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Copper-Catalyzed Defluorinative Borylation and Silylation of *gem*-Difluoroallyl Groups

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Cite This: *Org. Lett.* 2020, 22, 6805−6809 Read Online

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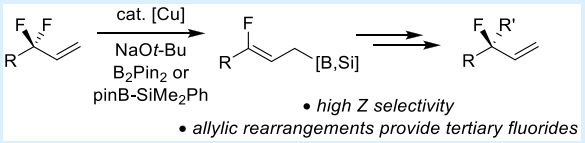
ABSTRACT: Stereodefined (*Z*)-fluoroalkenes are bioisosteres of amides and synthetic precursors to value-added fluorinated compounds, but their stereoselective synthesis remains challenging. Herein, we report a copper-catalyzed formal S_N2' defluorinative borylation of 3-substituted 3,3-difluoropropenes to form 3-fluoroallylboronic esters in high yields with excellent *Z*/*E* ratios. The primary 3-fluoroallylboronic esters undergo several synthetic sequences involving S_E2' substitutions, S_N2' substitutions, and sigmatropic rearrangements to provide tertiary allylic fluorides.



Several fluorinated moieties are used to mimic common functional groups found in bioactive molecules, while altering medicinally relevant properties, such as lipophilicity, metabolic stability, conformation, and pK_a.[1] For example, −F, −CF_2H, and −CF_2− groups can mimic −H, −OH, and −C(O)− groups, respectively.[2,3] A fluorinated motif of particular interest is the (*Z*)-fluoroalkene because the geometries and dipole orientations of these groups are similar to those of amides. Because the hydrolytic stability and lipophilicity of (*Z*)-fluoroalkenes are higher than those of amides, they serve as bioisosteres for peptide bonds in protease-resistant peptidomimetics.[4] In addition to these properties that are valuable for drug design, fluoroalkenes serve as synthetic intermediates to secondary and tertiary alkyl fluorides via hydrogenations,[5−9] sigmatropic rearrangements,[10,11] allylic substitutions,[12,13] nucleophilic allylations,[14] Sigman−Heck reactions,[15] and cycloadditions.[16,17]

The synthesis of fluoroalkenes in high isomeric purity is important for several applications. For example, only the (*Z*) isomers of fluoroalkenes serve as bioisosteres for amide bonds (amides exist predominantly in their *trans* form), and stereospecific reactions of fluoroalkenes require geometrically pure olefins. Furthermore, the separation of geometric isomers of olefins is often difficult, making high stereoselectivity an important goal. Traditional methods to prepare fluoroalkenes, such as Wittig and Horner−Wadsworth−Emmons olefinations,[18,19] Julia−Kocienski olefinations,[20] Peterson olefinations,[21] Shapiro reactions,[22] and alkyne hydrofluorinations,[23,24] often provide the corresponding monofluoroalkenes with low stereoselectivities. Improved reagents and catalysts for these types of reactions are limited.[25,26]

Due to these challenges and the wide availability of highly fluorinated building blocks,[27] new approaches to the synthesis of fluoroalkenes based on the selective activation of C−F bonds with transition-metal complexes have emerged.[28] These reactions typically proceed by sequences involving *β*-fluoride elimination or oxidative addition of C−F bonds.[29−35] Several of these methods proceed with excellent stereoselectivity.

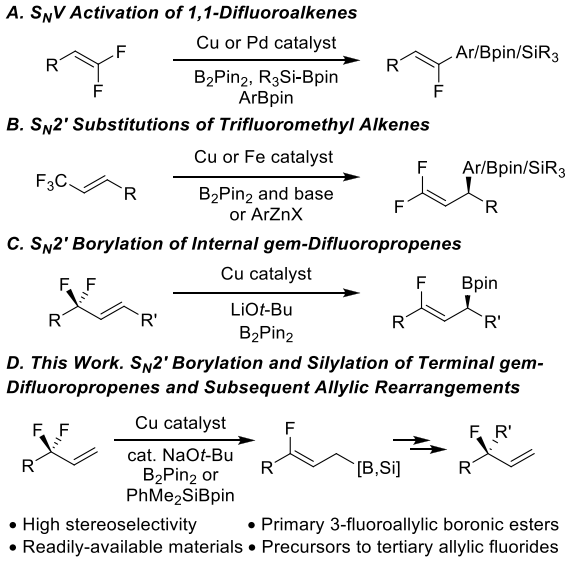
Prominent examples of such catalytic reactions include formal S_NV borylations and silylations of 1,1-difluoroalkenes catalyzed by copper[36−41] and formal S_NV arylations of 1,1-difluoroalkenes catalyzed by palladium (Scheme 1A).[42] In addition, formal S_N2' functionalizations of trifluoromethyl alkenes to provide 1,1-difluoroalkenes have been catalyzed by copper and iron (Scheme 1B).[43−47] Recently, Hoveyda and Ito reported the asymmetric formal S_N2' defluorinative borylation of 1,3-disubstituted 3,3-difluoropropenes (Scheme 1C).[14] These reactions provide access to secondary 3-fluoroallylboronic esters but not to primary 3-fluoroallylboronic esters that are useful for several reaction sequences involving allylic substitutions or sigmatropic rearrangements.

