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A Mild and Regioselective Route to Fluoroalkyl Aromatic Compounds via Directed Cycloaddition Reactions

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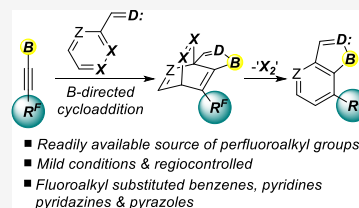


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ABSTRACT: The synthesis of perfluoroalkyl-substituted (hetero)arenes by benzannulation strategies is complementary to ring functionalization approaches as it obviates the need for pre-existing functionality and innate regiocontrol. We report a mild and regiospecific boron-directed benzannulation method as a vehicle for accessing a range of perfluoroalkyl-substituted (hetero)aromatic building blocks that can be readily elaborated through established C–B bond functionalization processes.



INTRODUCTION

Organofluorine compounds are widely established high-value materials because of their unique chemical and physical properties.¹ For example, perfluoroalkyl chains can impart impressive thermal and chemical stability, and for this reason, such compounds have found application in numerous fields of material science. Of particular importance are CF₃-substituted (hetero)aromatic compounds, and these are ubiquitous among marketed medicines because of their favorable physicochemical properties (Figure 1).²

Broadly speaking, there are three general approaches to incorporating trifluoromethyl groups into (hetero)aromatic compounds. “Programmed trifluoromethylation” is a popular approach that exploits a pre-existing functional handle, such as a (pseudo)halide or boronate, to deliver the CF₃ group to a precise location on the substrate.³ An alternative strategy is “innate trifluoromethylation” of a C–H group, typically through the reaction of the parent (hetero)arene with a trifluoromethyl radical.⁴ A final strategy that has received relatively little recent attention is (hetero)benzannulation using one or more CF₃-substituted precursors. Specifically, cycloaddition reactions of this type are complementary to the two strategies outlined earlier because the final position of the CF₃ is dictated by neither the presence of existing functional groups nor by the innate preference of the parent (hetero)arene. However, a drawback is that these reactions typically require harsh conditions and deliver products with poor regiocontrol.⁵ We report herein that boron-directed cycloadditions⁶ allow rapid and regiocontrolled synthesis of fluoroalkyl-substituted (hetero)arenes under mild conditions to deliver products that can be further elaborated through the C–B bond (Scheme 1).

RESULTS AND DISCUSSION

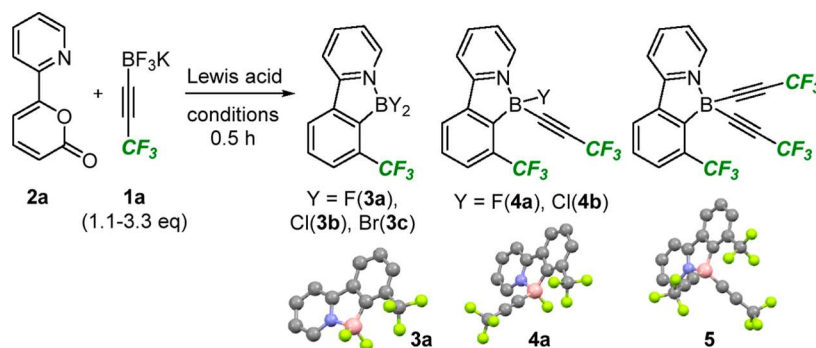
We began our studies by devising an efficient synthesis of the required perfluoroalkyl-substituted alkynyl trifluoroborate salts.

We were interested in pursuing a route that avoided the use of glassware-etching substances such as HF or KHF₂ and were attracted to the work of Ramachandran⁷ that employed the hydrofluorocarbon R-245fa (1,1,1,3,3-pentafluoropropane) as a convenient trifluoromethylacetylide precursor. In addition to reproducing this route, we were able to extend this approach to commercial perfluoroalkyl chain-substituted terminal alkynes to produce a small family of alkyne substrates 1a–c (Scheme 2).

