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Letter

FON: An Innovative Fluorinated Group via Hydroetherification-Type Reactivity

Sanaz Rajabalinia, Hedieh Lotfian, Sabrina Hoford, Muyuan Wang, Maxime A. Siegler, Thomas Lectka,* and Travis Dudding*

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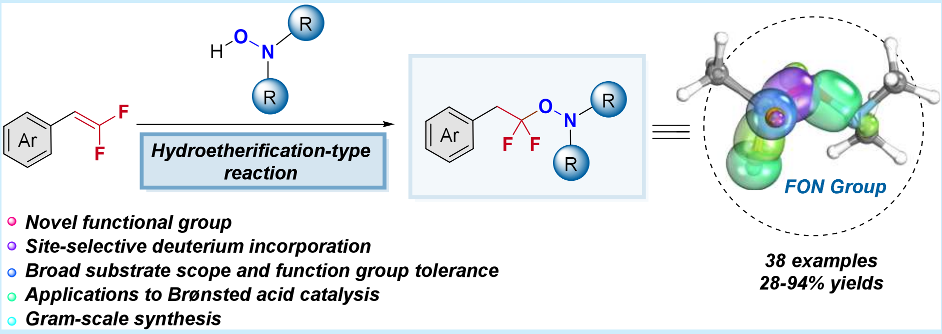

ABSTRACT: An efficient strategy for preparing the novel *O*-difluoroalkylhydroxylamine fluorinated functional group, coined FON, is reported. This analogue of medicinally important *β*-phenethyl ether scaffolds in uniting *gem*-difluoro and N−O moieties is synthesized in one step via chemo- and regioselectivity metal-free hydroetherification-type additions. As shown, this unique mode of reactivity is realized for a diverse substrate scope and applied to gram-scale synthesis and site-selective deuterium incorporation. Lastly, a mechanistic understanding with implications in Brønsted acid catalysis is offered.

Today, fluorinated functional groups are prized for their ability to bestow unique chemical and physical properties to molecules[1] including oxidative stability,[2] high lipophilicity,[3] and improved bioavailability.[4] For instance, the ketone bioisostere difluoromethylene (CF_2) motif has been widely utilized to adjust the biophysical properties of small molecules and serves as a key structural element in medicinal chemistry.[4b] In light of this worth, we speculated that fluorinated homologues of *β*-phenethyl ethers[5] or as we coin here FON group-containing compounds corresponding to *β*-phenethyl hydroxylamine scaffolds incorporating a CF_2 moiety and N−O unit would be a valuable addition to Chemists' toolbox (Figure 1a).[6] The acronym FON derives from the sequence of non-carbon heavy atoms F, O, and N of this *O*-difluoroalkylhydroxylamine group. Central to this assumption was the privileged status of *β*-phenethyl ethers as important structural motifs found widely in pharmaceuticals and natural products in addition to being a common synthetic intermediate.[7] At the same time, it was anticipated that this novel group would bring with it unique stereoelectronic features[1,8] and potentially useful biological activities.

Crucial to this aim of FON group synthesis, however, was the need for an unprecedented intermolecular Markovnikov addition of hydroxylamines to *gem*-difluorostyrenes through hydroetherification-type reactivity (Figure 1b). Against this backdrop, hydroetherification reactions are a powerful synthetic strategy having gained considerable traction in the past decade with examples in transition metal, electrochemistry, and photocatalysis.[9] Nonetheless, obstacles to this objective included *N*- vs *O*-chemo- and regioselectivity control over hydroxylamine addition further complicated by the propensity of *gem*-difluoroalkenes[10] to undergo defluorination in reactions with nucleophiles (Figure 1b).[11] Meanwhile, intermolecular Cope-type hydroamination could not be ruled out as a competing reaction,[12] while *β*-phenethyl ether synthesis is typically hindered by multistep hydroboration/oxidation/substitution sequences or Brønsted acid, metal, and photoredox-catalyzed alcohol addition methodologies.[13]

Despite these potential barriers and building upon our longstanding interest in fluorinated compounds,[14] we disclose here the unprecedented FON group and its synthesis by novel intermolecular *O*-hydroxylamine additions to *gem*-difluorostyrenes. This synthetic strategy allows for the efficient assembly of a broad substrate scope in moderate to excellent yields with