Herein, we report the formal S_N2' defluorinative borylation and analogous silylation of 3-substituted 3,3-difluoropropenes to provide primary 3-fluoroallylboronic esters and 3-fluoroallylsilanes in high yields with excellent *Z*/*E* selectivities (Scheme 1D). The 3-fluoroallylboronic ester products are sensitive to base-mediated decomposition; consequently, we developed conditions under which sodium *tert*-butoxide serves as a substoichiometric initiator, and fluoride, which is eliminated over the course of the reaction, induces transmetalation of a Bpin group to copper. The primary 3-fluoroallylboronic esters undergo reaction sequences that are currently unknown for secondary 3-fluoroallylboronic esters. For example, the primary 3-fluoroallylboronic esters convert to

Received: July 12, 2020
Published: August 25, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02321
Org. Lett. 2020, 22, 6805−6809

Scheme 1. Transition-Metal-Catalyzed Synthesis of Fluoroalkenes by C−F Activation



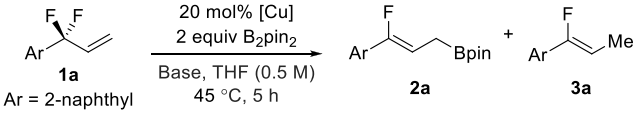
tertiary allylic fluorides by oxidation and formal S_N2' substitutions catalyzed by copper or iridium[12,13] or by oxidation and tetramisole-catalyzed sigmatropic rearrangements to provide tertiary allylic fluorides.

To initiate our investigation of the defluorinative borylation of 3-substituted 3,3-difluoropropenes, we treated 2-(1,1-difluoroallyl)naphthalene (**1a**)[48] with bis(pinacolato)diboron and a variety of bases in the presence of a copper catalyst. Although 3-fluoroallylboronic ester **2a** formed in moderate yield, a significant quantity of the formal hydrodefluorination product **3a** also formed, and full conversion of the starting material was observed (Table 1, entries 1−3).

We hypothesized that base-promoted protodeboronation of allyl boronate **2a** could be forming fluoroalkene **3a**. Consistent with this proposal, reactions conducted with substoichiometric quantities of sodium *tert*-butoxide (0.4 equiv instead of 2.0 equiv) provided 3-fluoroallylboronic ester **2a** in excellent yield without concomitant formation of the formal hydrodefluorination product **3a** (Table 1, entry 4). This result suggests that the fluoride, which is eliminated over the course of this reaction, promotes transmetalation of a Bpin group to copper. Reactions conducted with Xantphos, IMes, and dppe occurred in lower yields than did reactions conducted with PCy_3 (Table 1, entries 6−8).

With conditions identified for the formal S_N2' defluorinative borylation of 2-(1,1-difluoroallyl)naphthalene, we investigated the defluorinative borylation of a variety of analogous electrophiles (Scheme 2). Due to the instability of the allylboronic esters **2a**−**2k** to chromatography, we determined the yield and *Z*/*E* selectivity of the defluorinative borylation by ^{19}F NMR spectroscopy and isolated the corresponding alcohols **4a**−**4k** after oxidation of the crude allylboronic esters. Electrophiles bearing electron-neutral (**1a**, **1b**), electron-rich (**1c**, **1d**), and electron-poor arenes (**1e**) underwent defluorinative borylation in good to excellent yields and in uniformly high stereoselectivity.[49] (1,1-Difluoroallyl)arenes bearing an unprotected benzylic alcohol (**1f**), an aryl bromide (**1g**), or an *ortho* substituent (**1h**) also underwent defluorinative boryla-

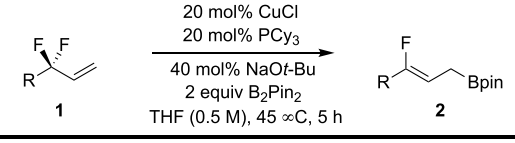
Table 1. Investigation of Reaction Conditions for Defluorinative Borylation of 3-Substituted 3,3-Difluoropropenes

