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Catalytic Enantioselective Synthesis of Allylic Boronates with a Trisubstituted Alkenyl Fluoride and Conversion to Compounds with a F-Substituted Stereogenic Quaternary Center

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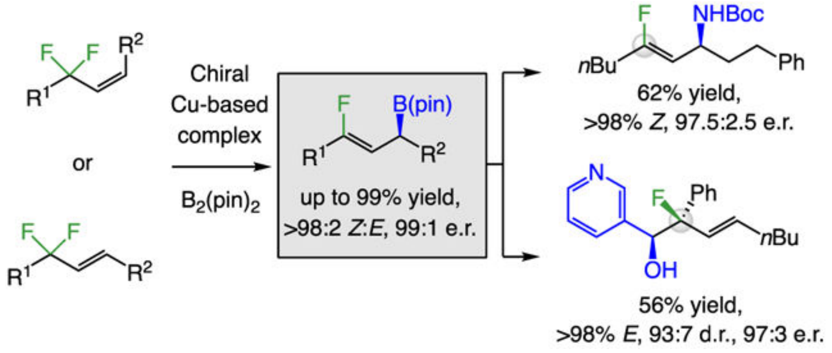
Abstract

The first catalytic method for diastereo- and enantioselective synthesis of allylic boronates bearing a *Z*-trisubstituted alkenyl fluoride is disclosed. Boryl substitution is performed with a *Z*- or an *E*-allyldifluoride and is catalyzed by bisphosphine–Cu complexes, affording products in up to 99% yield, >98:2 *Z*:*E* selectivity, and 99:1 enantiomeric ratio. A variety of subsequent modifications are feasible; notable examples are diastereoselective additions to aldehydes/aldimines to access homoallylic alcohols/amines containing a fluoro-substituted stereogenic quaternary center.

Graphical Abstract



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Keywords

Boron; Copper; Enantioselective catalysis; Fluorine; Synthetic methods

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Stereoselective strategies for synthesis of organofluorine compounds are in high demand, as such entities are capable of exhibiting entirely distinct modes of, and/or improved, activity.[1] Catalytic enantioselective methods that may be used to prepare fluorine-containing organic molecules are therefore key, and compounds that contain a single fluorine atom are particularly valuable.[2] For instance, trisubstituted alkenyl fluorides are peptide bond mimics (Scheme 1a),[3] and those bearing a fluoro-substituted stereogenic quaternary carbon center are isosteric with a more common tertiary stereogenic carbon center (Scheme 1a).[4] Still, effective methods that generate such organofluorine compounds with high diastereo- and enantioselectivity remain uncommon.[5,6]

Catalytic approaches to cleaving one of several C–F bonds in a fluoro-organic moiety has recently received significant attention.[1c,7-8] Directly relevant to the present work are two reports on catalytic γ-boryl substitution of trifluoromethyl-substituted alkenes to generate enantiomerically enriched *gem*-difluoroallylic boronates.[8c-d] We reasoned that a practical catalytic method for enantioselective synthesis of allyl–B(pin) products that contain a trisubstituted alkenyl fluoride[9] unit would represent a notable advance. The resulting products might then be used to prepare an assortment of otherwise difficult-to-access unsaturated fluoro-organic entities efficiently and in high stereochemical purity (Scheme 1b). Herein, we disclose the first catalytic strategy for enantioselective synthesis of (*Z*)-γ-monofluoroallylic boronates by boryl substitution reactions[10] involving a *Z*- or an *E*-allyldifluoride substrate; reactions are catalyzed by easily accessible bisphosphine–Cu complexes (Scheme 1b), and the products can be converted to numerous desirable derivatives, including those with a fluoro-substituted stereogenic quaternary carbon center.

