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Communication

Direct Bioisostere Replacement Enabled by Metallaphotoredox Deoxydifluoromethylation

Edna Mao,[§] Cesar N. Prieto Kullmer,[§] Holt A. Sakai, and David W. C. MacMillan*

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ABSTRACT: The replacement of a functional group with its corresponding bioisostere is a widely employed tactic during drug discovery campaigns that allows medicinal chemists to improve the ADME properties of candidates while maintaining potency. However, the incorporation of bioisosteres typically requires lengthy de novo resynthesis of potential candidates, which represents a bottleneck in their broader evaluation. An alternative would be to directly convert a functional group into its corresponding bioisostere at a late stage. Herein, we report the realization of this approach through the conversion of aliphatic alcohols into the corresponding difluoromethylated analogues via the merger of benzoxazolium-mediated deoxygenation and copper-mediated $C(sp^3)-CF_2H$ bond formation. The utility of this method is showcased in a variety of complex alcohols and drug compounds.

In medicinal chemistry, the strategy of bioisosteric replacement can result in drug candidates with improved pharmacokinetic profiles and enhanced likelihood of clinical success (Figure 1).[1−3] However, the preparation of bioisosteric analogues often entails multistep de novo syntheses and the use of high-energy reagents.[4−8] Alternatively, late-stage functionalization strategies that permit the direct, one-step conversion of a functional group to its corresponding bioisostere may offer significant advantages in efficiency, thereby providing entry to an expanded chemical space and accelerating the drug discovery process.

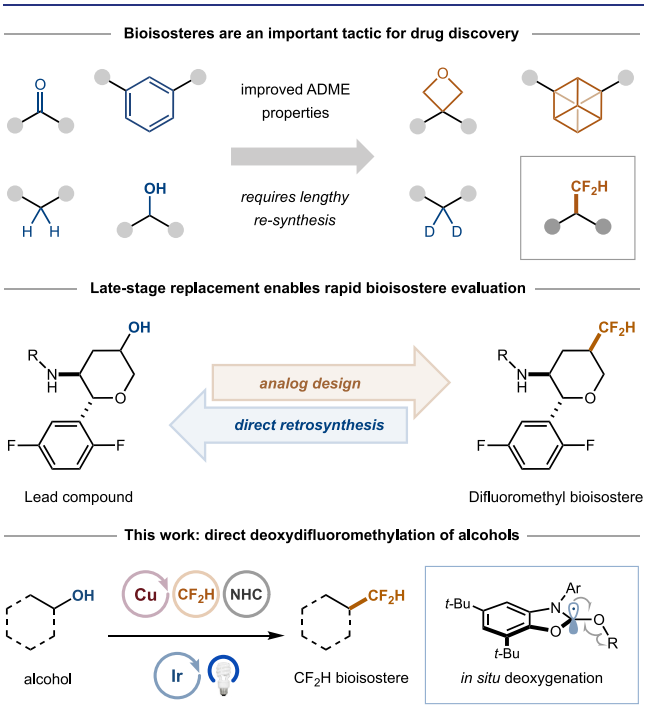

Figure 1. Bioisosterism as a strategy for drug discovery.

As pertinent functionalities in drug molecules, hydroxyl groups are found in approximately 37% of approved therapeutics and modulate a variety of important pharmaceutical properties, including potency and solubility.[9] However, these groups are also hydrophilic and nucleophilic and are prone to facile metabolic oxidation. Consequently, their applicability is highly situational and difficult to predict a priori. In contrast, the bioisosteric difluoromethyl group retains the ability to participate in hydrogen-bonding interactions yet is significantly more lipophilic, metabolically stable, and chemically inert.[10−12] To date, the difluoromethyl group has been most commonly explored in the form of $X-CF_2H$[13−15] and $C(sp^2)-CF_2H$[16,17] groups. Notably, although sp^3-enriched drug candidates tend to exhibit improved pharmacological properties with higher clinical success rates,[18] the incorporation of $C(sp^3)-CF_2H$ groups into pharmaceutical candidates remains conspicuously underexplored. This incongruity arises from the synthetic difficulties in efficiently incorporating difluoromethyl groups into pharmaceutically relevant compounds. Important recent advances have relied on electrophilic, nucleophilic, and radical difluoromethyl sources to build $C(sp^3)-CF_2H$ groups from a variety of functionalities, such as acidic $C(sp^3)-H$ bonds, alkyl amines, alkyl halides, alkenes, and ketones.[19] Specifically, the Liu[20] and Xiao[21] groups have demonstrated the conversion of aliphatic hydroxyl groups directly into difluoromethyl motifs. These methods, while pioneering, suffer from concerns about substrate scope as they

