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Diastereo-, Enantio-, and *anti*-Selective Formation of Secondary Alcohol and Quaternary Carbon Stereocenters by Cu-Catalyzed Additions of B-Substituted Allyl Nucleophiles to Carbonyls

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03495 Read Online

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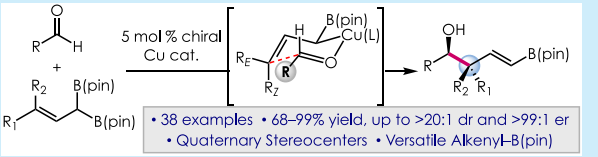
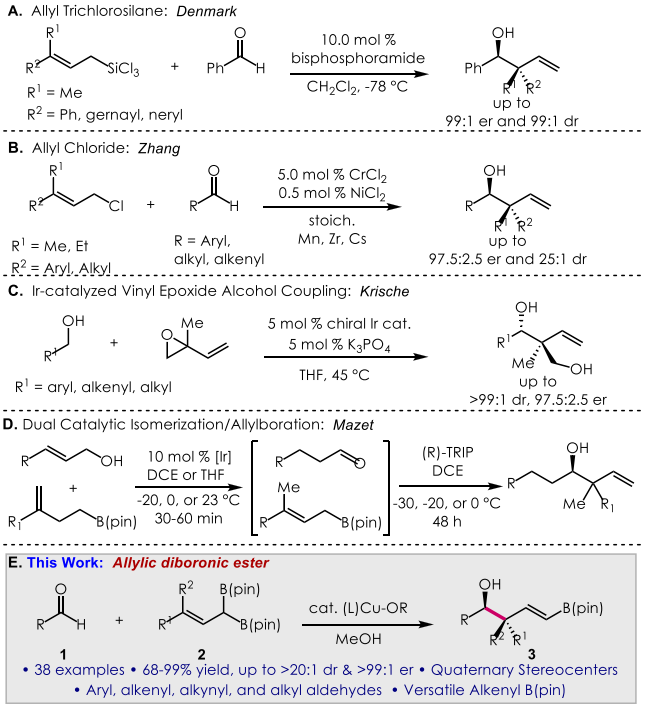
ABSTRACT: A general method for the synthesis of secondary homoallylic alcohols containing α-quaternary carbon stereogenic centers in high diastereo- and enantioselectivity (up to >20:1 dr and >99:1 er) is disclosed. Transformations employ readily accessible aldehydes, allylic diboronates, and a chiral copper catalyst and proceed by γ-addition of in situ generated enantioenriched boron-stabilized allylic copper nucleophiles. The catalytic protocol is general for a wide variety of aldehydes as well as a variety of 1,1-allylic diboronic esters. Hammett studies disclose that diastereoselectivity of the reaction is correlated to the electronic nature of the aldehyde, with dr increasing as aldehydes become more electron poor.



Numerous biologically important compounds contain quaternary carbon stereogenic centers, and catalytic enantio- and diastereoselective reactions that deliver them are highly desirable.[1] Homoallylic alcohols comprising a vicinal carbon stereocenter can be prepared by catalytic additions of substituted allyl fragments to aldehydes;[2−4] however, related transformations that deliver quaternary carbon stereogenic centers enantio- and diastereoselectively are difficult. While there are many examples for the construction of quaternary stereocenters via aldehyde allylation,[5] few enantioselective methods exist. Prior disclosures include the enantiospecific intermolecular addition reactions of allylzincs derived from enantioenriched alkynylsulfoxides,[6] as well as transformations with enantioenriched allylsilanes[7] and allylboronic esters.[8] In contrast, catalytic enantioselective versions are scarce.[9] One study shows the catalytic enantioselective reactions of γ,γ-disubstituted allyl trichlorosilanes with aldehydes are efficiently promoted by chiral bisphosphoramide (Scheme 1A).[10] Another disclosure includes a Cr-catalyzed allylation utilizing γ,γ-disubstituted allyl chlorides (Scheme 1B); however, the use of four transition metals, two in stoichiometric amounts, detracts from the method.[11] Elegant studies by Krische describe Ir-catalyzed reductive couplings of vinyl epoxides, dienes, and allenes with in situ generated aldehydes (Scheme 1C).[12] A more recent approach involves a dual isomerization/enantioselective allylation sequence with allylic alcohols and homoallylic boronic esters, catalyzed by an Ir/chiral phosphoric acid protocol.[13] In the case of quaternary stereogenic centers, however, a wide range of dr and er were observed.

