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Trifluoromethylation

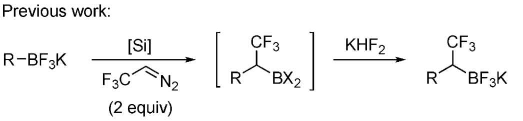
Diastereoselective Synthesis of Vicinally Bis(trifluoromethylated) Alkylboron Compounds through Successive Insertions of 2,2,2-Trifluorodiazoethane**

Gary A. Molander and DaWeon Ryu*

***Abstract:** The usefulness of embedded CF_3 substituents within organic substructures necessitates the development of diverse methods for incorporating this functional group. A recently reported route to α-trifluoromethylated alkylboron compounds by an α-transfer mechanism has now been extended to the synthesis of unprecedented, vicinally ditrifluoromethylated alkylboron compounds in a diastereoselective fashion. The utility of these products is highlighted by conversion of the C−B bond into other functional groups.*

The strategic placement of fluorine or fluorinated moieties within organic substructures imparts useful properties to these molecules.[1] In particular, the addition of trifluoromethyl groups has been demonstrated to boost the metabolic profile of many compounds,[2] and CF_3-containing building blocks increasingly find application in specialty materials.[3] Therefore, it is of ongoing interest to develop reliable methods for the installation of trifluoromethyl subunits into a variety of organic substructures.

The emergence of CF_3 reagents with different reactivities has revolutionized direct trifluoromethylation, and a tremendous amount of progress has been made especially in $C(sp^2)$−CF_3 bond formation.[4] Although $C(sp^3)$−CF_3 bonds can be constructed readily through carbonyl chemistry, the absence of this key functional group normally requires further manipulation of the CF_3 reagents and/or unprecedented reaction partners and conditions.[5] An advancement in the preparation of trifluoromethylated alkyl systems by a complementary protocol was introduced by our research group in 2013 [Eq. (1)].[6] Instead of a direct CF_3 reagent, a trifluoromethylating agent (CF_3CHN_2[7]) was used in conjunction with tricoordinate organoboron compounds to generate the first stable α-trifluoromethylated alkylboron compounds through an α-transfer mechanism.



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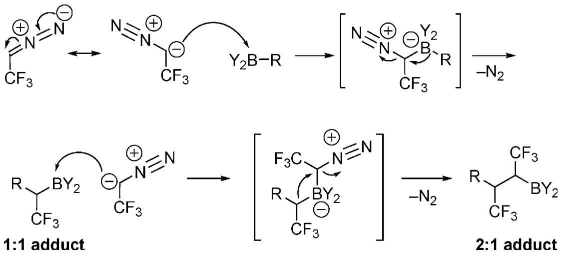
During the optimization of this process, the formation of a side product whose molecular weight exceeded that of the desired product by exactly one trifluoroethyl group was sometimes observed. On the basis of the mechanism of the process, the nature and source of this material was readily apparent. Because a new organoboron compound was generated in an iterative process after the initial α-transfer, the product of the first diazo insertion (1:1 adduct) was acting as a reactant for a second insertion (Scheme 1). This reactivity pattern had precedent in several boron-promoted polymerizations of diazoalkanes and structurally similar reagents (e.g., sulfoxide ylides) by an analogous α-transfer mechanism.[8]



Scheme 1. α-Transfer mechanism.

Methods for the incorporation of trifluoromethyl substituents on adjacent carbon atoms are extremely rare[9a] and, when asymmetric, mostly rely on pericyclic reactions[9b] or subsequent hydrogenation[9c,d] to dictate diastereoselectivity. In the isolated example of a diastereoselective aldol reaction, only one carefully designed substrate was reported.[9e]

Herein, we report the development of a method in which successive, highly diastereoselective trifluoroethylidene-insertion reactions produce unprecedented, vicinally bis(trifluoromethylated) alkylboron compounds. Not only can multiple trifluoroethyl subunits be inserted in a stereocontrolled manner, but the regenerated boron center can be further transformed through organoboron transformations, thus adding significant synthetic utility. Furthermore, these alkylboron compounds are solids that are indefinitely bench-stable, so they can be used as convenient hexafluorinated building blocks. The developed method enables the synthesis of novel libraries of fluorinated structures that cannot be made by existing methods.