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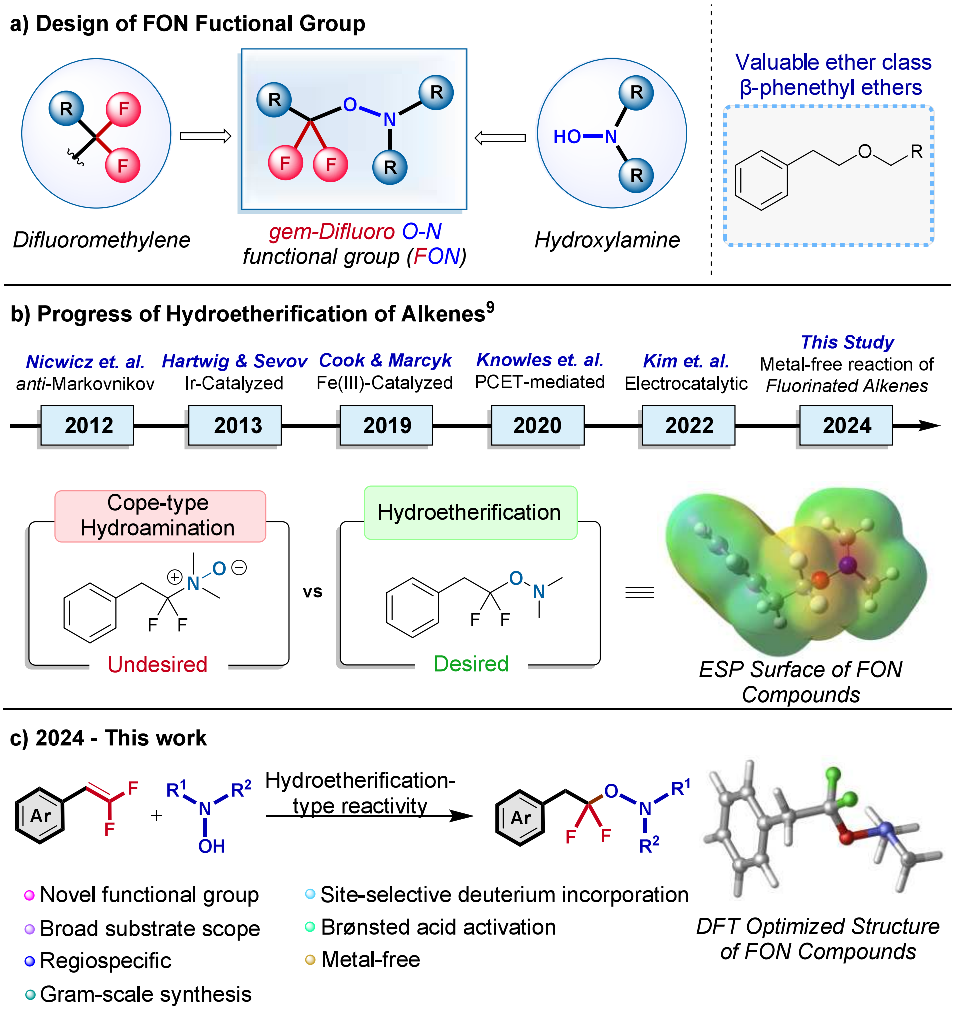


Figure 1. (a) Design of the FON functional group, (b) development of alkene hydroetherification timeline and *N*- vs *O*- selectivity, and (c) current hydroetherfication-type synthesis of FON.