While significant advances in quaternary stereocenter synthesis by aldehyde allylation have been made, addition to alkyl aldehydes remains a significant challenge, and variation at the quaternary carbon center is largely absent. Furthermore,

Scheme 1. Catalytic Enantioselective Additions to Aldehydes with γ,γ-Disubstituted Allyl Reagents



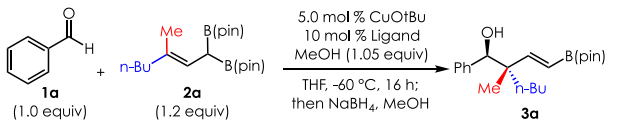
Received: October 20, 2020

very few catalytic, enantioselective methods exist that afford products in high diastereo- and enantioselectivities. Our objective was the development of a general protocol for setting quaternary centers in homoallylic alcohols by employing γ,γ-disubstituted allylic 1,1-diboronate esters. Allylic 1,1-diboronic esters have been employed in the crotylation and prenylation of aldehydes;[14,15] however, extension of these methods for enantio- and diastereoselective allyl addition beyond prenylation to set quaternary stereocenters has not been achieved.

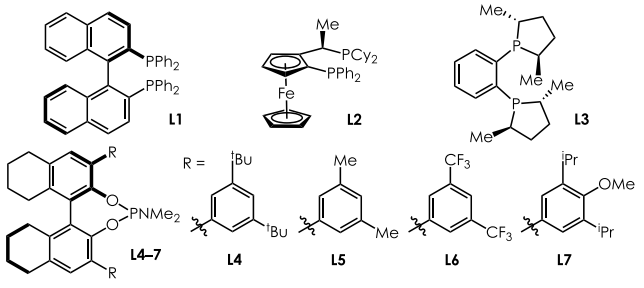
Encouraged by our previous studies regarding the enantio- and diastereoselective reactions of γ,γ-disubstituted allylic 1,1-bis(boronates) with aldimines[16] and ketones,[17] we envisioned the stereoselective reaction in Scheme 1E. The enantio- and diastereoselective preparation of complex secondary homoallyl alcohols with vicinal quaternary carbon stereocenters bearing a functional *E*-alkenylboron can be achieved by catalytic reactions between an array of aldehydes (**1**) and readily accessible stereodefined **2**.

We began our studies with the reaction of benzaldehyde (**1a**) and allyl diboronic ester **2a** (Table 1). An initial control reaction between **1a** and **2a** in THF at −60 °C, followed by an aqueous (entry 1) and $NaBH_4$ (entry 2) workup, revealed significant background addition of unreacted **2a** occurs upon workup (38% conv, >20:1 dr vs <2% conv). This outcome highlighted the need for a reductive quench during catalyst optimization. In the presence of 5 mol % CuOtBu, 10 mol % ligand, and 1.05 equiv MeOH in THF at −60 °C, several classes of chiral ligands were examined. Bidentate phosphines **L1**−**3** proved ineffective, <2−8% conversion to **3a** (entries 3−5). Switching to phosphoramidite **L4** delivered **3a** in 89% yield (>98:2 γ-allylation) in 2.7:1 dr and >99:1 er (entry 6). Notably, < 2% conversion to **3a** is observed in the absence of methanol (entry 7). Investigation of phosphoramidite 3,3′-aryl substitution (entries 8−10) identified 3,5-*i*-Pr-4-OMe substitution (**L7**) as optimal (>99:1 er, 4:1 dr) (entry 10). In an effort to further improve the dr, the reaction with **L7** was run at −78 °C; however, this resulted in no improvement in selectivity. To test if a reductive workup was necessary given the high conversion with **L7** in 16 h, the equivalent reaction with aqueous workup was found to afford a near identical result (98% NMR yield, 4:1 dr, 98.5:1.5 er). Consequently, provided catalytic reactions proceed to >98% consumption of aldehyde, a reductive workup is not required.[18]