At the outset of these studies, it was unclear as to whether the product of double diazo insertion (2:1 adduct) could be

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[*] Prof. G. A. Molander, D. Ryu
Roy and Diana Vagelos Laboratories, Department of Chemistry
University of Pennsylvania
231 South 34th Street, Philadelphia, PA 19104-6323 (USA)
E-mail: gmolandr@sas.upenn.edu

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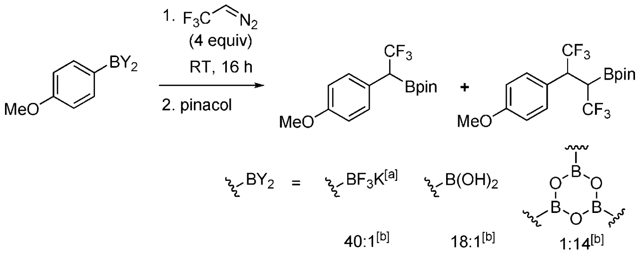
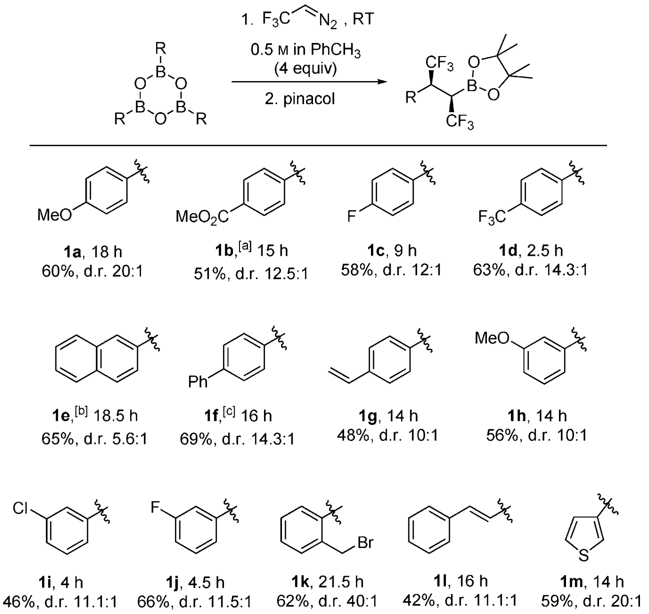
generated selectively. Because 1:1 adducts were formed in high yields from the reaction of two equivalents of trifluorodiazoethane with dihaloboranes (generated in situ from RBF_3K) at room temperature or 40 °C,[10] an increase in the reaction temperature was deemed necessary to force the second insertion. However, side products, notably *gem*-difluoroalkenes from β-fluoride elimination of a B−F moiety, were prone to form at elevated temperatures, in which case further diazo addition was terminated. The challenge was to find a boron source that would yield the desired 2:1 adduct at a temperature at which the 1:1 adduct was still reactive, but β-F elimination was subdued.

When cyclic arylboroxines, prepared by thermal azeotropic removal of water from boronic acids,[10] were treated with an excess of trifluorodiazoethane at 60 °C, the β-F elimination product from the 2:1 adduct was obtained relatively cleanly. Encouraged by this result, we tested more reaction conditions and were pleased to find that at room temperature, not only were boroxines still reactive, but the C−B bond remained intact. Comparison of the reaction of (4-methoxyphenyl)boroxine and those of the corresponding dihaloborane and boronic acid clearly demonstrated that boroxines were the most effective boron source for 2:1 adduct formation (Scheme 2).



Scheme 2. Ratio of the 1:1 adduct to the 2:1 adduct, as determined by ^{19}F NMR spectroscopy. [a] p-$CH_3C_6H_4SiCl_3$ (1.05 equiv) was added. [b] Ratio of the 1:1 adduct to the major diastereomer of the 2:1 adduct.