Turning our attention to the arene forming step, we were disappointed to find that subjecting pyridine-substituted 2-pyrone 2a to alkyne 1a in the presence of BF₃·OEt₂ in CH₂Cl₂ at 40 °C resulted in very low conversion to the corresponding difluoroborane 3a (Table 1, entry 1). Upon changing the solvent to 1,2-dichloroethane and heating the reaction at 80 °C, 100% conversion was achieved (Table 1, entry 2), providing a mixture of products 3a, 4a, and 5 that were characterized by X-ray crystallography. Changing the solvent to toluene provided a marginal improvement in the yield of 3a, but a significant amount of byproduct 4a persisted (entry 3). Attempts to converge this mixture to a single product by disproportionation (treatment with BF₃·OEt₂ to generate 3a or with a combination of BF₃·OEt₂ and 1a to generate 5) failed to bring about a change in composition (see the Supporting Information for more details). We next investigated the use of a stronger Lewis acid in BCl₃^{6d} (Table 1, entry 4) and were pleased to find that a vigorous reaction took place at room temperature in 30 min to deliver the dichloroborane 3b which was isolated in 92% yield. BBr₃ was also successful in promoting the reaction (Table 1, entry 5), affording the

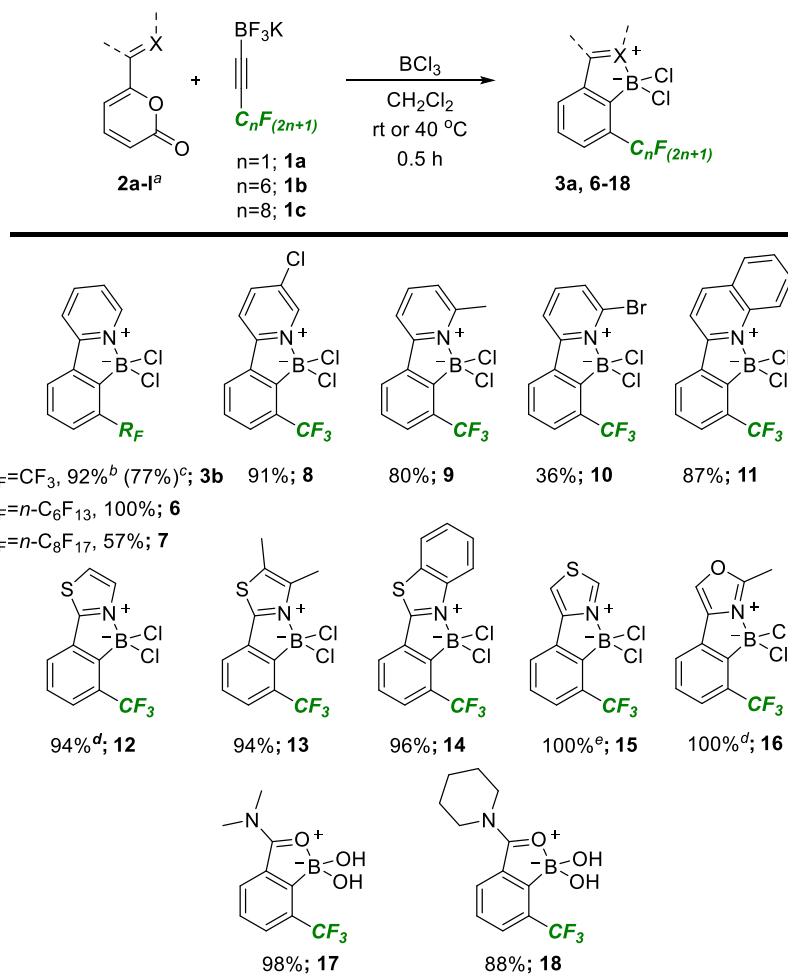
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Table 1. Optimization of the Boron-Directed Cycloaddition