Table 1. Reaction Optimization[a]



entry	ligand	alcohol	NMR yield (%)[b]	dr[b]	er[c]
1[d]	-	-	38	>20:1	-
2	-	-	<2	-	-
3	**L1**	MeOH	<2	-	-
4	**L2**	MeOH	<2	-	-
5	**L3**	MeOH	8	nd	nd
6	**L4**	MeOH	89	2.7:1	>99:1
7	**L4**		<2	-	-
8	**L5**	MeOH	70	1.5:1	>99:1
9	**L6**	MeOH	>98	1:1	99:1
10	**L7**	MeOH	98	4:1	>99:1
11[e]	**L7**	MeOH	94	4:1	>99:1
12[f]	**L7**	MeOH	98	4:1	98.5:1.5



[a]Reactions performed under a N_2 atmosphere. [b]NMR yield and diastereomeric ratios (dr) determined by analysis of ^1H NMR spectra of crude reactions with hexamethyldisiloxane as the internal standard. [c]Enantiomeric ratios (er) determined by SFC analysis. [d]No CuOtBu, ligand, or $NaBH_4$ quench. [e]Reaction at −78 °C. [f]No $NaBH_4$ quench. See the SI for details.

The robustness of the reaction conditions was surveyed, and it was found to be broad. As shown in Scheme 2A, a wide variety of aromatic substrates are tolerated, including those containing electron-donating groups (**3b**), halogens (**3c**−**d**), and electron-withdrawing ester (**3e**), nitrile (**3f**), nitro groups (**3g**−**h**) and trifluoromethyl (**3i**), to deliver products in excellent yields and er. Notably, meta and ortho substituted arenes undergo efficient and selective reaction (**3h**−**k**). Furthermore, a range of heteroarene products including pyridine (**3k**), furan (**3l**), and thiophene (**3m**) moieties are accessible in excellent yield and er albeit in 3:1−4:1 dr. In reactions with aldehydes containing extended π-systems, such as indole (**3n**), benzofuran (**3o**), and benzothiophene (**3p**), products are generated in higher diastereoselectivity in excellent yields and enantioselectivities. Moreover, synthesis of indole **3n** on a 1.0 mmol scale demonstrated robustness of the protocol.

The catalytic protocol also extends to alkenyl, alkynyl, and alkyl aldehydes (Scheme 2B). Unsaturated cinnamyl, tiglic, and cyclohexenyl aldehyde substrates are converted to homoallylic alcohol products **5a**−**c** in excellent yield and ≥99:1 er, and 4:1−6:1 dr, respectively. In addition, reaction with enantioenriched (−)-myrtenal delivers **5d** in 82% yield and 9:1 dr. Reactions of alkynyl aldehydes also react efficiently; however, a decrease in diastereoselectivity results. For example, propargylic alcohol **5e** is formed in 84% yield, 2:1 dr, and 98.5:1.5 er (major) and >99:1 er (minor). High yields and selectivity are similarly observed with more challenging, less electrophilic aliphatic aldehydes. For example, a variety of alkyl-substituted aldehydes bearing *t*-Bu (**5f**), cyclic (**5g**−**i**), and β-branching (**5j**) were found to react smoothly to deliver desired products in 68−99% yield, ≥ 99:1 er, and >20:1−4:1 dr. Additionally, no adverse effects arising from a pendant alkene moiety in reactions with 4-pentenal and (−)-citronellal to afford **5k** and **5l** were observed.