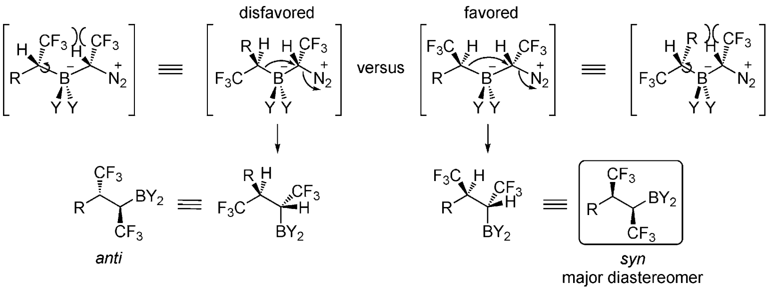
Under the optimized reaction conditions, a broad range of *para*- and *meta*-substituted arylboroxine substrates could be used (Scheme 3). Because of steric effects, *o*-substituted arylboroxines were generally reluctant reaction partners, but **1k** was obtained in good yield. Various functional groups, such as ester, ether, vinyl, and halide groups, were tolerated, and an alkenylboroxine also smoothly underwent the reaction. However, among the many heteroaryl substrates tested, only one example was successful; in this case, the desired product **1m** was isolated in high enough yield with the C−B bond intact. Because boroxines have to be prepared from the corresponding boronic acids, substrate availability is limited by the stability of boronic acids under thermal conditions. Many heteroarylboroxines simply could not be made because extensive protodeboronation of the boronic acids occurred upon heating.



Scheme 3. Scope of the reaction with respect to the boroxine substrate. In all cases, only the major diastereomer was isolated, and the diastereomeric ratio was determined by ^{19}F NMR spectroscopy before separation. [a] The reaction was carried out with CF_3CHN_2 (8 equiv). [b] The reaction was carried out at a 1 M concentration in $ClCH_2CH_2Cl$ with CF_3CHN_2 (5 equiv). [c] The reaction was carried out at 37 °C at a 1 M concentration in $PhCH_3$ with CF_3CHN_2 (6 equiv).

With lower-molecular-weight substrates, 3:1 adducts were sometimes identified by GCMS, but most of the time the formation of such adducts was not detected, probably because of solubility issues. Insoluble solids that sometimes precipitated in small amounts from the solution at the end of the reaction were conjectured to be polyinsertion products. After quenching with pinacol, the major diastereomers of alkyl pinacol boronates were isolated upon recrystallization in good yields, considering that the reaction was essentially a three-step process. The configuration of **1d** was confirmed as *syn* by X-ray crystallography.

Subsequent to the initial synthetic studies, a rationale for the observed high diastereoselectivity was sought. The proposed intermediates leading to the two diastereomers are shown in Scheme 4. For the migration to occur, the leaving group is required to be antiperiplanar to the migrating group. Furthermore, for both diastereomers, the transition structures before the migration are likely to be those in which *syn*-pentane interactions are minimized.



Scheme 4. Proposed intermediates of the two diastereomers.

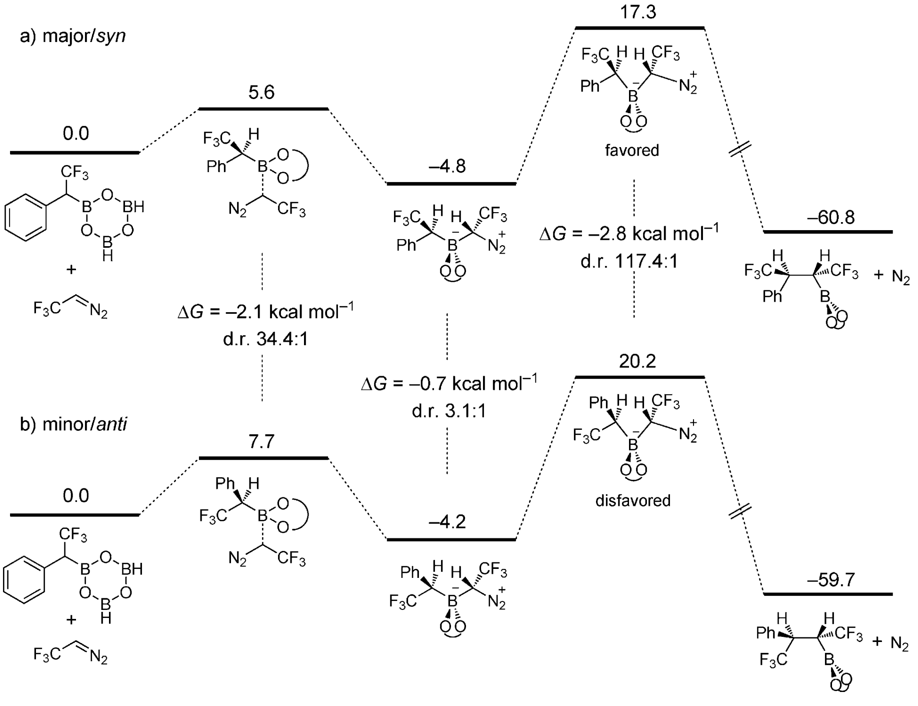
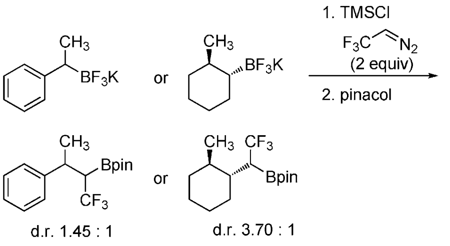


