigation of the proposed borylative amino-allylation process was performed according to the sequence given in Table 1 utilizing phthalimido-allene **4a** with *p*-anisaldehyde (**9**; R^1 = PMP) using a variety of commercially

Table 1. Enantioselective Borylative Aminoallylation/Protonolysis[a]



[a]Aldehyde (0.200 mmol), **4a** (0.210 mmol), CuCl (5 mol %), (*R,R*)-Ph-BPE (6 mol %), NaOtBu (0.200 mmol), B_2pin_2 (0.400 mmol) (see the Supporting Information for details). Diastereomeric ratios (dr) were determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [b](*S,S*)-Ph-BPE was used.

available chiral bis(phosphine) ligands.[15] Due to the sensitivity of intermediate **11** to protonolysis during silica gel chromatography, reaction analysis was carried out on protonolysis product **5** after treatment with AcOH. These optimization studies[15] identified the conditions listed in Table 1 as optimal affording **5a** in excellent yield and diastereo- and enantioselectivity. Overall, this process enables access to products identical to those produced by Krische's[7a] method (Figure 1C) without the use of an expensive Ir catalyst and is significant because aldehydes are problematic electrophiles in Cu-catalyzed reductive coupling reactions employing hydride-reducing agents due to the preference for aldehyde reduction over coupling.[16,17] The generality of this process was next examined (Table 1), which afforded improved results for less electron-deficient aromatic aldehydes (**5a−g**), and the reaction was accommodating to heteroaromatic aldehydes (**5h** and **5i**). The yield was somewhat decreased with sterically hindered aromatic (**5e**), electron-poor (**5c**), and aliphatic (**5k−p**) aldehydes. Notably, excellent diastereo- and enantioselectivities could be obtained when employing aliphatic aldehydes bearing small R^1 groups (**5k** and **5l**), and reduced diastereocontrol was observed only when R^1 was *i*-Pr (**5m**). Overall, all of the reaction products were obtained with enantioselectivites of >90% ee except in the case of cinnamaldehyde (**5j**); however, the chemoselectivity for reductive coupling over potential conjugate borylation[12,18] of **9j** is notable. Finally, selective formation of the *anti*-diastereomer in the reaction was confirmed by comparison of **5j**, **5l**, and **5o** to the literature.[7a] This is in contrast to reductive borylative allylation reactions utilizing carbon-substituted allenes that are *syn*-selective.[11a]

While the described borylative aminoallylation followed by protonolysis (Table 1) allows access to valuable products of a formal hydrogenative reductive coupling, arguably the power of the current transformation lies in its ability to functionalize the C−B bond of **11** to a wide variety of other motifs using well-established organoborane chemistry. Toward that end, subsequent oxidation of the C−B bond of **11** was next demonstrated to allow for incorporation of additional heteroatoms into the final products [**12** (Table 2)]. Overall, the methyl ketone formal aldol products could be obtained in equivalent yields and stereoselectivities compared to those obtained when employing a protonolysis workup.

Due to the synthetic power of the Suzuki−Miyaura cross-coupling reaction for the preparation of C−C bonds,[19] we also examined the use of reaction products **11** in subsequent Pd-catalyzed cross-coupling reactions to generate further functionalized 1,1-disubstituted olefins [**13** (Table 3)]. The development of the optimized reaction conditions shown proved to be particularly trying.[15] The optimal ligand, base, and solvent were identified using isolated **11a** and 4-iodotoluene.[15] Again, because isolation of vinyl boronate **11** is problematic due to protonolysis during silica gel chromatography, a one-pot telescoped process was next examined. Unfortunately, this optimized system failed during the initial attempts. Control experiments implied that leftover pinacol in the crude mixture acted as a catalyst poison, inhibiting the cross-coupling reaction. To circumvent this problem, the aminoallylation workup was modified to include a $NaIO_4$ treatment to convert the remaining pinacol into acetone.[15] Gratifyingly, this approach allowed for successful telescoping of the crude aminoallylation reaction into the cross-coupling. Good overall yields could be obtained in the tandem process, producing highly functionalized 1,1-disubstituted alkenes with excellent