Finally, the scope of the quaternary carbon stereocenter was investigated by varying the substituents introduced on the allyldiboron reagent (Scheme 3). Notably, diastereomers **6b** and **6c** could be synthesized stereospecifically by subjecting either *E*- or *Z*-allyldiboronates to the reaction conditions, with both obtained in high dr and er. The increased sterics associated with α-branched cyclohexyl and cyclopropyl reagents are tolerated to produce **6d** and **6e** in excellent yield and selectivity. Moreover, after a single recrystallization, **6e** could be enriched to 20:1 dr, and the X-ray structure was

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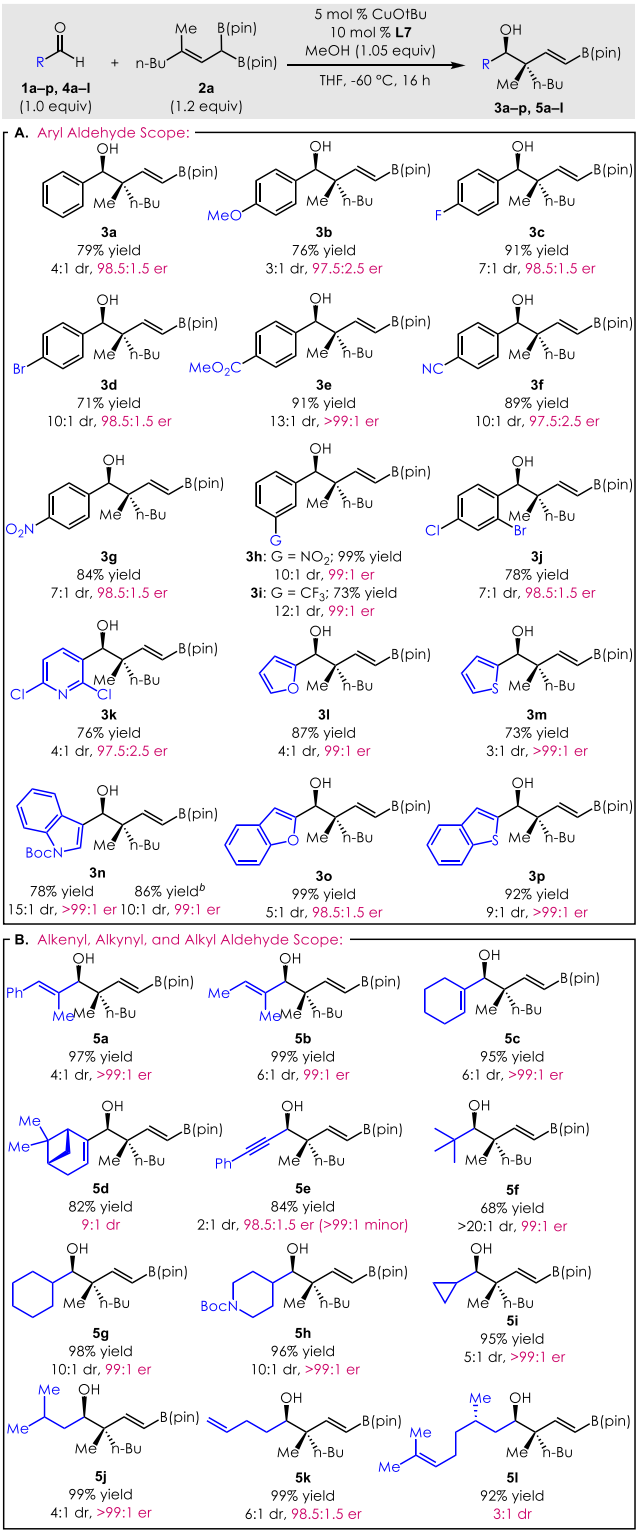
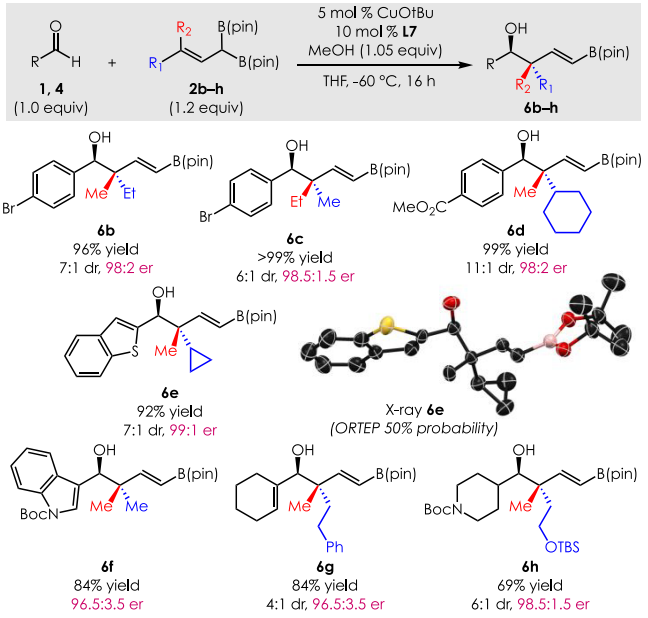
Scheme 2. Aldehyde Scope[a]



