HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2022 November 20.

Published in final edited form as:

J Am Chem Soc. 2022 July 13; 144(27): 11961–11968. doi:10.1021/jacs.2c04807.

Deoxytrifluoromethylation of Alcohols

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Abstract

Deoxy-functionalization of alcohols represents a class of reactions that has had a profound impact on modern medicine. In particular, deoxyfluorination is commonly employed as a means to incorporate high-value fluorine atoms into drug-like molecules. Recently, the trifluoromethyl (CF_3) group has garnered attention from medicinal chemists due to its ability to markedly improve the pharmaceutical properties of small-molecule drug candidates. To date, however, there remains no general means to accomplish the analogous deoxygenative trifluoromethylation of alcohols. We report herein a copper metallaphotoredox-mediated direct deoxytrifluoromethylation, wherein alcohol substrates are activated *in situ* by benzoxazolium salts for C(sp^3)–CF_3 bond formation.

The structural topology of drug candidates is inextricably linked to the state of the art of chemical synthesis.[1–4] Consequently, novel synthetic methods that provide access to underexplored chemical space can enable the discovery of breakthrough therapeutics.[5,6] Nowhere is this relationship more apparent than the case of fluorine in drug discovery.

While the benefit of fluoroalkyl groups in medicinal chemistry has long been understood,[7] it was not until robust synthetic methods for the construction of C–F bonds emerged that these motifs were viewed as feasible synthetic targets. Indeed, a stark increase in the number of fluorinated FDA-approved drugs occurred in the years following the first disclosure of deoxyfluorination reagents such as diethylamino-sulfur trifluoride (DAST) (Figure 1a).[8]

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Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c04807.
Additional experimental details, including procedures, photographs of experimental setup, characterization data, and spectra (PDF)

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

In recent years, the trifluoromethyl group has become one of the most widely utilized fluoroalkyl groups in drug discovery, due to its ability to increase drug potency and oral bioavailability while decreasing the rate of oxidative clearance.[9,10] In 2020 alone, nearly 10% of top selling small-molecule drugs contained at least one trifluoromethyl group. However, only 3% of these top selling drugs contain an aliphatic trifluoromethyl group [$C(sp^3)$–CF_3].[11] This discrepancy represents an opportunity for the development of novel $C(sp^3)$–CF_3 bond forming reactions.

Among limited examples to date, copper has emerged as the metal of choice for catalytic $C(sp^3)$–CF_3 bond formation. Facile reductive elimination from formal Cu(III) centers has enabled significant advancements in the trifluoromethylation of aliphatic radical precursors such as carboxylic acids,[12,13] alkyl bromides,[14,15] alkyl iodides,[16] xanthate esters,[17,18] and C–H bonds.[19–21] At present, however, the largest reservoir of aliphatic building blocks—the alcohol—remains underutilized for the construction of $C(sp^3)$–CF_3 bonds.

Alcohols are among the most abundant sources of functional $C(sp^3)$ carbon atoms (Figure 1b).[22–25] Chemical transformations, such as deoxyfluorination, that make use of this feedstock material have already proven critical to the treatment of human disease (*vida supra*), making alcohols the ideal precursors for aliphatic trifluoromethyl groups. By analogy, we anticipate that such a deoxytrifluoromethylation reaction would enable unprecedented access to fluorinated organic frameworks that are of paramount importance to global health. To this end, two pioneering methods have been developed. However, both protocols require activating the alcohols as xanthate esters in a separate synthetic step and either employ expensive CF_3 sources[17] or are limited in scope.[18] Consequently, there remains no general method for the direct conversion of native alcohols to aliphatic trifluoromethyl groups.[26]

Our group recently reported that N-heterocyclic carbene (NHC) precursors can condense with alcohols under mild conditions to form adducts susceptible to metallaphotoredox activation without any purification or workup. This discovery led to the development of a robust nickel-mediated deoxyarylation protocol.[27] Given the diversity of alcohol chemical matter, and the importance of trifluoromethyl groups in medicinal chemistry, we recognized an opportunity to exploit this activation mode for the deoxytrifluoromethylation of alcohols via copper metallaphotoredox catalysis (Figure 1c).

Our mechanistic design is detailed in Figure 2. We envisioned that aliphatic alcohol **1** would first be activated *in situ* by condensation with benzoxazolium salt **2**, forming NHC–alcohol adduct **3**. Excitation of photocatalyst **4** [$Ir(dF(OMe)ppy)_2(5,5'(CF_3)bpy)PF_6$] by blue light is known to produce a highly oxidizing excited state (**5**, $E_{1/2}^{red}[*Ir^{III}/Ir^{II}]$ = +1.60 V vs SCE in MeCN)[14] that could be quenched by **3** via single-electron transfer (SET). Subsequent deprotonation of the now acidified methine C–H (pK_a ~10)[27] would provide α-amino radical **7**, which can undergo exothermic β-scission[28] of the alcohol C–O bond to afford alkyl radical **9** and inert byproduct **8**. Concurrently, formal reduction of electrophilic CF_3 source **10** in the presence of Cu(I) is known to give rise to Cu(II)–CF_3 species[19] **12**, capable of trapping the newly generated alkyl radical **9** at near diffusion controlled rates.[29] Reductive

elimination from the resulting putative alkyl–Cu(III)–CF_3 complex **13** would furnish the desired aliphatic trifluoromethylated product **14**.[30]