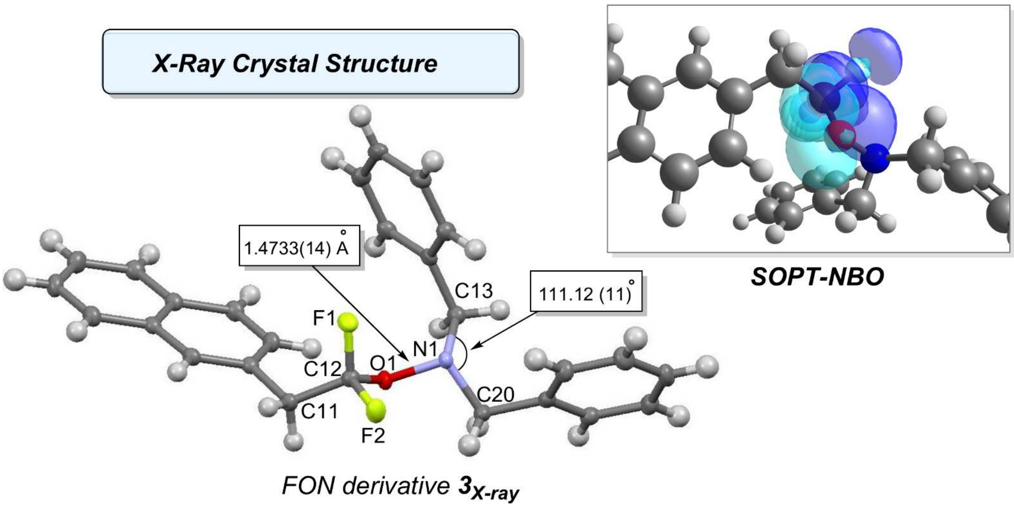
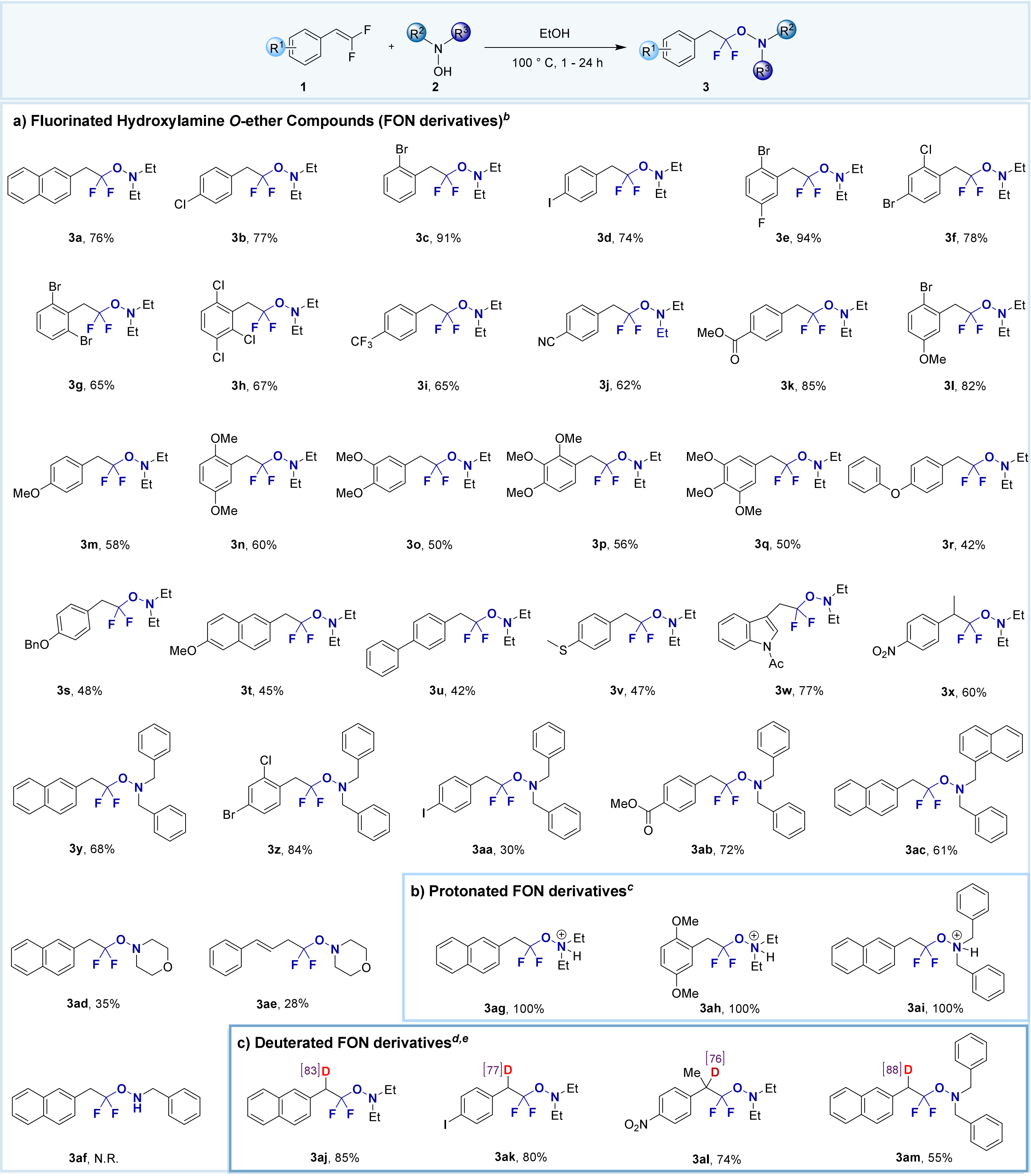


Figure 2. Crystal structure of compound $\mathbf{3}_{\text{X-ray}}$ (purple = N, red = O, green = F, gray = carbon). Displacement ellipsoids are given at 50% probability.

exquisite chemo- and regioselectivity, including for site-selective deuterium incorporation. Furthermore, computational and experimental mechanistic studies providing insight into this reactivity are offered and, with it, clues for new Brønsted acid catalysts (Figure 1c).