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are either limited to activated alcohols (benzylic/α-carbonyl) or necessitate the use of harsh reagents that are incompatible with complex pharmaceuticals. We envisioned that a mild and general one-step deoxygenative difluoromethylation procedure amenable to late-stage diversification would be of value to practitioners of medicinal chemistry.

Metallaphotoredox catalysis has emerged in recent years as a valuable platform for the construction of previously elusive $C(sp^3)-C(sp^3)$ bonds from common organic functionalities, including a variety of traditionally challenging fluorinated motifs.[22−28] Within this framework, conversion of a hydroxyl group to a difluoromethyl group would proceed through two stages: (i) activation of the hydroxyl group into a reactive intermediate and (ii) formation of the $C(sp^3)-CF_2H$ bond from this intermediate. Our laboratory recently disclosed a novel alcohol activation mode that converts aliphatic alcohols into their corresponding deoxygenated alkyl radicals via condensation of the alcohols with a benzoxazolium salt (termed "NHC") and subsequent photochemical oxidation.[29] We reasoned that an alkyl radical thus formed could react with a copper cocatalyst and an electrophilic CF_2H reagent to forge the desired $C(sp^3)-CF_2H$ bond, thereby achieving direct bioisostere replacement.

The overall reaction design is outlined in Figure 2. First, an aliphatic alcohol (**2**) is activated by in situ condensation with a

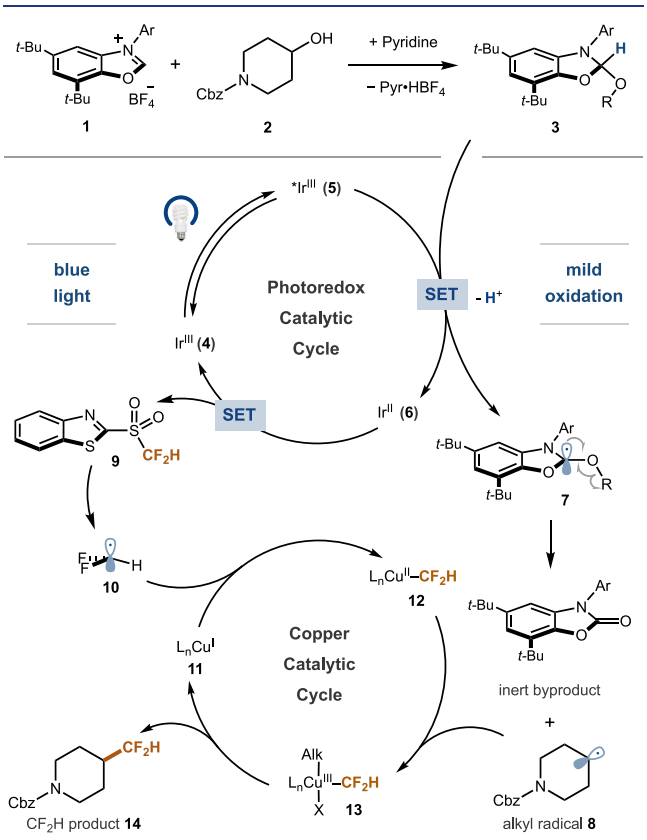
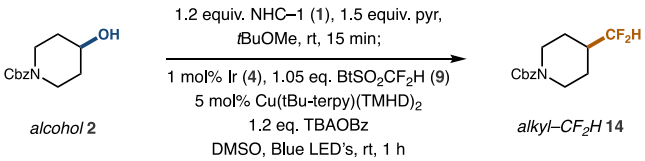


Figure 2. Proposed mechanism for deoxydifluoromethylation.