Following an extensive optimization campaign, we identified the conditions outlined in Table 1 as optimal. Alcohol **15** was condensed with NHC salt **2** under mildly basic conditions, then subjected to irradiation with blue light, along with 1 mol % photocatalyst **4**, 5 mol % Cu(terpy)Cl_2 (**17**), 1.5 equiv of dMesSCF_3 (**10**), 1.6 equiv of quinuclidine, and 2 equiv of tetrabutylammonium chloride (TBACl) in DMSO. After 8 h, the trifluoromethylated product **16** was obtained in 84% yield. The presence of exogenous chloride anion (Cl^-) proved critical to the overall success of this transformation. Control experiments revealed that this effect is unique to soluble chloride sources and not general for other X-type ligands (see the SI for details). Prior work from our lab has shown that chloride anions can modulate the coordination sphere of copper complexes, resulting in a proposed shift in redox properties and reactivity.[19] While the exact role of Cl^- in the present transformation remains under investigation, preliminary data suggest this X-type ligand is suppressing off-cycle reduction of dMesSCF_3 (**10**) to fluoroform (CHF_3) by low-valent copper. This proposal is supported by four key observations: (1) in the absence of chloride anion, consumption of dMesSCF_3 is rapid and causes the reaction to stall; (2) unproductive consumption of dMesSCF_3 is mediated by both copper and light; (3) Cl^- modulates the ligand sphere of Cu^I(terpy)Cl as measured by UV–vis spectroscopy; (4) Cl^- suppresses reduction of dMesSCF_3 by Cu^I(terpy)Cl. For a more detailed discussion, see Supporting Information Section 5.

Curiously, control experiments revealed that a modest yield of 27% was obtained in the absence of a photocatalyst but in the presence of 450 nm light (entry 5). This result suggests a minor background reaction possibly mediated by a photoactive copper species.[31]

With optimized conditions in hand, we sought to evaluate the scope of the present transformation. We were pleased to find that a variety of structurally diverse primary alcohols readily underwent deoxytrifluoromethylation in good to excellent yields (Table 2). Unactivated primary alcohols were trifluoromethylated to afford **18**, **19**, and **20** in 80%, 85%, and 66% yield, respectively. Alcohols proximal to cyclic (**21**, 77% yield) and acyclic (**22** and **23**) amines also underwent efficient bond formation (72–77% yield). Notably, a primary alcohol containing a coordinating pyrazole moiety was trifluoromethylated to afford **24** in 68% yield.

In addition, activated, benzylic alcohols were trifluoromethylated in good to high yields (**25**, 82% yield) including those bearing a pyridinyl nitrogen in the 2- (**26**, 63% yield), 3- (**27**, 75% yield), and 4- (**28**, 49% yield) position. Gratifyingly, a hindered neopentyl alcohol was trifluoromethylated to deliver **29** in a synthetically useful 44% yield.

We next turned our attention to secondary alcohols. A variety of cyclic substrates of different ring sizes were well tolerated in this transformation, allowing construction of the desired C(sp^3)–CF_3 bond in good to excellent yields (**14**, **16**, **30**–**35**, 52–86% yield). Bicyclic and spirocyclic ring systems, often used as bioisosteres for saturated heterocycles,[32] were trifluoromethylated in 56–72% yield (**36** and **37**) and 54–70% yield (**38**–**40**). Acyclic

secondary phenyl butanol underwent deoxytrifluoromethylation to give **41** in 74% yield. Notably, alcohols bearing reactive functional groups, such as alkyl bromides, were amenable to trifluoromethylation, delivering product **42** (79% yield), which is poised for orthogonal functionalization. Lastly, it is important to note that the carboxylic acids and alkyl bromides corresponding to Cbz-prolinol (**21**), bicyclic lactone (**37**), and [3.3]spirocycle (**38**) either are not commercially available or are prohibitively expensive, highlighting the practical utility of this new alcohol-based cross-coupling protocol.[33]

Quaternary trifluoromethylaryl cyclopropanes are of particular interest to medicinal chemists for their ability to function as bioisosteres for aryl *tert*-butyl groups.[34,35] Traditionally, these motifs are prepared through a multistep synthetic sequence requiring the use of hazardous reagents and forcing temperatures.[36] Although significant progress has been made in the last 5 years,[37] the synthesis of these fluoroalkyl groups remains a significant challenge. To this end, we subjected a series of arylcyclopropanols to a modified set of reaction conditions (see Supporting Information Section 7) and were delighted to observe that the desired trifluoromethylated quaternary center was formed in good to high yields (**43**–**45**, 54–74% yield). For additional examples and limitations see the Supporting Information, Table S9.