We began by searching for an optimal ligand for the transformation of *Z*-alkene **1a**, which was accessed in three steps and 51% overall yield by using previously reported protocols[11] (Scheme 2a). We began by evaluating (*R*,*S*)-josiphos as the ligand, largely because it had proved to be optimal in our previous studies on γ-boryl substitution reactions with trifluoromethyl-substituted alkenes. While appreciable efficiency and stereoselectivity was observed [93:7 *Z*:*E*, 83.5:16.5 enantiomeric ratio (e.r.)], further screening revealed that benzP* is a superior option. Thus at 5.0 mol % catalyst loading, **2a** was generated in 93% yield, 95:5 *Z*:*E* selectivity, and 97:3 e.r. Although the reaction with the closely related (*R*,*R*)-quinoxP* was similarly effective (93% yield, 95:5 *Z*:*E*, 96:4 e.r.), catalysts derived from other ligands were much less so (e.g., josiphos, binap, or segphos).[12] With *E*-alkene **4a** as the substrate (Scheme 2b), the reaction with phenyl-bpe and LiO*t*Bu was optimal, affording **2b** with the opposite sense of enantioselectivity in 51% yield[13], >98:2 *Z*:*E*, and 95:5 e.r. The reaction with *Z*-alkene **1a** under these latter conditions, afforded preferentially the same (*S*)-**2a** enantiomer that was generated with benzP*, albeit in lower yield (70% yield, 94:6 *Z*:*E*, 96:4 e.r.), indicating that a stereoisomerically pure *Z*- or *E*-alkene starting material is needed for high enantioselectivity.

Importantly, the above routes are complementary. Under conditions A, the reaction time is two hours (vs 14 h, conditions B), and the yield is higher. On the other hand, the *E*-alkenes for conditions B can be prepared in two steps, and because cross-metathesis with **Ru-1** is utilized, allylic alcohol products can be directly and more easily prepared.[14]

The method has considerable scope (Scheme 3). Benzyl ether **2c**, silyl ether **2d**, and acetate **2e** were isolated in 90–99% yield, 90:10–95:5 *Z*:*E*, and 96:4 e.r. (Scheme 3a). Phthalimide **2f** was obtained in somewhat lower yield (56%) owing to partial decomposition during purification.[13] Other products included those bearing two *n*-alkyl moieties (**2g**). Reaction of a substrate with a more hindered cyclohexyl alkenyl substituent was efficient and highly stereoselective (**2h**); crystallographic analysis of **2h** allowed us to confirm the identity of the major enantiomer formed. Me-substituted **2i** was synthesized with similar efficiency and er but the *Z*:*E* ratio was lower (83:17). A plausible rationale (Figure 1) is that, with a smaller substituent (G), there is less energy gap between **I** and **II**; similar arguments apply if Cu–F elimination proceeded with syn stereochemistry. Thus, in cases where the alkene bears a relatively diminutive moiety, such as **2i**, the *Z*:*E* ratio will be lower.

Products **2j-l** were generated under conditions B in 52–63% yield[13], 98:2 *Z*:*E*, and 93.5:5–96:4 e.r.; these allylic alcohols provide the opportunity for investigation of various hydroxy-directed transformations. We synthesized **2m** under conditions A with excellent *Z*:*E* ratio, albeit in lower yield (30%) and diminished e.r. (88.5:11.5), presumably due to the sizeable silyl group. The reaction with a difluoro-substituted terminal alkene delivered **2n** in 95% yield, and 94:6 e.r. but, as expected (see Figure 1), as a mixture of olefin isomers. Finally, we prepared aryl-substituted **2o** and **2p**; the formerly disclosed boryl substitution reactions with F_3C-substituted alkene substrates are confined to aliphatic variants.[8c-d] The ability to prepare allylic difluorides efficiently by cross-metathesis is key, rendering reactions with more functionalized substrates feasible; the examples presented in Scheme 3b (**4**→**5a** or **5b**) are illustrative.

For a rationale regarding the high enantioselectivities, DFT studies were performed (M06L/def2-TZVPP//M06L/def2-SVP level) on model substrates (Me-substituted; Figure 2).[12] These investigations point to significant steric pressure in the transition states leading to the minor enantiomers (**IV** and **VI** vs **III** and **V**).

The enantiomerically enriched products may be modified stereospecifically (other than C–B oxidation). For instance, homoallylic boronate **6** and allylic amide **7** (Scheme 4a) were obtained in 98% and 62% yield, respectively,[15,16] without detectable loss in stereoisomeric purity. Such organofluorides cannot be readily accessed by an alternative method (catalytic or otherwise).

