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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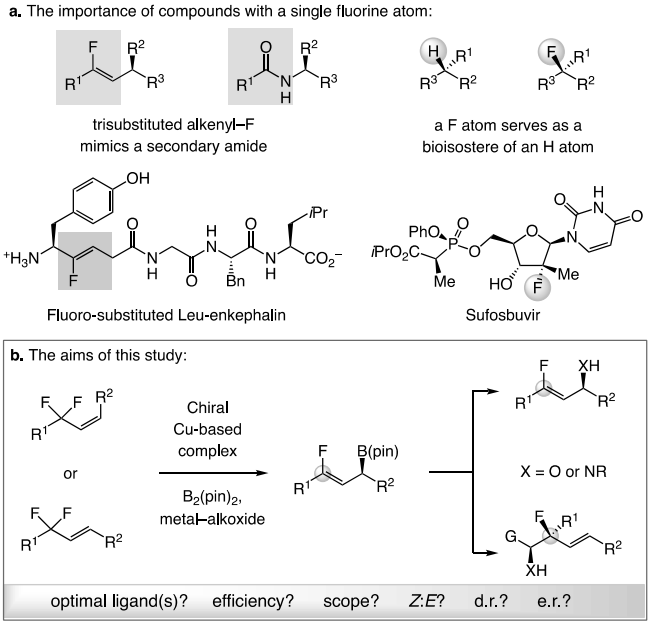
Abstract: The first catalytic method for diastereo- and enantioselective synthesis of allylic boronates bearing a *Z*-trisubstituted alkenyl fluoride is disclosed. Boryl substitution is performed with a *Z*- or an *E*-allyldifluoride and is catalyzed by bisphosphine–Cu complexes, affording products in 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.

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.