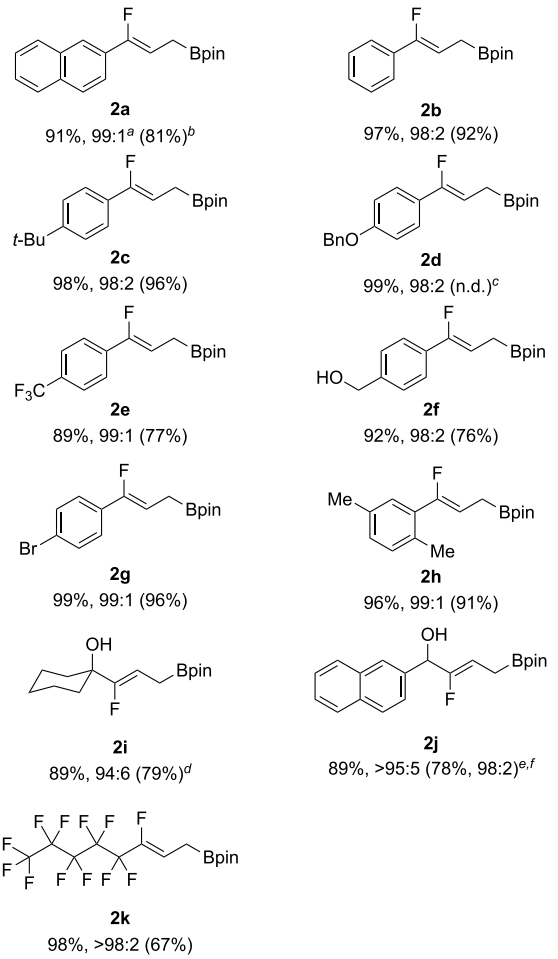


entry	catalyst	base (equiv)	yield **2a** (*Z*/*E*)[a]	yield **3a**[a]
1	CuCl + PCy_3	LiO*t*-Bu (2.0)	57% (94:6)[b]	9%
2	CuCl + PCy_3	NaO*t*-Bu (2.0)	44% (>99:1)[b]	34%[b]
3	CuCl + PCy_3	KO*t*-Bu (2.0)	4% (98:2)[b]	0%
4	**CuCl + PCy_3**	**NaO*t*-Bu (0.4)**	**98% (99:1)[b]**	**0%**
5	CuCl + PCy_3	NaO*t*-Bu (0.2)	78% (>99:1)[c]	0%
6	Cu(xantphos)Cl	NaO*t*-Bu (0.4)	74% (>99:1)[c]	0%
7	Cu(IMes)Cl	NaO*t*-Bu (0.4)	89% (99:1)[b]	3%[b]
8	CuCl + dppe	NaO*t*-Bu (0.4)	59% (99:1)[c]	2%

[a]Determined by ^{19}F NMR with fluorobenzene as an internal standard. [b]Full conversion of **1a** observed by ^{19}F NMR. [c]Remaining mass balance corresponds to unconverted **1a**. Ideal conditions used for investigation of the scope are shown in bold.

Scheme 2. Investigation of the Scope of 3-Substituted 3,3-Difluoropropenes That Undergo Defluorinative Borylation



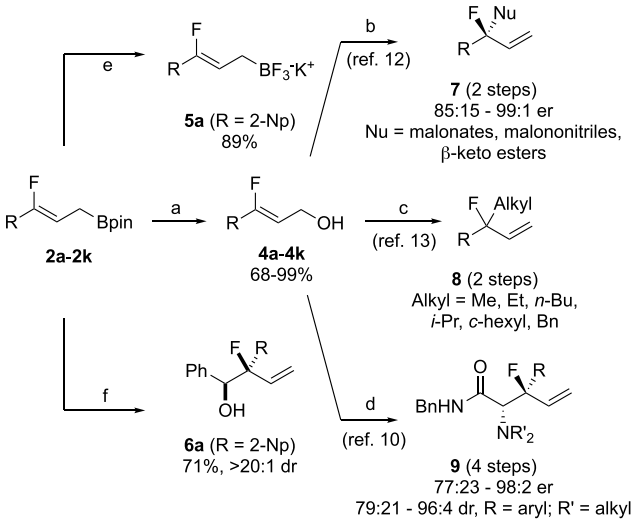


https://dx.doi.org/10.1021/acs.orglett.0c02321
Org. Lett. 2020, 22, 6805−6809

tions in high yields with excellent stereoselectivity. An aliphatic tertiary alcohol bearing a *gem*-difluoroallyl group (**1i**) also underwent defluorinative borylation in high yield and high selectivity. Secondary alcohol **1j** underwent defluorinative borylation with only moderate *Z*/*E* selectivity with the catalyst derived from CuCl and PCy_3 (87:13 *Z*/*E*); however, reactions of alcohol **1j** conducted with catalytic Cu(xantphos)Cl provided product **2j** with excellent selectivity (>95:5 *Z*/*E*). Lastly, 1*H*,1*H*,2*H*-perfluorooctene (**1k**) underwent defluorinative borylation to provide the corresponding highly fluorinated allyl boronic ester **2k** in excellent yield and excellent stereoselectivity.[50]