Figure 1. Energy profiles calculated at B3LYP/6-31G(d), PCM (benzene) for the addition of CF_3CHN_2 to the 1:1 adduct and subsequent α-transfer leading to a) major and b) minor diastereomers. Relative free energies are given in $kcal\,mol^{-1}$.

On the basis of this hypothesis and to probe why the transition structure leading to the *syn* product was favored, we performed DFT calculations (Figure 1). Our calculations on a simplified system suggest that the reaction is kinetically controlled and that the α transfer is the rate-limiting step. The transition structure leading to the major diastereomer is lower in energy (potentially owing to a minimization of dipolar interactions), in agreement with the experimental results.

We were curious to see whether the observed diastereoselectivity would translate to other systems with similar transition structures. When alkyltrifluoroborates [Eq. (2)]

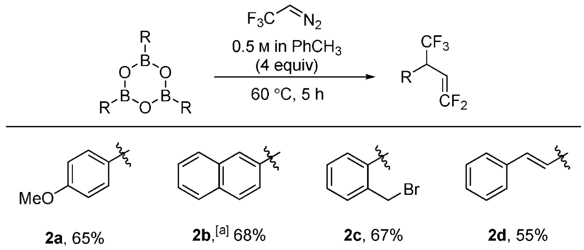


(2)

were treated with chlorotrimethylsilane (TMSCl) and trifluorodiazoethane, much lower diastereoselectivities were observed. Although a definitive statement cannot be made because more than one variable was altered, the effect of an adjacent trifluoromethyl group on the diastereoselectivity, whether it be steric or electronic, seems to be important.

Next, transformations of the organoboron intermediates generated were investigated. β-Fluoride elimination from the 2:1 adduct to form 1,1,4,4,4-pentafluorobut-1-ene derivatives proceeded readily. Simply heating the initial reaction mixtures with trifluorodiazoethane gave the products of β-F elimination, and this procedure was general across all the substrates described in Scheme 3. Selected substrates that gave nonvolatile products are shown in Scheme 5. With the alkenyl substrate, no rearrangement to form a conjugated system was detected; this result, in line with β-F elimination of transition-metal complexes,[11] supports the mechanism of elimination of B–F moieties.

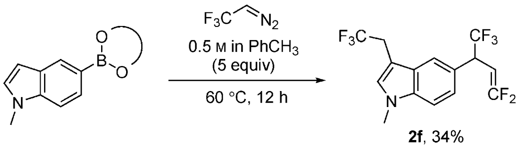
One interesting exception was found with an indole substrate. Under the standard conditions for the synthesis of alkylboron compounds (Scheme 3), the starting material 5-indolylboroxine was barely consumed, but when heated to higher reaction temperatures, the C–B bond did not stay



Scheme 5. β-F elimination of 2:1 adducts. [a] The reaction was carried out at a 1 M concentration in $ClCH_2CH_2Cl$ with CF_3CHN_2 (5 equiv).

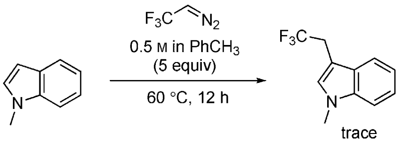
intact. Furthermore, even the product of β-F elimination from the 2:1 adduct could not be obtained in high yield because of the formation of a side product, which was initially misidentified (on the basis of GC/MS and ^{19}F NMR spectroscopic analyses) as the product of β-F elimination from the 3:1 adduct. Because we were not able to stop the reaction after two diazo additions, conditions were then optimized for three diazo additions. However, complete characterization revealed that the product was actually trifluoroethylated at the 3-position of the indole ring [Eq. (3)].