At the outset of this study in exploring FON group synthesis, we reacted *gem*-difluoroalkene substrate **1a** with commercially available diethyl hydroxylamine (**2a**) (1.5 equiv) in THF to afford hydroetherification product (**3a**) in good yield (80%) in 1 h. Subsequent scanning of solvents and reagent stoichiometries

Table 1. Substrate Scope of (a) Fluorinated Hydroxylamine *O*-Ether (FON) Compounds (3a−3af) and (b) Protonated (3ag−3ai) and (c) Deuterated FON Derivatives (3aj−3am)[a]



a) Fluorinated Hydroxylamine *O*-ether Compounds (FON derivatives)[b]

3a, 76% **3b**, 77% **3c**, 91% **3d**, 74% **3e**, 94% **3f**, 78%

3g, 65% **3h**, 67% **3i**, 65% **3j**, 62% **3k**, 85% **3l**, 82%

3m, 58% **3n**, 60% **3o**, 50% **3p**, 56% **3q**, 50% **3r**, 42%

3s, 48% **3t**, 45% **3u**, 42% **3v**, 47% **3w**, 77% **3x**, 60%

3y, 68% **3z**, 84% **3aa**, 30% **3ab**, 72% **3ac**, 61%

3ad, 35% **3ae**, 28%

3af, N.R.

b) Protonated FON derivatives[c]

3ag, 100% **3ah**, 100% **3ai**, 100%

c) Deuterated FON derivatives[d,e]

3aj, 85% **3ak**, 80% **3al**, 74% **3am**, 55%

[a] Isolated yields. [b] General conditions: **1** (1 equiv) and **2** (1.5 equiv) in EtOH (0.5 M) at 100 °C afforded compounds **3a−3x** in 1 h and **3y−3af** in 24 h. [c] Dried HCl was bubbled into **3** in Et_2O at rt. [d] **1** (1 equiv) and **2** (1.5 equiv) in EtOD (0.5 M) at 100 °C afforded compounds **3aj−3al** in 4 h and **3am** in 24 h. [e] Numbers between brackets represent the level of deuterium incorporation.

lead to an optimal set of robust reaction conditions utilizing low-cost, chemically green EtOH with moderate heating to achieve complete conversion to compound **3a** (see Supporting Information (S.I.)). An X-ray structure was next obtained from a single crystal of FON derivative $\mathbf{3}_{\text{X-ray}}$ to better understand the structure and bonding of our CF_2−ON group. Notably, the solid-state structure revealed a number of striking features such as a pyramidal nitrogen (θ(C13)−(N1)−(C20) = 111.12(11)°) with a lone pair oriented *syn* to the *gem*-difluoro group and opposite to the oxygen lone pairs. Further was an *anti*-

alignment between the *gem*-difluoro group and oxygen lone pairs minimizing lone pair-lone pair repulsion, while unremarkably the N(1)−O(1) bond distance of 1.4733(14) Å was consistent with the structural parameters of most reported X-ray structures of N−O bonds.[15] Present as well were underpinning stereoelectronic effects resulting in the preferred Z-shaped (N1)−(O1)−(C12)−(C11) conformation linked to significant oxygen lone pair donation into low-lying vacant σ^*_{C-F} orbitals ($O_{LP} \rightarrow \sigma^*_{C-F}$, $E_{NBO} = -19.0$ and -20.5 kcal/mol) identified by second-order perturbation theory natural bond orbital (SOPT-NBO) analysis (Figure 2) and associated barrier to bond rotation of 6.0 kcal/mol about the (C2)−(C1)−(O12)−(N13) estimated dihedral (see SI for details).