[a]Reactions performed under N_2 atmosphere. Yields of purified products after SiO_2 Chromatography. Experiments were run in duplicate. Diastereomeric ratios (dr) determined by analysis of ^1H NMR spectra of purified products. Enantiomeric ratios (er) determined by HPLC or SFC analysis. See the SI for details. [b]1.0 mmol scale.

obtained to confirm the relative and absolute stereochemistry. Lastly, transformations of allyl diboronate reagents containing

Scheme 3. 1,1-Allylic Diboron Scope[a]



[a]See Scheme 2. See the SI for details.

homobenzyl and silyl ether moieties generate competent nucleophiles; for example, alkenyl and aliphatic aldehyde derived products **6g–h**, delivered in 4:1–6:1 dr and ≥96.5:3.5 er, are illustrative.

To assess the importance of the allyl diboronate moiety, a comparison to monoboryl reagent **7** was evaluated (Scheme 4A). Under standard conditions with a $NaBH_4$ quench, <5% conversion to homoallylic alcohol product **8** is observed; the control reaction in the absence of Cu/**L7** affords **8** in 66% NMR yield and 9:1 dr. Support for an enantio-determining transmetalation step in the reaction mechanism was provided by Swern oxidation of alcohol **3a** to ketone **9** in 53% yield, and 97.5:2.5 er (Scheme 4B). The high er of the product strongly suggests an enantioselective transmetalation to form a stereodefined allylic nucleophile, and diastereoselectivity is the result of facial selectivity with the aldehyde. Further evidence for this is found in the high er of the minor diastereomer of **5e** (see SI for details). To gain insight into interesting diastereoselectivity trends observed with aryl aldehydes, a Hammett plot was constructed (Scheme 4C). Satisfactory correlations between dr and the electronic effects of the substituents were observed. Notably, it was also found that substituent constant σ_p- values provided the best correlation for the electron-poor aldehydes (p-CO_2Me, p-CN, p-NO_2).[19] The plot in Scheme 4C shows that electron-withdrawing substituents result in improved diastereoselectivity in the reaction (ρ = 0.96, R^2 = 0.95), indicating the electrophilicity of the aldehyde (vs C = O Lewis basicity) impacts the diastereoselectivity of the reaction.[20] These data are consistent with C–C bond formation being diastereo-determining.[21] At larger σ values, a change in slope of the Hammett plot of opposite sign is observed (ρ = −0.26, R^2 = 0.95), indicating a lower sensitivity of the allyl addition reaction to electronic changes. The break in the plot is suggestive of a change in the diastereo-determining step likely toward aldehyde coordination influencing stereoselectivity.

The effect of catalyst versus substrate control with chiral aldehydes was examined with α-stereogenic amino aldehydes