stoichiometric amount of an NHC salt (**1**) to form an amide acetal adduct (**3**). Excitation of the photocatalyst (**4**) produces a long-lived excited state (**5**) ($E_{1/2}^{red}[Ir^{III}*/Ir^{II}]$ = +0.66 V versus SCE) that can be reductively quenched by the adduct via single-electron transfer (SET).[29] Subsequent deprotonation of the now acidified methine C−H (pK_a = ∼10) provides an α-amino radical (**7**), which undergoes exothermic β-scission of the alcohol C−O bond to afford an alkyl radical (**8**) and 1 equiv of an inert aromatized byproduct. Single-electron reduction of an electrophilic CF_2H reagent[30] (**9**) by the reduced Ir^{II} photocatalyst (**6**) liberates difluoromethyl radical (**10**), which in the presence of Cu(I) (**11**) forms Cu(II)−CF_2H species (**12**). The alcohol-derived alkyl radical (**8**) is trapped onto the copper at near-diffusion-controlled rates to form a putative alkyl−Cu(III)−CF_2H complex (**13**) from which a favorable reductive elimination furnishes the desired difluoromethylated product (**14**).

Extensive optimization studies revealed that stirring N-Cbz-piperidin-4-ol (**2**) with NHC salt **1** (1.2 equiv) and pyridine (1.5 equiv) in methyl *tert*-butyl (MTBE) [0.1 M] followed by syringe filtration and subsequent 450 nm irradiation in the presence of $[Ir(dFMeppy)_2(dtbbpy)]PF_6$ (2 mol %), bis-(2,2,6,6-tetramethyl-3,5-heptanedionato)copper(II) [Cu-$(TMHD)_2$] (5 mol %), tri-*t*Bu-terpy (5 mol %), tetrabutylammonium benzoate (TBAOBz) (1.2 equiv), and electrophilic CF_2H reagent **9** (1.05 equiv) in 5:1 DMSO/MTBE [0.017 M] provided the desired product in 70% yield (Table 1, entry 1). We found this methodology to be relatively robust because it tolerates both oxygen and adventitious moisture (entries 2 and 3). Furthermore, the procedure is amenable to a variety of user-friendly modifications that facilitate the practical application of this protocol (entries 4−6). All catalysts and light are necessary for the efficient formation of the desired product (entries 7−10).

Table 1. Optimized Conditions and Control Reactions[a]



entry	deviation	yield[b]
1	none	70%
2	no degassing	67%
3	with 50 equiv of H_2O	58%
4	no preligation	60%
5	450 nm Kessil lamp	60%
6	no filtration (+1.2 equiv of TBAOBz)	65%
7	no photocatalyst	0%
8	no copper catalyst	0%
9	no ligand	26%
10	no light	0%

[a]Reactions performed on 0.05 mmol scale with alcohol (1 equiv), NHC-1 (1.2 equiv), pyridine (1.5 equiv), MTBE (0.10 M), 15 min; 2-[(difluoromethyl)sulfonyl]benzo[*d*]thiazole (1.05 equiv), TBAOBz (1.2 equiv), $Cu(TMHD)_2$ (5 mol %), *t*Bu-terpy (5.5 mol %), 5:1 DMSO/MTBE (0.017 M), integrated photoreactor (450 nm, 100% light intensity), 4 h. [b]Yield determined by ^{19}F-NMR analysis.

With these conditions in hand, we investigated the scope of this transformation (Table 2). We were pleased to observe that a variety of unactivated primary alcohols could be directly converted into their difluoromethyl analogues in good yields (**15**−**19**, 51−70% yield). Additionally, an array of structurally and electronically diverse unactivated secondary alcohols served as competent substrates in this transformation. Aliphatic acyclic secondary alcohols were difluoromethylated in good efficiencies (**20** and **21**, 70% and 58% yield). Furthermore, an