The method may be used for synthesis of homoallylic alcohols with a fluoro-substituted allylic stereogenic quaternary carbon center (Scheme 4b). Under the conditions introduced by Aggarwal,[17] **2o** was transformed to fluorohydrin[18] **8a**, likely via **A**, in 54% yield, >98:2 *E*:*Z* ratio, and 99:1 e.r. The absolute stereochemistries of **2o** and **8a** were strongly suggested by crystallography with Cu X-ray source.[12] We synthesized other fluorohydrins with similar efficiency and complete stereospecificity. Reaction of **2o** with sterically demanding 2-methylbenzaldehyde and 2-bromobenzaldehyde afforded **8b** and **8c**. Heterocyclic aldehydes (**8d-e**) and an enal (**8f**) were suitable substrates. Because compounds with F-substituted quaternary allylic carbon centers that contain only aliphatic substituents are unstable to chromatography, **8g** was obtained after catalytic hydrogenation. Perhaps even more valuable are β-fluoroamines, as a β-fluorosubstituent can lower the pK_a of a neighboring improving pharmacological properties.[19] We used the reaction of **2o** with N-trimethylsilyl benzaldimine **9** (Scheme 4c) to generate homoallylic amide **10** in 59% overall yield, >98:2 *E*:*Z* ratio, >98:2 d.r., and without any loss in e.r. (98:2).

In closing, we put forth a bisphosphine–copper-catalyzed method for γ-boryl substitution of difluoro-substituted *Z*- or *E*-alkenes. The approach offers facile access to an assortment of (*Z*)- γ-monofluoroallylic boronates in high selectivity. The applicability of the approach is illustrated by stereospecific synthesis of several key types of organo-fluorine compounds. In view of the general importance of F-containing organic molecules, and the paucity of broadly applicable catalytic strategies for their diastereo- and enantioselective synthesis, this advance represents a key step forward.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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[12]. See the supporting information for details.

[13]. The products with polar functionalities tend to show lower yield after isolation because stacking and partial decomposition occurs in silica-gel chromatography.

[14]. Moreover, whereas NaOMe is optimal for conditions A (significant diminution in efficiency with LiOMe), there was 30–40% conversion to the desired product when NaOtBu was used under conditions B. The mechanistic origin of these differences is under study.