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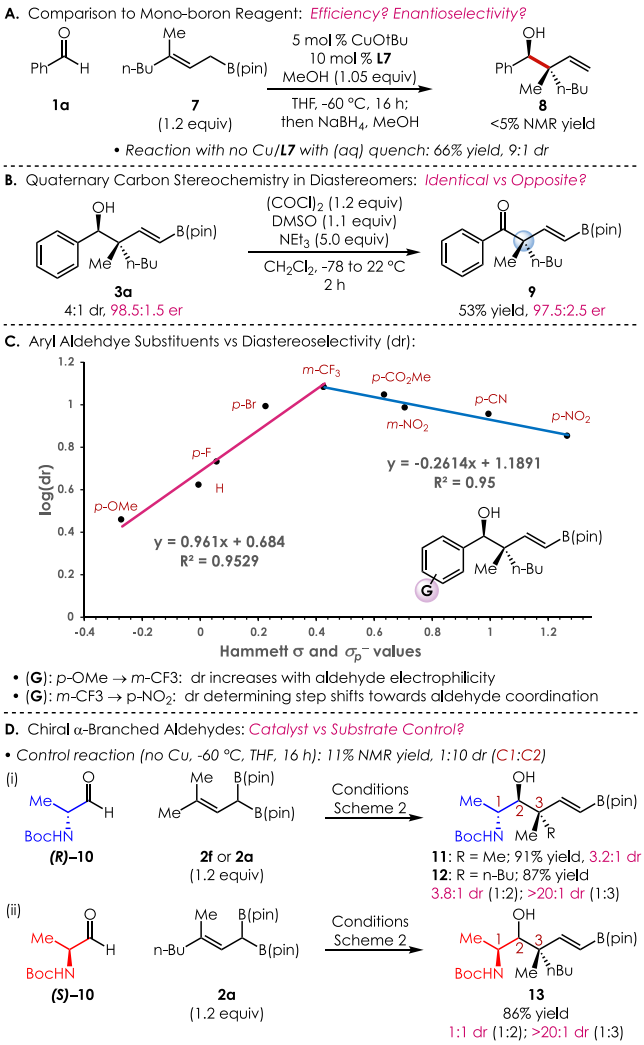
Scheme 4. Mechanism Experiments[a]

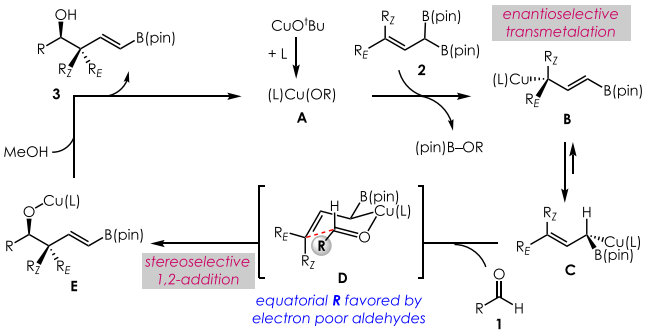


[a]See the SI for details.

(Scheme 4D). Treatment of D-alanine-derived (*R*)-**10** with optimal reaction conditions with Me,Me-diboron **2f** results in high conversion to **11** as a 3.2:1 (C1:C2) mixture of diastereomers. In addition, when (*R*)-**10** is subjected to the same conditions with *n*-Bu,Me diboron **2a**, amino alcohol **12** is obtained in very similar diastereoselectivity (3.8:1 dr, (C_1:C_2)), indicating the substituents on the allylcopper do not play a significant role in affecting the facial selectivity of the aldehyde. In contrast, reaction with aldehyde (*S*)-**10** clearly indicates a matched−mismatched situation, as homoallylic alcohol **13** is obtained in diminished stereoselectivity (86% yield, 1:1 dr, C1:C2).[22]

Based on the above findings a catalytic cycle and stereochemical model is proposed in Scheme 5 to rationalize our observations. The reaction likely proceeds via S_E2' transmetalation of (L)Cu−OMe (**A**) with diboronate **2**.[23,24] Subsequently, a rapid 1,3-suprafacial shift to the less sterically encumbered boron-stabilized allyl copper species **C** must occur faster than C−C bond rotation in **B** to prevent isomerization of alkene geometry.[25] Coordination of aldehyde **1** results in cyclization through **D**, affording Cu-bound product **E**. As apparent in the crystal structure of **6e**, the large substituent occupies the pseudoequatorial position in **D**, resulting in the