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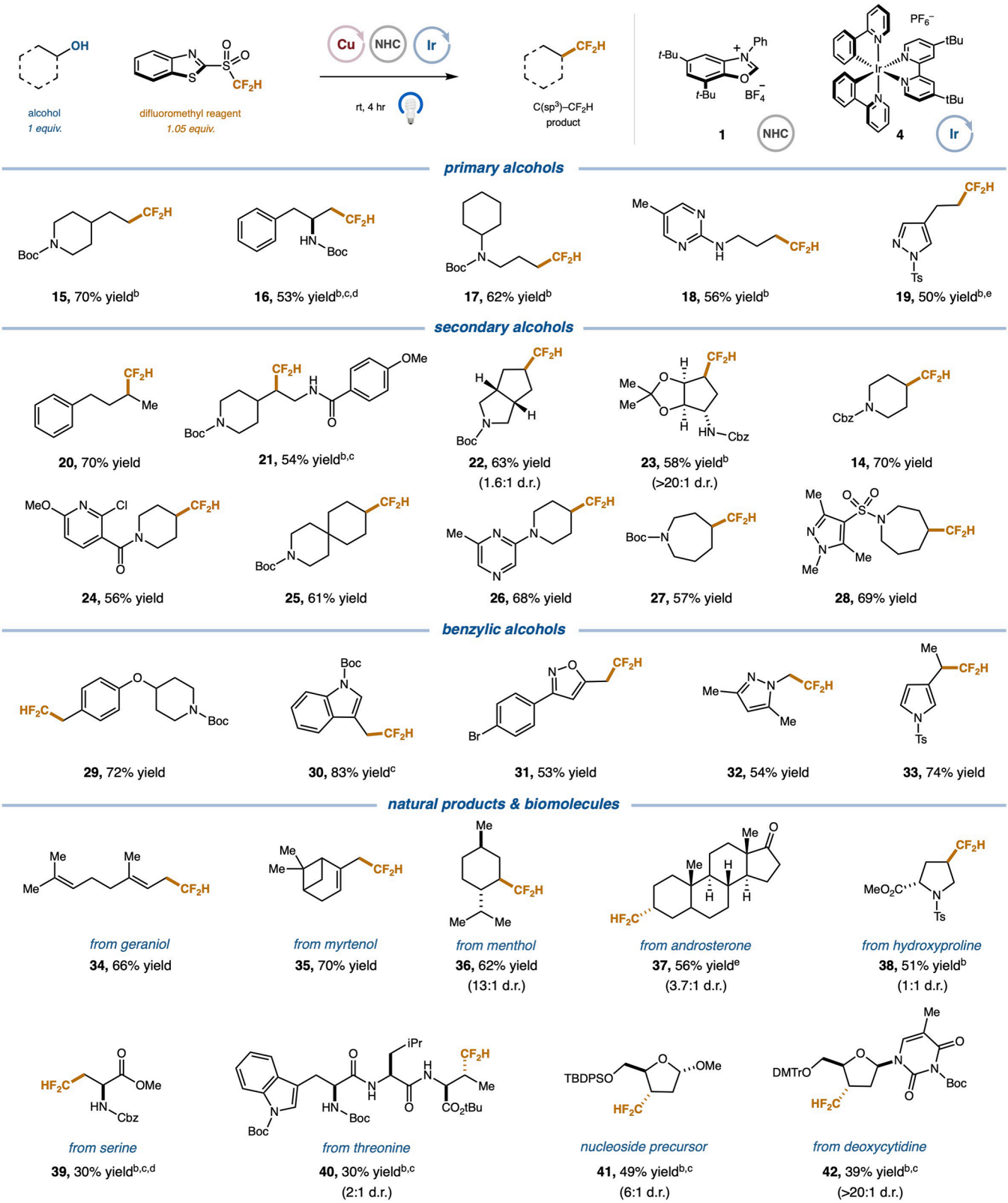
Table 2. Scope of Building Blocks and Biomolecules[a]



[a]Reactions performed on 0.5 mmol scale with alcohol (1 equiv), NHC-1 (1.2 equiv), pyridine (1.5 equiv), MTBE (0.10 M), 15 min; 2-[(difluoromethyl)sulfonyl]benzo[*d*]thiazole (1.05 equiv), TBAOBz (1.2 equiv), $Cu(TMHD)_2$ (5 mol %), *t*Bu-terpy (5.5 mol %), 5:1 DMSO/MTBE (0.017 M), integrated photoreactor (450 nm, 100% light intensity), 4 h. Yields are isolated unless otherwise specified. [b]Performed with *o*-OMe-NHC and $\{Ir[dF(Me)ppy]_2(dtbbpy)\}PF_6$ (2 mol %). See the Supporting Information for experimental details. [c]Copper loading deviates, see the Supporting Information. [d]>99% ee. [e]Yield determined by ^{19}F-NMR analysis.