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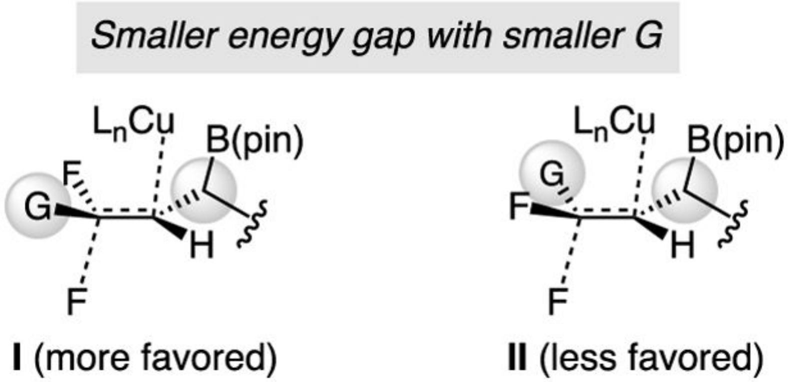
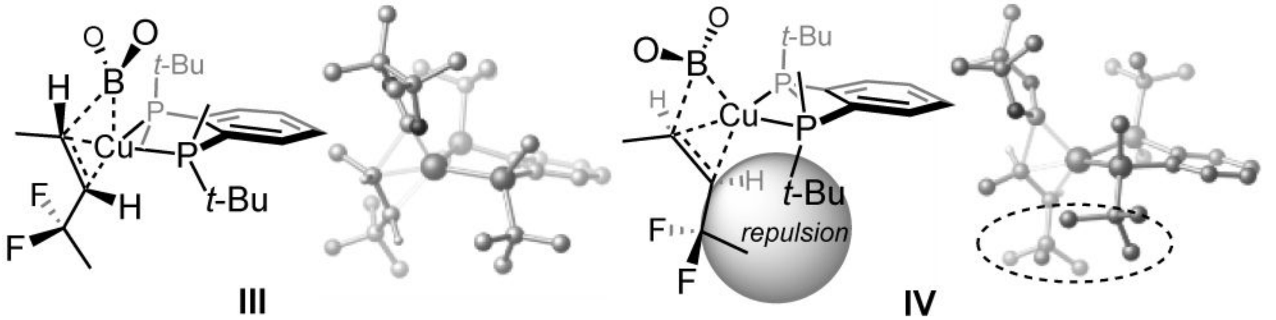
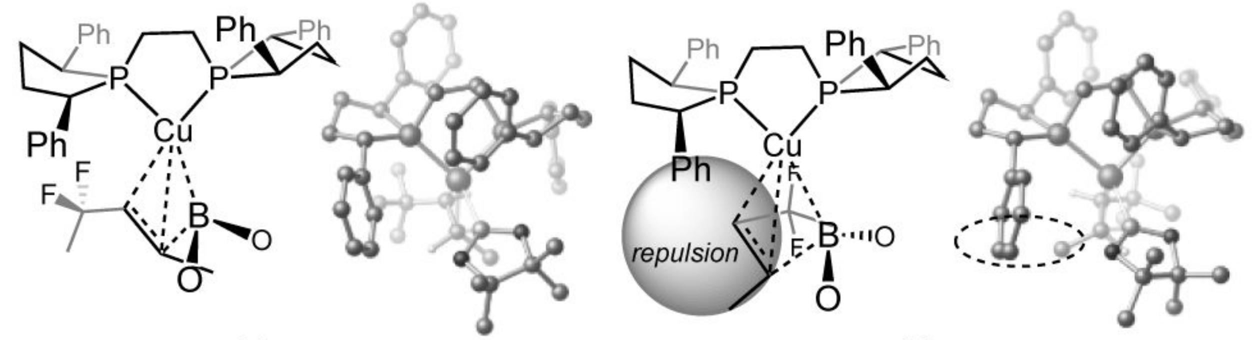


Figure 1.

Origin of variations in *Z*:*E* ratios.



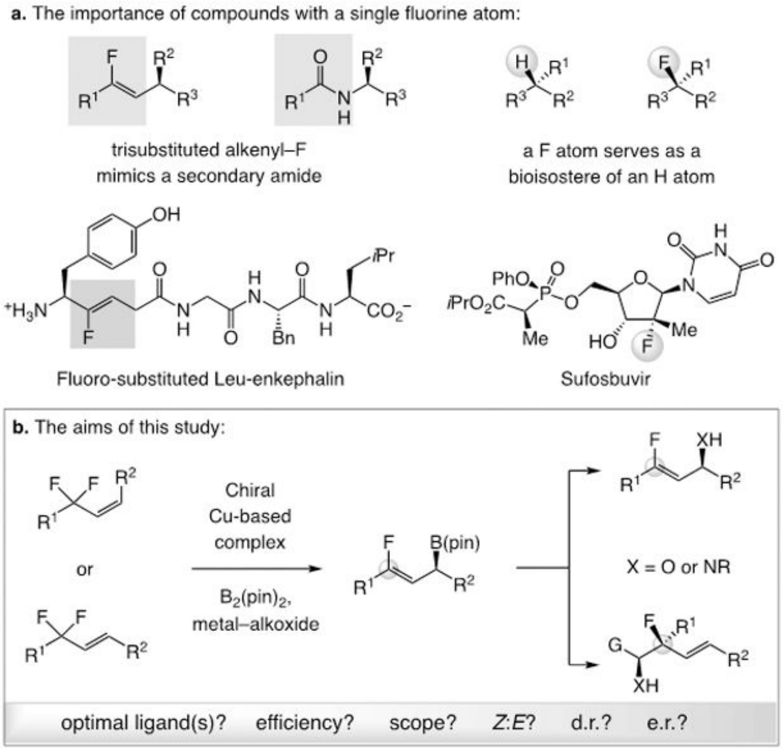
III with *Z*-alkene & benzP* (major) **IV** with *Z*-alkene & benzP* (minor)