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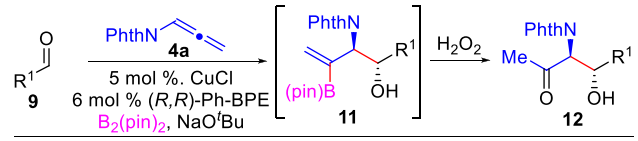
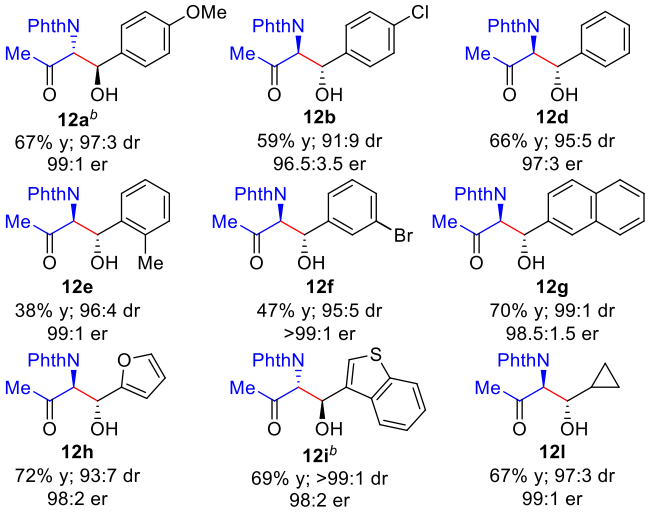
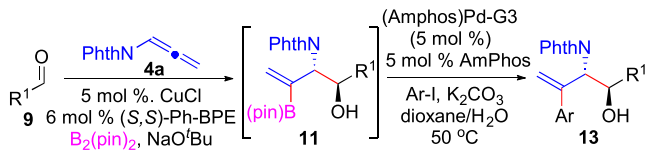
Table 2. Enantioselective Borylative Aminoallylation/Oxidation[a]

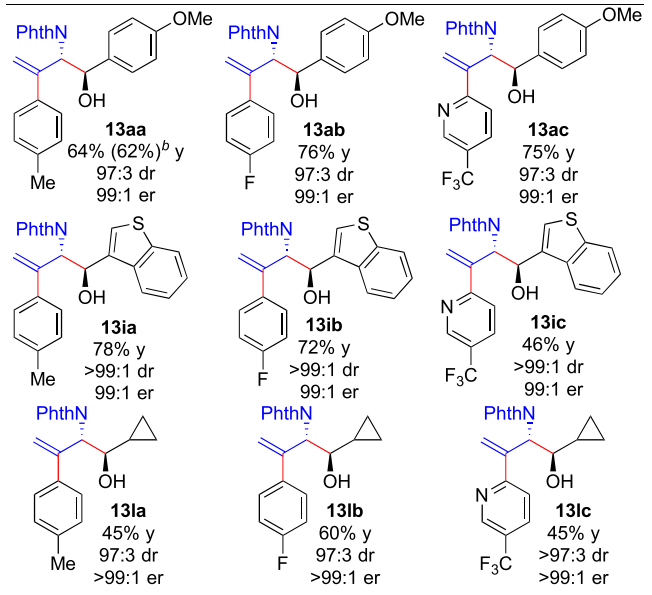




[a]Performed using 0.200 mmol of aldehyde (1 equiv) (see the Supporting Information for details). [b](*S,S*)-Ph-BPE was used.

Table 3. Enantioselective Borylative Aminoallylation/Cross-Coupling[a]



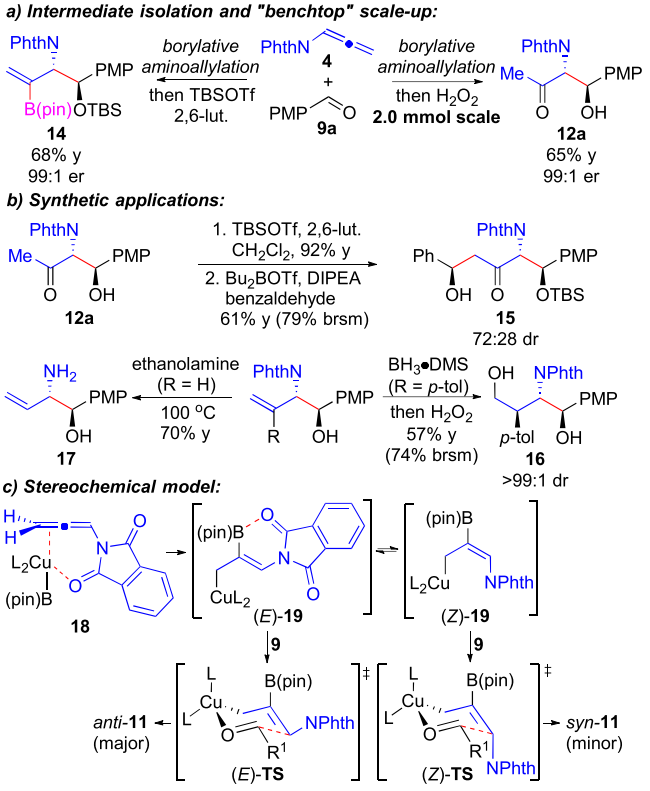


[a]Performed using 0.200 mmol of aldehyde (1 equiv) (see the Supporting Information for details). AmPhos = [4-(*N,N*-dimethylamino)phenyl]di-*tert*-butyl phosphine. [b]The cross-coupling reaction was performed using 4-bromotoluene at 70 °C for 3 h.

levels of stereocontrol that would be difficult to prepare by other means. An aryl bromide could also be successfully coupled via the developed protocol (**13aa**).