Although never employed with trifluorodiazoethane, metal-catalyzed C–H functionalization of indoles by α-



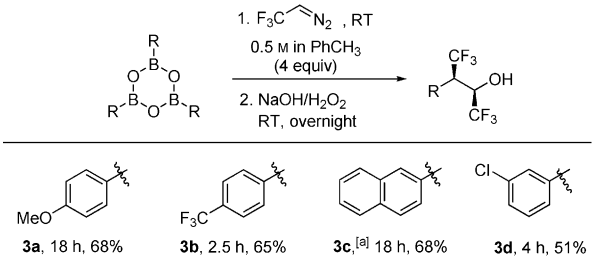
(3)

diazocarbonyl compounds via putative metal carbenoids is a well-established reaction.[12a] In the metal-free transformation reported herein, it is possible that thermolysis of trifluorodiazoethane occurs to give the trifluoroethylated indole; similarly, it has been demonstrated that heating ethyl diazoacetate with indole, followed by hydrolysis, gives 3-indolylacetic acid.[12b] A control experiment with 1-methylindole [Eq. (4)] suggests that pentafluorinated indole (the product of β-F elimination from the 2:1 adduct) undergoes electrophilic substitution more readily than unsubstituted indole.

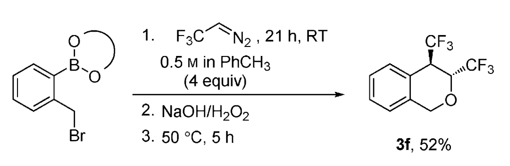


(4)

Oxidation of the C–B bond was carried out as part of a one-pot, three-step reaction. A diverse group of arylboroxines smoothly underwent the transformation to provide single diastereomers of alcohols upon purification (Scheme 6). With (2-bromomethyl)phenylboroxine, oxidation was followed by intramolecular ring closure to give a cyclic ether [Eq. (5)].

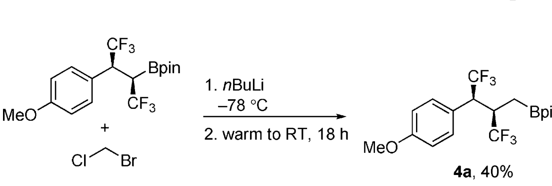


Scheme 6. Oxidation of the organoboron intermediate. [a] The reaction was carried out at a 1 M concentration in $ClCH_2CH_2Cl$ with CF_3CHN_2 (5 equiv).



(5)

Successful C–C bond formation was possible by Matteson homologation [Eq. (6)]. Unfortunately, it was not a high-yielding transformation because β-F elimination competed as a major side reaction. Although nucleophilic displacement of the halide is normally strongly favored over competing elimination in α-halo boronic esters,[13] we suspect that in the present case the formation of LiF provides a major driving force for elimination (Scheme 7). Nonetheless, the product was isolated with complete stereoretention as expected.



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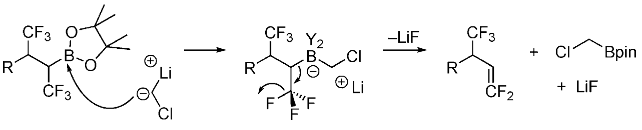

Scheme 7. Side reaction in the Matteson homologation.

In conclusion, a mild, metal-free, and operationally simple procedure has been developed for the synthesis of unique, vicinally bis(trifluoromethylated) organoboron compounds. The introduction of two trifluoromethyl substituents on adjacent carbon atoms in a diastereoselective fashion, along with the conversion of the C–B bond into other functional groups, opens new synthetic possibilities within the realm of polyfluorinated organic materials.

Experimental Section

A cyclic boroxine (0.33 mmol) was added to a 20 mL Biotage microwave vial equipped with a stir bar. The vial was sealed and purged with argon three times. A solution of CF_3CHN_2 in toluene (ca. 0.5 M, ca. 4 mmol, 8 mL) was added under an argon atmosphere, and the reaction mixture was stirred at room temperature for a specified amount of time. Pinacol (124 mg, 1.05 mmol) in CH_2Cl_2 (2 mL) was then added under argon, and the reaction mixture was stirred for a further 1 h. The crude product mixture was passed through a plug of Celite, washed with CH_2Cl_2 (3×3 mL), and concentrated under vacuum. The desired product was recrystallized from a solution of the crude product in CH_2Cl_2/hexanes.

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