The utility of the fluorinated allylic boronic esters as synthetic intermediates is illustrated in Scheme 3. The boronic

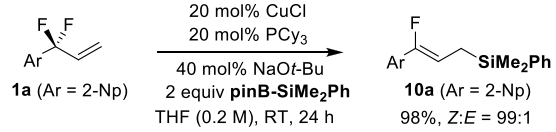
Scheme 3. Synthetic Applications of 3-Fluoroallylboronic Esters



esters converted to functionalized fluoroalkenes and tertiary allylic fluorides. For example, 3-fluoroallylboronic esters **2a**−**2k** underwent oxidization with alkaline hydrogen peroxide to provide the corresponding allylic alcohols **4a**−**4k** in high yield (Scheme 3, route a). These allylic alcohols convert to the corresponding allylic esters, phosphates, or halides, and we previously demonstrated that the resulting derivatives undergo iridium-catalyzed allylic substitutions with soft nucleophiles to provide enantioenriched tertiary allylic fluorides (Scheme 3, route b).[12,51] Konno, Ishihara, and co-workers have shown that the corresponding phosphates undergo copper-mediated S_N2' reactions with organometallic reagents to provide racemic tertiary allylic fluorides (Scheme 3, route c),[13] and Smith and co-workers have demonstrated that the corresponding bromides undergo a two-step process involving a tetramisole-catalyzed [2,3]-sigmatropic rearrangement to form enantioenriched α-amino-β-fluoro amides (Scheme 3, route d).[10] We demonstrated that boronic ester **2a** also forms the corresponding potassium trifluoroborate salt **5a** in high yield under standard conditions for conversions of boronic acids to trifluoroborates (Scheme 3, route e),[52] and we showed that boronic ester **2a** undergoes a formal S_E2' reaction with benzaldehyde to form tertiary allylic fluoride **6a** with high diastereoselectivity (Scheme 3, route f).

Because copper-catalyzed silylation reactions are mechanistically related to copper-catalyzed borylation reactions, we considered that the S_N2' defluorinative silylation of 3-substituted-3,3-difluoropropenes might occur under the reaction conditions we developed for defluorinative borylation. Indeed, the reaction of 2-(1,1-difluoroallyl)naphthalene (**1a**) with a silylborane ($PhMe_2Si$−Bpin) and NaO*t*-Bu in the presence of copper chloride and tricyclohexylphosphine afforded allyl silane **10a** in excellent yield and stereoselectivity (Scheme 4). While the chemistry of these products has not been explored, this reaction shows a method to generate allylsilanes containing fluorine.

Scheme 4. Defluorinative Silylation of 2-(1,1-Difluoroallyl)naphthalene (1a)



In conclusion, we have developed a formal S_N2' defluorinative borylation and silylation of 3-substituted-3,3-difluoropropenes to provide primary 3-fluoroallylboronic esters and 3-fluoroallylsilanes in excellent stereoselectivity. The starting 3-substituted-3,3-difluoropropenes are prepared in one step from commercial compounds, and the products undergo reaction sequences that lead to products that preserve the fluoroalkene moiety or that convert the fluoroallyl unit to one containing a tertiary allylic fluoride. Overall, the sequences initiated by the new copper-catalyzed allylic substitutions of a boryl or silyl group for one fluorine of a geminal difluoromethylene unit lead to the conversion of readily available compounds containing a difluoromethylene group to functionalized (*Z*)-fluoroalkenes that serve as amide isosteres or chiral tertiary alkyl fluorides that serve as fluorinated analogs of tertiary stereocenters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02321.

Experimental procedures, characterization data, and NMR spectra for all novel compounds (PDF)

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Author Contributions

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https://dx.doi.org/10.1021/acs.orglett.0c02321
Org. Lett. 2020, 22, 6805−6809

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NSF (CHE-1955635) for financial support. T.W.B. gratefully acknowledges the National Science Foundation for a predoctoral fellowship, and J.L.Y. gratefully acknowledges the UC Berkeley Summer Undergraduate Research Fellowship and the Rose Hills Foundation. We thank the UC Berkeley College of Chemistry's NMR facility for resources provided and the staff for their assistance. Instruments in the CoC-NMR facility are supported in part by NIH S10OD024998.

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https://dx.doi.org/10.1021/acs.orglett.0c02321
Org. Lett. 2020, 22, 6805−6809