The observed sensitivity of **11** to protodeboronation under a variety of isolation conditions was hypothesized to arise from anchimeric assistance of the neighboring OH group by activation of the C−B bond through O-lone pair electron donation to the vacant B p orbital. To test this, alcohol protection was performed *in situ* by quenching the borylative aminoallylation reaction at −78 °C with TBSOTf (Scheme 1a). This afforded **14** that could be isolated by silica gel

Scheme 1. Synthetic Applications and Stereocontrol



chromatography in a reaction yield (68%) similar to that of **5a** obtained from direct protonolysis (72%). This process enables the opportunity to isolate the intermediate boronate compound should that be desired for the development of other downstream C−B functionalizations. The borylative aminoallylation was also scaled to 2.0 mmol with a "benchtop" setup using standard Schlenk techniques to afford **12a** with comparable results.

The powerful synthetic potential of our developed methodology stems from its ability to access chiral aminoalcohol equivalents bearing additional functionalities for further synthetic manipulations to arrive at heteroatom-rich complex chiral architectures quickly from readily available starting materials. To highlight this potential, the subsequent transformations highlighted in Scheme 1b were performed. A boron-mediated aldol reaction of TBS-protected **12a** with benzaldehyde afforded **15** with moderate substrate stereocontrol (72:28 dr) at the newly formed hydroxy stereocenter. Notably, this allows quick access to a stereodefined 1,3,5-O-2-N-substituted carbon framework in only three synthetic steps from **4**. Alternatively, hydroboration afforded a single

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diastereomer of 1,4-O-2-N-substituted carbon synthon **16** bearing three contiguous stereocenters, and cleavage of the *N*-phthaloyl group to **17** was possible.

One intriguing feature of the described borylative aminoallylation utilizing allenimide **4a** was the selective formation of the *anti*-diastereomer.[20] Previous reports[11a] of Cu-catalyzed borylative allylation reactions using carbon-substituted allenes with carbonyl electrophiles are *syn*-selective even when using the same ligand (e.g., BINAP).[15] We propose this phenomenon is due to the ability of the *N*-phthaloyl group to coordinate to the catalyst and/or boron to direct the reaction through (*E*)-**19** (Scheme 1c).[7g−i,21] It is well established that Cu-catalyzed reductive allylation reactions proceed through Zimmerman−Traxler chairlike transition states,[7e−j,10,11] and often, product selectivity is dictated by Curtin−Hammett kinetics of rapidly equilibrating Cu(σ-allyl) complexes.[7j,10c] For carbon-substituted allenes, such an analysis predicts that the major *syn*-diastereomer of the product is generated through (*Z*)-**19** via (*Z*)-**TS**.[11] Additionally, borylcupration of allenes is proposed to occur at the more accessible terminal olefin of the allene away from the more sterically hindered substituent of the internal olefin of the allene furnishing a C-substituted analogue of (*Z*)-**19** selectively.[11,22] In this case, even if $\sigma-\pi-\sigma$ equilibration between (*Z*)-**19** and (*E*)-**19** can occur, (*Z*)-**TS** is arguably more favorable due to the steric penalty of a *cis*-relationship between the substituent of the allene and the bulky B(pin) group present in (*E*)-**19** leading to *syn*-selectivity with C-substituted terminal allenes. In contrast, borylcupration of **4a** may lead directly to (*E*)-**19** through an *N*-phthaloyl-directed intermediate **18**. At this point, either $\sigma-\pi-\sigma$ equilibration is not possible because (*Z*)-**TS** is likely more favorable based on steric grounds or interaction of the *N*-phthaloyl group with the vacant p orbital of the B(pin) group of (*E*)-**19** facilitates reaction through (*E*)-**TS** to favor *anti*-**11** as the major product.

In conclusion, we have developed a highly enantio- and diastereoselective Cu-catalyzed borylative aminoallylation of aldehydes for the rapid synthesis of chiral heteroatom-rich organic compounds using readily available starting materials. The Cu catalyst system disclosed is inexpensive and widely commercially available, and the reaction proceeds under ambient conditions to provide good yields of the products with high levels of stereocontrol. Notably, access to a wide array of diverse functionalities was achieved from the same reaction intermediate through simple changes in the post-reaction workup, and the synthetic potential of the method was demonstrated through subsequent transformations of the functional groups installed through the borylative aminoallylation process.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01459.

Experimental procedures, characterization data for all compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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