entry	solvent	T (°C)	Lewis acid	Y	3a ^a	4a ^a	5 ^a
1	CH ₂ Cl ₂	40	BF ₃ ·OEt ₂ (3.3 equiv)	F	5%		
2	DCE	80	BF ₃ ·OEt ₂ (3.3 equiv)	F	64% (34%) ^b	27% (29%) ^b	9% (9%) ^b
3	toluene	80	BF ₃ ·OEt ₂ (3.3 equiv)	F	63%	29%	6%
4	CH ₂ Cl ₂	20	BCl ₃ (1.1 equiv)	Cl	100% (92%) ^b		
5	CH ₂ Cl ₂	20	BBr ₃ (1.1 equiv)	Br	82% (60%) ^b		

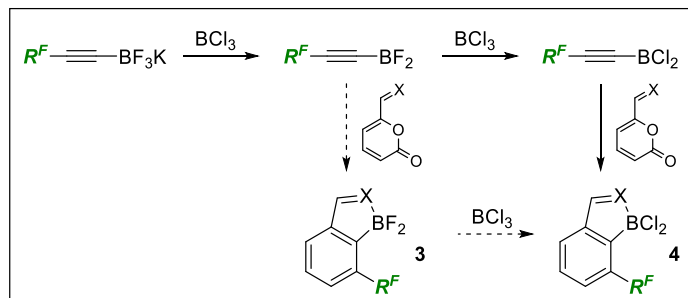
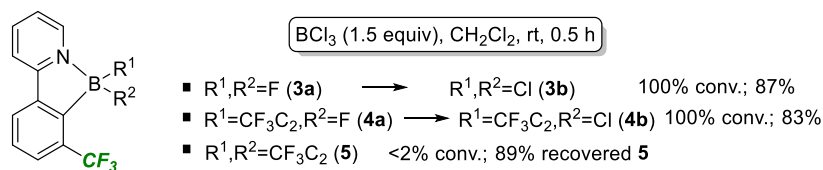
^aYield estimated by ¹H NMR spectroscopy. ^bYields in parentheses are of isolated products. DCE: 1,2-Dichloroethane.

Scheme 3. Scope of the Boron-Directed Cycloaddition^a

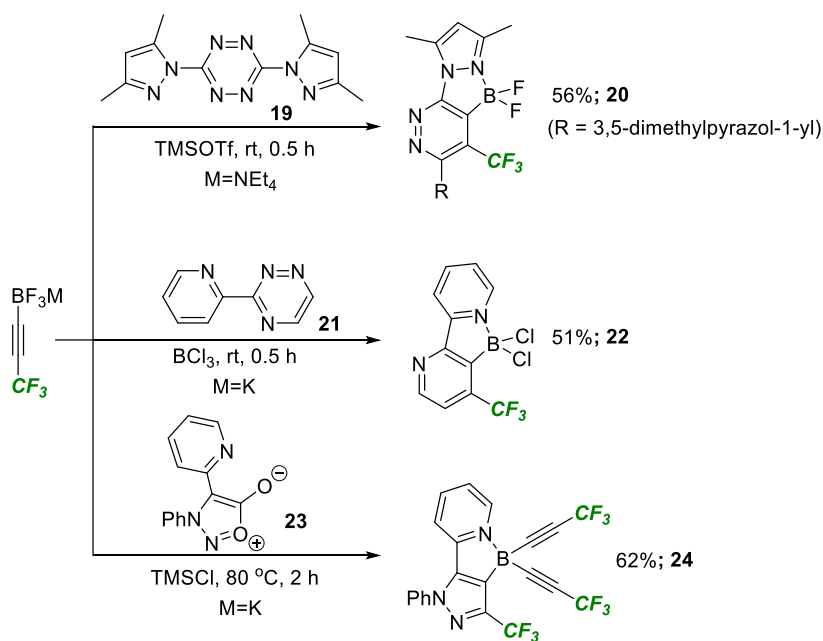
^aReactions carried out on 0.11 mmol of pyrone except where noted. ^bReaction carried out on 0.66 mmol of pyrone 2a. ^cReaction carried out on 4.30 mmol of pyrone 2a. ^dReaction stirred at 40 °C for 16 h. ^eReaction stirred at 40 °C for 24 h.