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

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

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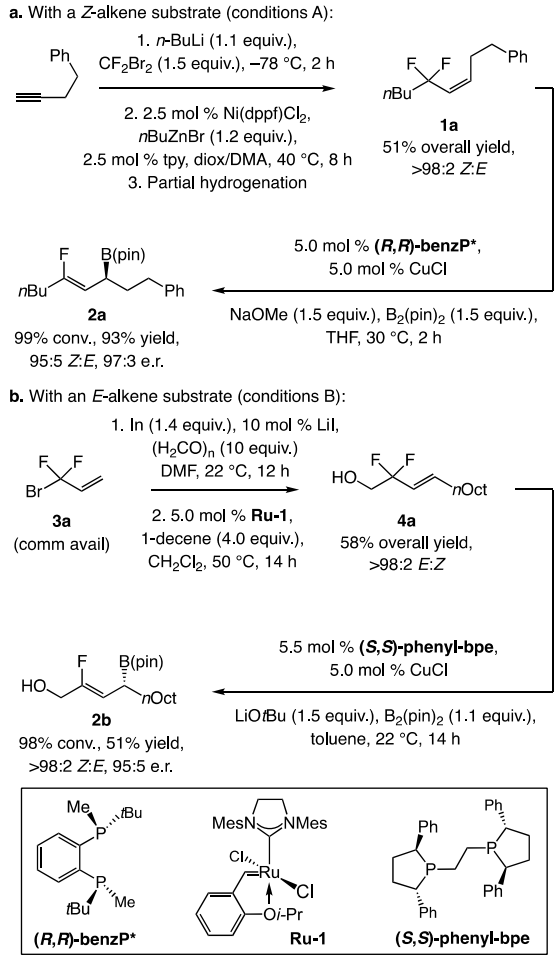
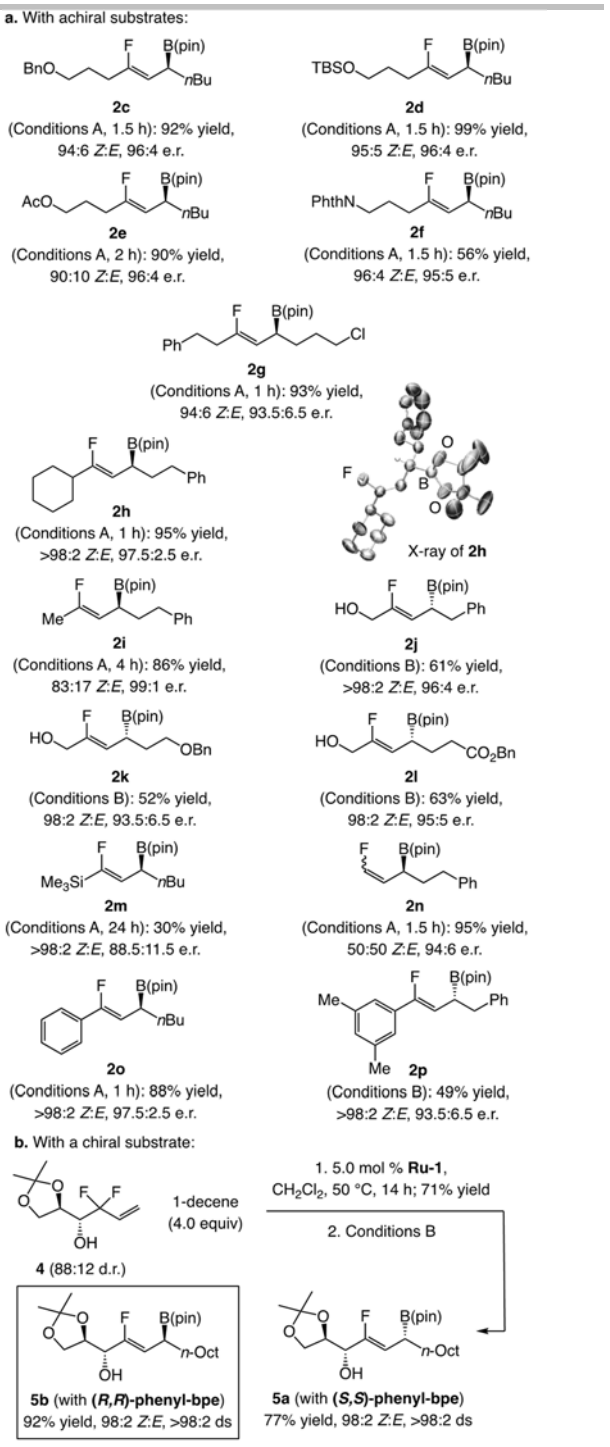
that benzP* is a superior option. Thus at 5.0 mol % catalyst loading, **2a** was generated in 93% yield, 95:5 *Z*:*E* selectivity, and 97:3 e.r. Although the reaction with the closely related (*R*,*R*)-quinoxP* was similarly effective (93% yield, 95:5 *Z*:*E*, 96:4 e.r.), catalysts derived from other 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.



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 ^{1}H 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.

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,



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.

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.

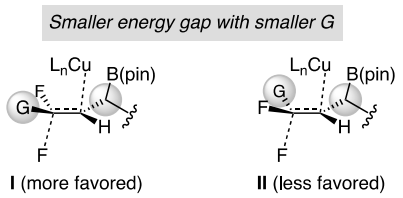


Figure 1. Origin of variations in *Z*:*E* ratios.

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**).