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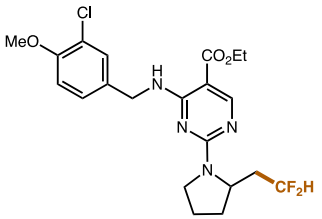
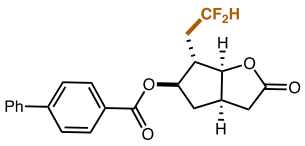
Table 3. Scope of Complex Alcohols and Pharmaceuticals[a]

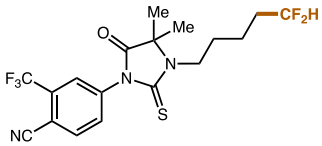
complex building blocks



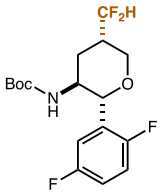
43, 43% yield[b,c]



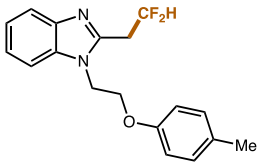
44, 59% yield[b]



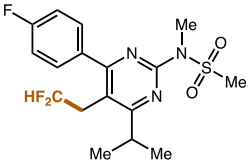
45, 43% yield[b,c]



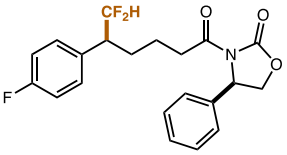
46, 64% yield[b] (2.3:1 d.r.)



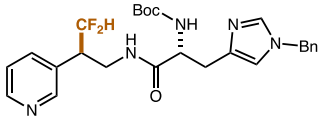
47, 74% yield



48, 85% yield

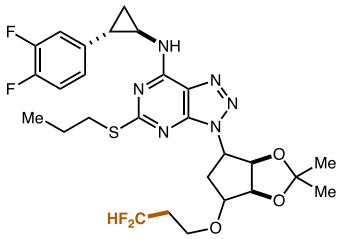


49, 55% yield (1:1 d.r.)



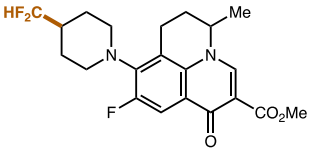
50, 52% yield[b] (1:1 d.r.)

pharmaceuticals



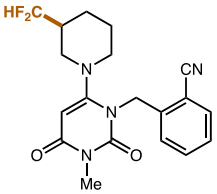
from ticagrelor

51, 45% yield[b,c]



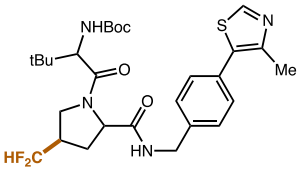
from nadifloxacin

52, 51% yield



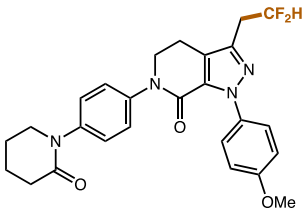
alogliptin analogue

53, 43% yield[b]



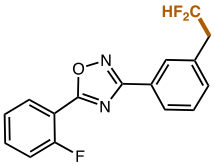
from VHL binder

54, 51% yield[b,c] (1:1 d.r.)



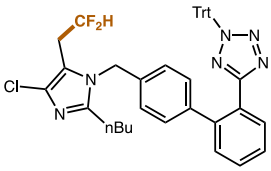
apixaban analogue

55, 89% yield



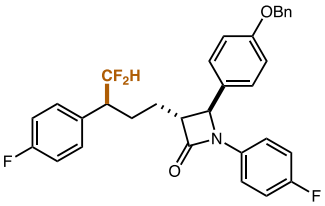
from ataluren

56, 75% yield



from losartan

57, 70% yield



from ezetimibe

58, 71% yield (1:1 d.r.)