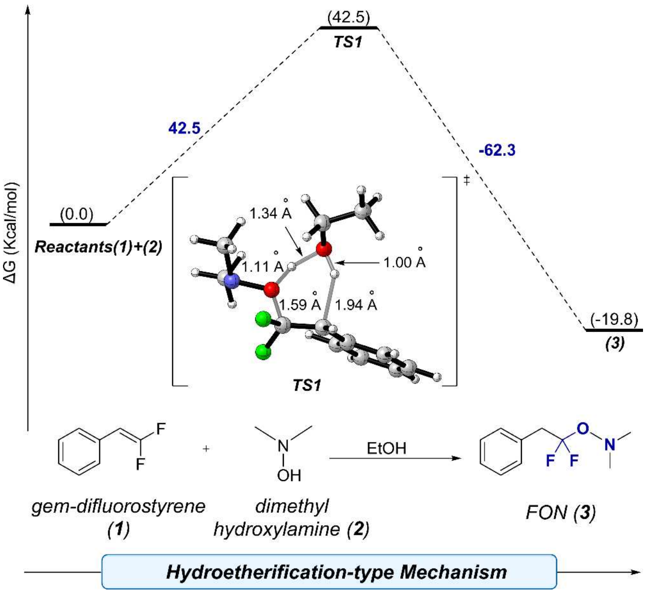
The scope of our FON group synthesis was next explored by preparing a diverse library of derivatives. To this end, *gem*-difluoroalkenes bearing F-, Cl-, Br-, and I-halogenated aryl groups (**1b**−**1h**) were reacted with hydroxylamine **2a** to afford fluorinated products (**3b**−**3h**) in good-to-excellent yields (Table 1a). Electron-withdrawing substituents such as $-CF_3$ (**1i**), cyano (**1j**), and ester (**1k**) were also tolerated, leading to the seamless formation of the desired products (**3i**−**3k**). Interestingly, substrates containing electron-donating methoxy groups (**1m**−**1u**) or a similar ether functionality reacted sluggishly to afford products (**3m**−**3u**) in slightly lower yields, thus indicating the preference for electron-deficient aryl groups in the reaction, although Br- and methoxy-substituted **1l** afforded the addition product (**3l**) in high yield. Meanwhile, acetylated indole (**1w**) reacted smoothly to afford product (**3w**) in moderate yield, whereas *para*-thiomethyl-substituted difluoroalkene (**1v**) led to lower amounts of product (**3v**). Proving to be a viable alkene partner as well was the sterically demanding *gem*-difluoropropenyl substrate (**1x**) with product (**3x**) formed in moderate yield. Moreover, this protocol facilitated access to a wide array of functionalized products using different hydroxylamines (**2a**−**2d**). This included the reactions of naphthyl (**1a**), halogenated (**1f**, **1d**), and ester (**1k**) based *gem*-difluoroalkenes with *N*,*N*-dibenzyl hydroxylamine (**2b**) to furnish the corresponding products (**3y**−**3ab**). Bulky, *N*-benzyl-*N*-naphthylhydroxylamine (**2c**) equally reacted to provide product (**3ac**); however, the use of 4-hydroxymorpholine (**2d**) resulted in reduced yields (**3ad**, **3ae**), and in the case of monosubstituted *N*-benzyl-hydroxylamine (**2e**) no product formation was observed. In addition, to demonstrate practicality, we applied our hydroetherification-type protocol for forging hydroxylamine *O*-ether compounds to the gram-scale synthesis of FON derivative **3a**. Notably, we were also able to prepare a subset of protonated analogs (**3ag**−**3ai**) from hydroxylamine *O*-ether compounds (**3a**, **3n**, **3y**) upon exposure to an etherate solution of HCl, thus adding to the handful of rare instances of reported examples of *N*-protonation of N−O linkages.[16]

Our protocol was then applied to site-specific benzylic deuteration,[17] which is a powerful strategy in medicinal chemistry for altering the absorption, distribution, metabolism, and excretion (ADME) properties of drug candidates.[18] Additionally, in synthetic chemistry, deuterium-labeled compounds are widely used for kinetic isotope effect studies and to track reaction pathways.[19] As such, applying our standard optimized conditions with EtOD as the solvent provided 77% or greater deuteration at the benzylic carbon of derivatives **3aj**−**3am** with no observed deuteration in other positions (Table 1c). Further, to acquire insight into the stability of FON compound hydrolysis studies monitoring the decomposition of **3a** over 2 days in a phosphate buffer solution at both room temperature and 100 °C resulted in no visible decomposition, thus corroborating the robustness of these compounds (see SI).

Next, owing to the lack of prior reports of intermolecular addition of hydroxylamines to styrene and related alkene derivatives, we sought to gain deeper insight into the mechanism of these hydroetherification reactions. To this end, we initially compared the reactions of naphthylstyrene and *gem*-difluoro styrene (**1**).