Scheme 5. Proposed Catalytic Cycle and Stereochemical Model

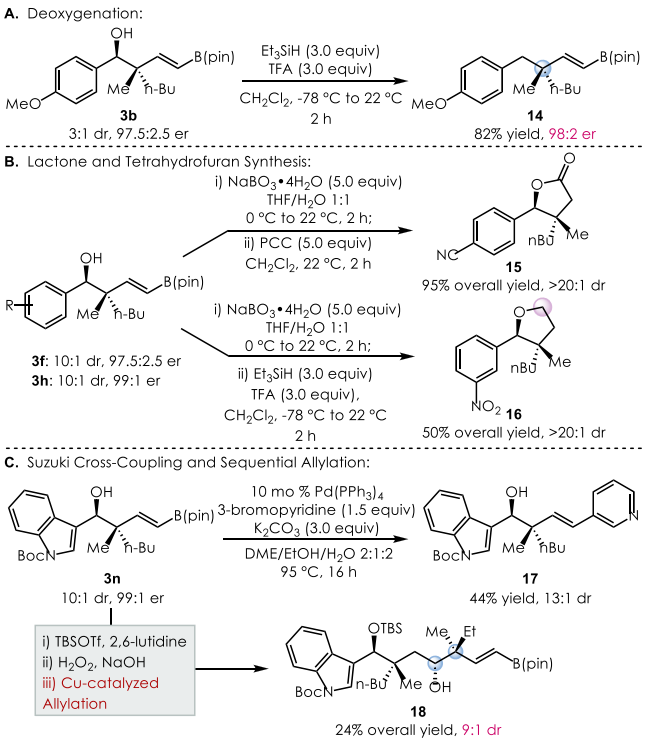


observed diastereoselectivity. Finally, protonation of intermediate **E** with MeOH releases product **3** and regenerates catalyst **A**. The observations in Table 1, which show MeOH is required for product formation and to obtain a high er, can be rationalized by slow reaction between **E** and **2**, as well as the requirement of (**L7**)-Cu−OMe species to facilitate highly enantioselective transmetalation. The enantioselective formation of intermediate **C** is supported by the enantiomeric ratio of the minor diastereomers, which in most cases is high (see **5e**, and SI for details).[26]

The utility of the method is showcased by the various chemical transformations depicted in Scheme 6. First, we investigated the reduction of enantio-enriched benzylic alcohol in **3b** (3:1 dr) by treatment with CF_3CO_2H and $HSiEt_3$ in CH_2Cl_2 to afford deoxygenated product **14** in 82% yield (Scheme 6A).[27]

Oxidation of the alkenyl boronic esters **3f** and **3h** results in hemiacetal formation (Scheme 6B), which followed by either

Scheme 6. Synthetic Utility[a]



[a]See the SI for details.

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PCC oxidation or silane reduction delivers substituted lactone **15** and tetrahydrofuran **16** in 95% an 50% overall yield, respectively. The versatility of the alkenyl boronic esters moiety was also demonstrated to be effective in Suzuki cross-couplings; for example, Pd-catalyzed reaction of **3n** with 3-bromopyridine affords N-heterocycle **17** in 44% yield and 13:1 dr. Lastly, the ability of the method to efficiently construct multiple acyclic quaternary carbon stereocenters was demonstrated by a three-step telescoped sequence (Scheme 6C). Beginning with indole **3n**, TBS protection of the alcohol followed by alkenyl boron oxidation results in the crude aldehyde, which was then subjected to Cu-catalyzed allyl addition with *E*-**2b** to afford alcohol **18** in 24% overall yield, and 9:1 dr with respect to the new stereogenic centers.

In conclusion, we have developed a versatile, robust Cu-catalyzed protocol for the enantio-, diastereo-, and *anti*-selective synthesis of vicinal homoallyl alcohol and quaternary carbon stereocenters. The method offers both broad aldehyde and quaternary stereocenter scopes and utilizes a simple (phosphoramidite)-Cu catalyst. Mechanism studies provide support for the intermediacy of an enantioenriched allyl copper species, as well as reveal a pronounced electronic effect of substituents on diastereoselectivity. Studies are ongoing to understand the factors that control stereoselectivity and to further develop stereoselective reactions with allyl diborons.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03495.

Experimental procedures and spectral and analytical data for all products (PDF)

Accession Codes

CCDC 1970642 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the United States National Institutes of Health, Institute of General Medical Sciences (R01GM116987). Core facilities in the Department of Chemistry at the University of North Carolina are supported by the National Science Foundation under grants: CHE1726291 (Mass spectroscopy); CHE0922858 and CHE1828183 (NMR spectroscopy). We thank Tia Cervarich of UNC for X-ray structure elucidation of **6e**.

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