[a]Reactions performed on 0.5 mmol scale with alcohol (1 equiv), NHC-1 (1.2 equiv), pyridine (1.5 equiv), MTBE (0.10 M), 15 min; 2-[(difluoromethyl)sulfonyl]benzo[*d*]thiazole (1.05 equiv), TBAOBz (1.2 equiv), $Cu(TMHD)_2$ (5 mol %), *t*Bu-terpy (5.5 mol %), 5:1 DMSO/MTBE (0.017 M), integrated photoreactor (450 nm, 100% light intensity), 4 h. All yields are isolated. [b]Performed with *o*-OMe-NHC and $\{Ir[dF(Me)ppy]_2(dtbbpy)\}PF_6$ (2 mol %). See the Supporting Information for experimental details. [c]Copper loading deviates; see the Supporting Information.

assortment of cyclic and heterocyclic difluoromethylated compounds bearing various functionalities were synthesized in good yields from five-membered (**21** and **22**, 63% and 58% yield), six-membered (**14** and **23**−**25**, 56−70% yield), and even seven-membered ring systems (**26** and **27**, 57% and 69% yield). Our studies demonstrated that this difluoromethylation protocol could be applied to primary and secondary benzylic alcohols to generate the desired products in high efficiencies (**29**−**33**, 53−83% yield). We next endeavored to apply this procedure to more complex alcohols, namely, those derived from naturally occurring biomolecules. To this end, we have successfully synthesized the difluoromethylated analogues of the terpenoid fragrances geraniol (**34**, 66% yield), myrtenol (**35**, 70% yield), and menthol (**36**, 62% yield), thereby demonstrating the potential utility of this method in the development of perfumes. Furthermore, the secondary alcohol-bearing hormone androsterone could be converted into its respective difluoromethylated analogue in good yield (**37**, 56% yield). Excitingly, alcohols derived from amino acids, such as hydroxyproline (**38**, 51% yield) and serine (**39**, 30% yield), could be difluoromethylated in synthetically useful yields, thereby allowing for access to noncanonical amino acids in one step. Furthermore, this transformation could be implemented toward a threonine-containing peptide in synthetically useful yield (**40**, 30% yield), which demonstrates a late-stage application of this method. Finally, this method allows direct

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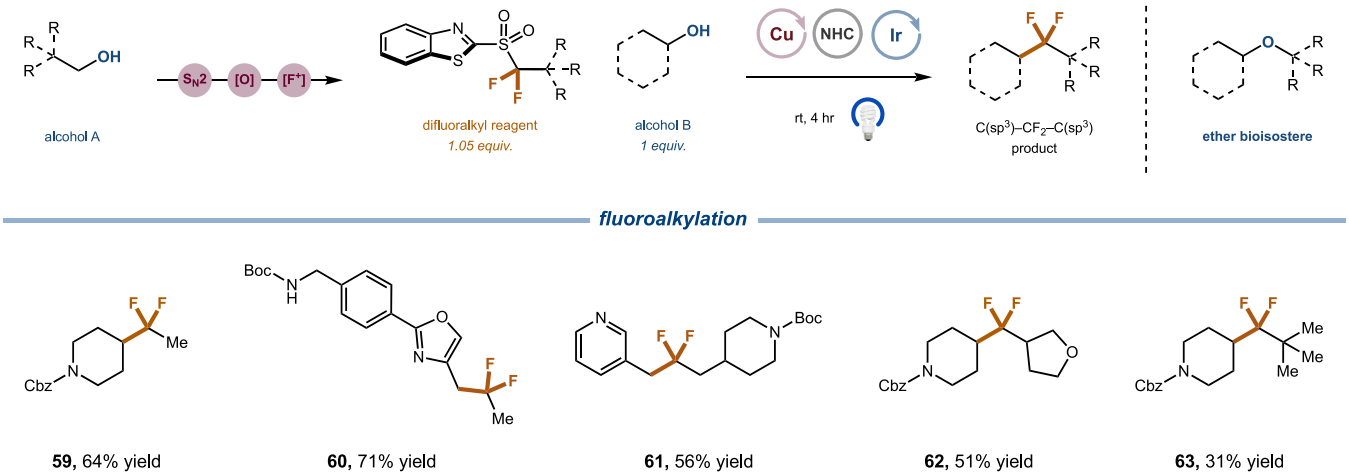
Table 4. Scope of Difluoroalkylation[a]



[a]Reactions performed on 0.5 mmol scale with alcohol (1 equiv), *o*-OMe-NHC (1.2 equiv), pyridine (1.5 equiv), MTBE (0.10 M), 15 min, difluoroalkyl sulfone (1.05 equiv) TBAOBz (1.2 equiv), $Cu(TMHD)_2$ (10 mol %), *t*Bu-terpy (11 mol %), 5:1 DMSO/MTBE (0.017 M), integrated photoreactor (450 nm, 100% light intensity), 4 h. All yields are isolated.