V with *E*-alkene & Ph-bpe (major) **Vi** with *E*-alkene & Ph-bpe (minor)

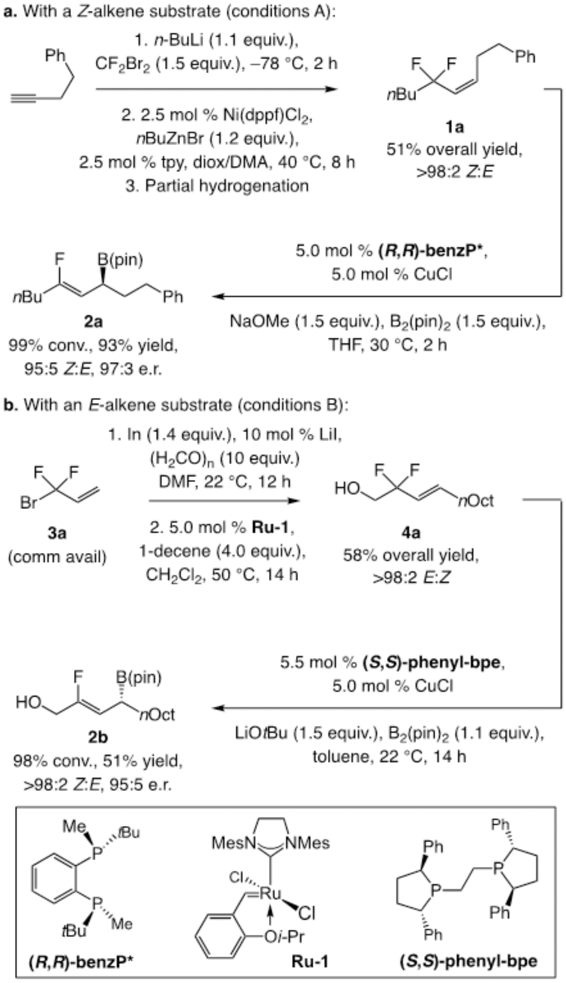
Figure 2.

Stereochemical models based on DFT studies.



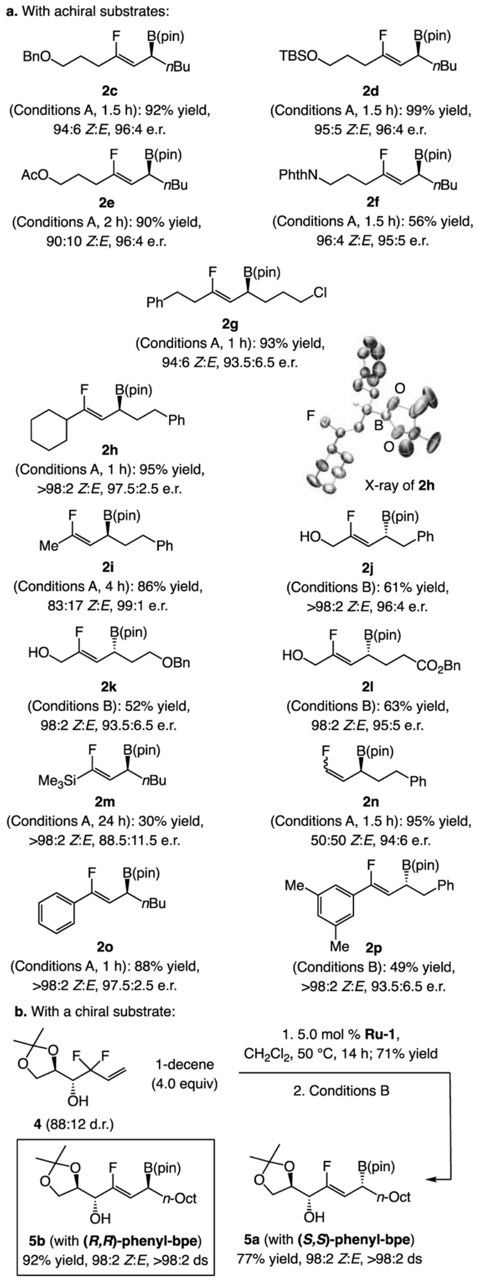
Scheme 1.