To our astonishment, even after 24 h no conversion was observed for the reaction of naphthylstyrene, while the fluorinated alkene substrate (**1**) provided a sole regioisomeric addition product in 1 h with >98% conversion. The basis of this remarkable difference is attributed to unfavorable pairing of styrene electrophilicity and hydroxylamine nucleophilicity, whereas *gem*-difluoro styrene is a more competent electrophile. This divergent outcome further originates from fluorine lone pair donation, resulting in alkene polarization and inductive effects reducing charge at the *gem*-difluoro-substituted carbon, enhancing reactivity. Supporting this fluorine effect were computed NBO charges (NBO charges = −0.338 and −0.339 e) and donor−acceptor interactions accompanied by a large degree of fluorine lone pair donation to the alkene π-systems ($F_{LP} \rightarrow \pi^*_{C=C}$) amounting to E_{NBO} energies of −28.1 and −29.3 kcal/mol in *gem*-difluoro styrene (**1**) (see SI). Informative as well was transition state **TS1** with a Gibbs free activation barrier ($\Delta G^{\ddagger}$) of 42.5 kcal/mol (Scheme 1). Defining this structure is a short O−C bond forming distance of 1.59 Å and a proton shuttle framework incorporating a molecule of alcohol solvent. Corroborating the role of proton transfer and solvent in these reactions were kinetic solvent isotope effect (KSIE) studies monitoring relative reaction rates by NMR time-course analysis measuring *gem*-difluoroalkene (**1a**) consumption in protium or deuterium ethanol to reveal a normal KSIE value ($k_{EtOH}/k_{EtOD} = 1.1$ at ∼95% consumption of **1a**). The origin of this KSIE is derived in large part from (1) hydroxylamine O−H vs O−D

Scheme 1. Calculated Mechanism for Hydroetherification-Type Reaction



[a]All energies (kcal/mol) were computed at the (IEFPCM = EtOH) ωB97X-D/6-31+G(d,p) level of theory.[20]

bond breaking and C−H vs C−D bond formation energies along with (2) hydrogen bond stabilization of charge build-up.

The critical role of proton shuttling in **TS1** led us to finally consider the prospect of utilizing a hydroxylamine conjugate acid to impart rate acceleration. To this end, the addition of protonated **2a** (20 mol %) to the reaction mixture of **1a** and **2a** in EtOH provided *O*-addition product **3a** in full conversion with an increased reaction rate of approximately 15% relative to optimized reaction conditions shown in Table 1a (see SI). Notably, this unique capacity of protonated hydroxylamines as catalysts is noteworthy and suggests opportunities for new applications in Brønsted acid catalysts. Further related studies revealed that this metal-free hydroetherification-type reactivity for FON group synthesis is feasible under HCl and HBF_4 acid catalyzed conditions, albeit with low levels of conversion. Given these promising early stage findings, the development of Brønsted acid catalyzed variants of FON group synthesis is the subject of further investigation that is beyond the synthetic scope of this current study.

To recap, an efficient approach for synthesizing a diverse library of novel fluorinated β-phenethyl homologue products featuring our novel FON functional group was disclosed. This one-step, chemo- and regioselective protocol employs cheap and/or readily available hydroxylamine and *gem*-difluorostyrene starting materials, in addition to allowing for site-selective deuterium incorporation. Furthermore, this unique reactivity exhibits broad functional group tolerance and delivers high yields while unlocking new opportunities for Brønsted acid catalysis. Considering the importance of organofluorine compounds and the demand for innovative strategies for their preparation, it is anticipated that our FON group holds much potential for expansion.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c04160.

Experimental procedures, crystallographic data, NMR spectra, and computational information (PDF)

Accession Codes

Deposition Number 2395443 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

■ AUTHOR INFORMATION

Corresponding Authors

Thomas Lectka − *Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States;* orcid.org/0000-0003-3088-6714; Email: lectka@jhu.edu

Travis Dudding − *Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1, Canada;* orcid.org/0000-0002-2239-0818; Email: tdudding@brocku.ca

Authors

Sanaz Rajabalinia − *Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1, Canada*

Hedieh Lotfian − *Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1, Canada*

Sabrina Hoford − *Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1, Canada*

Muyuan Wang − *Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States;* orcid.org/0009-0007-5562-9833

Maxime A. Siegler − *Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States;* orcid.org/0000-0003-4165-7810

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.4c04160

Author Contributions

S.R. and H.L. conducted all experimental work. Computational work was conducted by S.H. and T.D. Crystallographic data was obtained by M.W., M.S., and T.L.

Notes

The authors declare no competing financial interest.

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