dienes (Scheme 5). In the event, the Carboni–Lindsey reaction of tetrazine 19 took place at room temperature in the presence of TMSOTf to afford the expected CF₃-

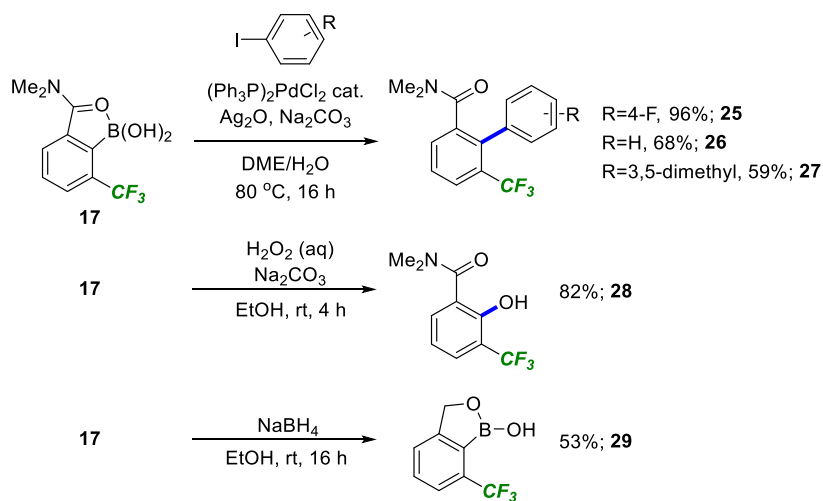
substituted pyridazine 20 in 56% yield. BCl₃ successfully promoted the cycloaddition of triazine 21 to generate the corresponding pyridine 22. Finally, pyrazole 24 was generated

Scheme 4. Investigation of Product Disproportionation Using BCl₃ and the Proposed Mechanism

Scheme 5. Accessing Fluorinated Heteroarenes



Scheme 6. C–B Bond Functionalization



from the boron-directed cycloaddition of sydnone **23**. In this case, the alkynylborane was formed instead of the corresponding dihaloborane analogue, in line with previous findings.^{6e} Overall, this study confirmed that fluoroalkyl trifluoroborate salts offer a convenient method to generate a range of fluorinated (hetero)arenes under mild conditions and with complete regiocontrol.

Our final objective was to investigate the reactivity of the boron handle for further elaboration. As shown in Scheme 6, efficient conditions for Suzuki–Miyaura cross coupling were uncovered using aryl iodides, affording the corresponding CF₃-substituted biaryls **25–27** in good yield. **17** was also converted to the phenol **28** in excellent yield after treatment with H₂O₂ under mild, basic conditions. Finally, the CF₃-substituted benzoxaborole **29** was prepared in useful yield by mild reduction of the amide by NaBH₄, highlighting the versatility of the intermediate **17** in the synthesis of low-molecular-weight building blocks.

In summary, we present the boron-directed cycloaddition as a novel entry into the important and rapidly developing field of fluoroalkyl-substituted (hetero)aromatic synthesis. A mild, BCl₃-promoted cycloaddition protocol was discovered, allowing convenient access to a range of fluoroalkyl-substituted benzene derivatives in good to excellent yield. The products obtained were amenable to further manipulation at the B center. Moreover, the directed cycloaddition concept was successfully extended to the synthesis of CF₃-substituted heteroaromatic compounds.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.2c00800>.

Details of experimental procedures and spectroscopic data and NMR spectral data (PDF)

Accession Codes

CCDC 2156098–2156100 and 2157487 contain 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.

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