access to difluoromethylated nucleoside analogues. Difluoromethylated deoxyribose (**41**, 49%) was obtained in useful yield; this product can serve as a linchpin intermediate toward the synthesis of difluoromethylated deoxynucleoside analogues, which have remained rare and unexplored motifs in the medicinal chemistry literature.[31] Moreover, direct deoxydifluoromethylation of protected deoxycytidine could be achieved in a synthetically useful yield (**42**, 39% yield), thereby allowing access to this coveted motif in one step.

We next explored the deoxydifluoromethylation of complex druglike compounds with the goal of demonstrating the potential of the method to serve as a robust, late-stage functionalization platform (Table 3). Accordingly, a range of structurally and electronically diverse primary and secondary aliphatic difluoromethylated compounds were synthesized in good yields (**43**−**46**, 43−64% yield). Moreover, complex druglike benzylic primary and secondary alcohols served as excellent substrates for this transformation (**47**−**50**, 52−85% yield). Finally, we investigated the scope of this transformation in the context of hydroxyl-containing pharmaceutical molecules. We were pleased to find that a variety of difluoromethylated drug analogues could be synthesized. The primary alcohol of ticagrelor acetonide was transformed into the difluoromethyl group in moderate yield (**51**, 45% yield). Several piperidinol-based and pyrrolidinol drug compounds—nadifloxacin, alogliptin, and a VHL binder[32]—yielded product in good efficiencies (**52**−**54**, 43−51% yield). The primary benzylic alcohols on analogues of apixaban (**55**, 89% yield), ataluren (**56**, 75% yield), and losartan (**57**, 70% yield) were converted to difluoromethyl groups in good yields. Finally, ezetimibe bearing a secondary benzylic alcohol was difluoromethylated in a good yield (**58**, 71% yield).

Recognizing that alkylated analogues of difluoromethyl radical precursor **9** could be readily synthesized in a modular fashion from the corresponding alcohols, we next sought to expand this method to encompass difluoroalkylation. *gem*-Difluoroalkanes have garnered interest as powerful modulators of pharmacokinetic properties and in some cases have been investigated as bioisosteres of functional groups, such as ethers and carbonyls.[10,33−36] However, these motifs are typically prepared from the corresponding ketones via harsh deoxyfluorination procedures.[37−40] Given the late-stage applicability of our protocol, we aimed to gain access to difluoroalkylated products from the corresponding alcohols (Table 4). Gratifyingly, slight modifications to the procedure resulted in a method that facilitates the efficient transformation of alcohols into primary−secondary (**59**, 64% yield), primary−primary (**60** and **61**, 71% and 56% yield), secondary−secondary (**62**, 51% yield), and secondary−tertiary (**63**, 31% yield) difluoroalkyl products. The last example is noteworthy considering the synthetic challenges encountered in the preparation of the corresponding secondary−tertiary ethers.[41]

In summary, we present herein an efficient protocol for the direct interconversion of aliphatic alcohols into their difluoromethyl bioisosteres. This transformation is applicable to a diverse range of substrates, including primary and secondary small alcohols and various biologically relevant alcohols. The versatility of this method in late-stage applications was highlighted through the direct functionalization of a broad scope of complex druglike alcohols and pharmaceuticals. Furthermore, the protocol was expanded to allow for the efficient deoxygenative difluoroalkylation of diverse alcohols. We expect that this reaction will prove valuable to the medicinal chemistry community and foster the discovery of novel difluoromethylated and difluoroalkylated therapeutics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c14460.

Additional experimental details, mechanistic studies, compound characterization, and spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

David W. C. MacMillan − *Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States;* orcid.org/0000-0001-6447-0587; Email: dmacmill@princeton.edu

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Authors

Edna Mao − *Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States*

Cesar N. Prieto Kullmer − *Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States*

Holt A. Sakai − *Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.3c14460

Author Contributions

[§]These authors contributed equally.

Notes

The authors declare the following competing financial interest(s): D.W.C.M. declares a competing financial interest with respect to the integrated photoreactor.

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