The significance and aims of this study. Abbreviations: R^1-R^3 = C-based moieties; pin = pinacolato.



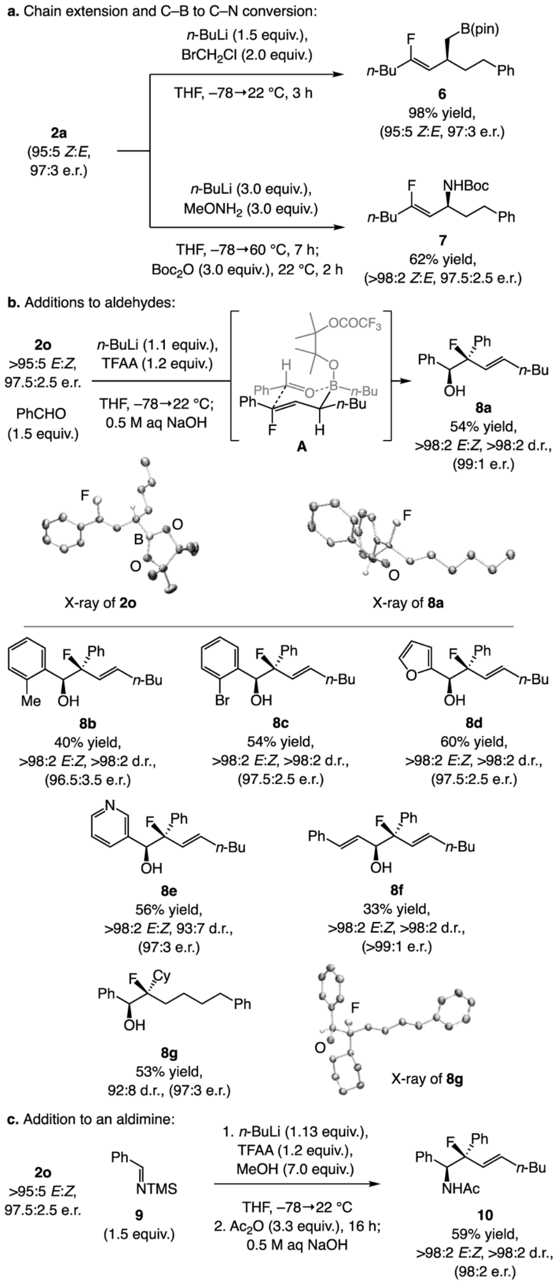
Scheme 2.

The initial studies involving representative *E* and *Z* Substrates. Reactions performed under N_2 atm. Conversion was determined by ^{19}F NMR analysis of unpurified mixtures. *Z*:*E* by GC or ^1H NMR spectra of unpurified mixtures (±2%). Enantioselectivity was determined by HPLC analysis of derived alcohols (±1%). Yield of purified products (±5%). See the Supporting Information for details. tpy = 2,6-bis(2-pyridyl)pyridine.



Scheme 3.

Scope of chiral allylic boronates. The same conditions were used as in Scheme 2. Conversion was determined by analysis of the ^{19}F NMR spectra of the unpurified mixtures. *Z:E* ratios were determined by GC or ^{19}F NMR analysis (±2%). Yields of purified products (±5%). Enantioselectivity was established by HPLC analysis of the saturated alcohols or corresponding ester derived from boronates (±1%). ds = diastereospecificity. See the Supporting Information for details.



Scheme 4.

Representative functionalization of chiral allylic boronates. *E*:*Z* by analysis of ^{1}H NMR spectra of unpurified mixtures. Yields of purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). For compounds **8f** and **10**, isolated by pentane wash of solid product; e.r. might be higher than allylic boronate. See the Supporting Information for details.