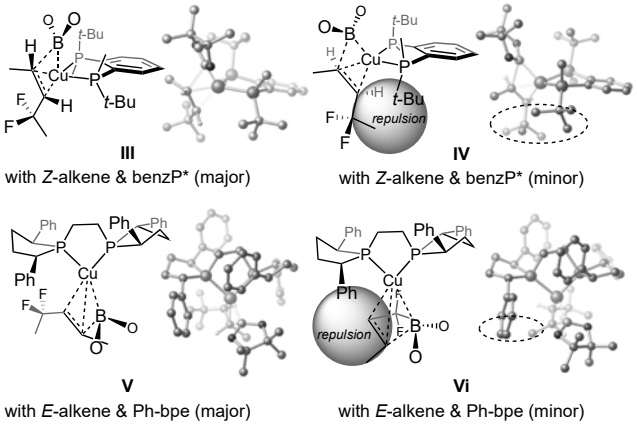
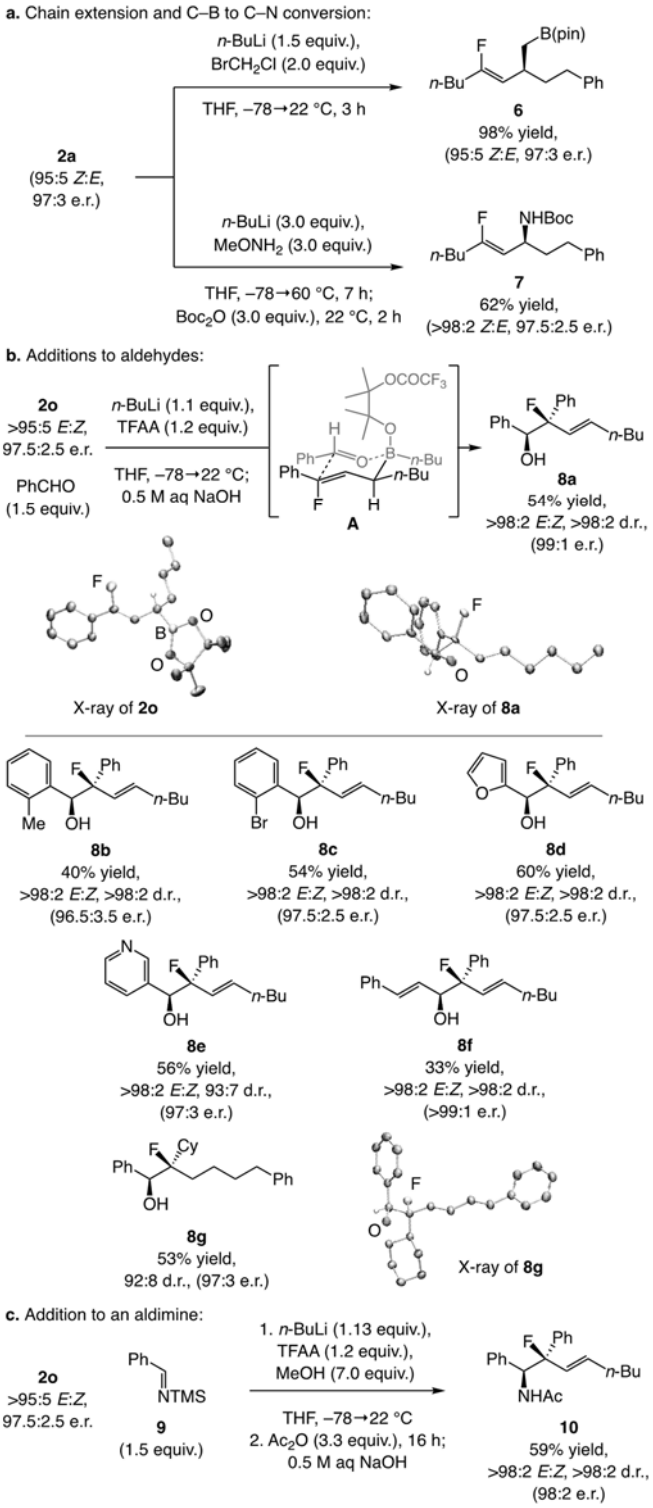


Figure 2. Stereochemical models based on DFT studies.

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**,



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.

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.

Acknowledgements

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Keywords: Boron • Copper • Enantioselective catalysis • Fluorine • Synthetic methods

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[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 NaO*t*Bu was used under conditions B. The mechanistic origin of these differences is under study.

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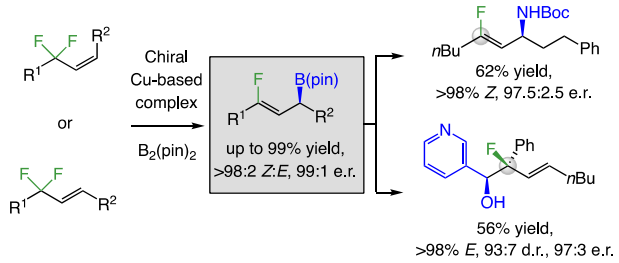

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