From the outset, we sought to develop a deoxytrifluoromethylation protocol that would be compatible with the structural idiosyncrasies of drug discovery campaigns.[6] Accordingly, we subjected a series of “drug-like” alcohols to this deoxytrifluoromethylation protocol (Table 3). We were pleased to find pyrazole and isoxazole sulfonamides delivered the desired products (**46** and **47**) in 86% and 72% yield, respectively. The successful synthesis of isoxazole **47** is of particular significance, given the propensity for the N–O bond to be cleaved via oxidative addition by low-valent metals.[38] Additionally, aryltriazole **48** and triazolopyrazine **49** were obtained from the corresponding alcohols in modest to good yields (44% and 54% yield, respectively).

Initial attempts to synthesize aminopyrimidine **50** under the standard protocol were beset by poor yields and observation of side products by UPLC/MS resulting from oxidation of the piperidine nitrogen.[39] By simply changing to a less oxidizing photocatalyst ($[Ir(F(Me)ppy)_2(dtbbpy)PF_6]$, $E_{1/2}^{red}[*Ir^{III}/Ir^{II}]$ = +0.77 V vs saturated calomel electrode (SCE) in MeCN)[40] we were able to suppress the formation of these oxidative byproducts and forge the desired $C(sp^3)$–CF_3 bond in 62% yield. Using these same modified conditions, chloropyridazine **51** was also obtained in 50% yield.

Installation of small trifluoromethylated alkyl groups on complex heteroarenes is often accomplished through Negishi coupling.[41] Although highly effective, this protocol requires that the corresponding organometallic reagent must first be made from an alkyl halide. An orthogonal strategy that harnesses widely available alcohols as coupling partners would greatly expand synthetic accessibility to this chemical space. Accordingly, we investigated the use of small diols as precursors to esoteric trifluoromethylated alkyl groups. We adopted an iterative functionalization strategy to synthesize complex pyrazolopyridine **54** in two steps from commercially available materials. Initial arylation of diol **52** under conditions previously reported by our group[27] delivered the monoarylated intermediate **53**

in 47% yield while leaving the second alcohol untouched. Exposure of this alcohol to deoxytrifluoromethylation delivered **54** in 68% yield.

Monosaccharides serve as building blocks for biologically important macromolecules, and fluorination of their highly oxygenated skeletons has the potential to greatly alter their physical properties.[42,43] As shown in Table 4, protected glucose **55** and furanose **56** were obtained via deoxytrifluoromethylation in 65% and 79% yield, respectively. Additionally, deoxyribose **57** was obtained in a synthetically useful 32% yield. Although modest in yield, we anticipate this building block can serve as a precursor to a library of synthetically challenging trifluoromethylated nucleoside analogues (*vide infra*).

At this stage we turned our attention to the long-standing challenge of synthesizing trifluoromethylated nucleoside derivatives. There are few published examples of nucleoside analogues with trifluoromethyl groups at the 3′ position of deoxyribose. Traditionally, these molecules require up to 11 synthetic steps to access.[44–49] Recently, Cook et al. reported a two-step approach to a 3′-(CF_3)-thymidine derivative, a major advancement in this field.[17] We were interested in further accelerating the synthesis of these targets by employing our one-step deoxytrifluoromethylation protocol. Pleasingly, direct trifluoromethylation of the 3′ hydroxyl group in dimethoxytrityl (DMT)-protected thymidine could be achieved in 38% yield (**58**). Two additional nucleosides, DMT-adenosine and DMT-5-methylcytidine, were also trifluoromethylated in 31% (**59** and **60**) yield. Although these products are formed in modest yield, the protocol described herein dramatically reduces the amount of time, effort, and resources required to access these elusive structures. Finally, we demonstrated the utility of our deoxytrifluoromethylation protocol in the context of late-stage functionalization of pharmaceutical agents. To our delight, a derivative of the cardiovascular drug Ticagrelor (**61**) was trifluoromethylated to deliver **62** in 63% yield.

In summary, we describe herein an efficient protocol for the direct deoxytrifluoromethylation of alcohols. A wide range of substrates are amenable to this transformation, including primary, secondary, and tertiary alcohols, monosaccharides, nucleosides, and complex drug-like molecules. We anticipate that this reaction will be of value to the medicinal chemistry community and will serve to accelerate the discovery of novel trifluoromethyl-containing therapeutics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors are grateful for financial support provided by the National Institute of General Medical Sciences (NIGMS), the NIH (under Award R35GM134897-02), the Princeton Catalysis Initiative, and kind gifts from Pfizer, MSD, Janssen, Bristol-Myers Squibb, and Genentech. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIGMS. N.E.I. and D.L.D. thank Princeton Universty, E. Taylor, and the Taylor family for an Edward C. Taylor Fellowship. A.M. acknowledges support from BioLEC (Bioinspired Light-Escalated Chemistry), an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, Basic Energy Sciences, under Award #DE-SC0019370. The authors thank Z. Dong, P. Sarver, and V. Bacauanu for helpful scientific discussions, B. Li and H. Sakai for graphic design support, and R. Lambert for assistance in preparing the manuscript.

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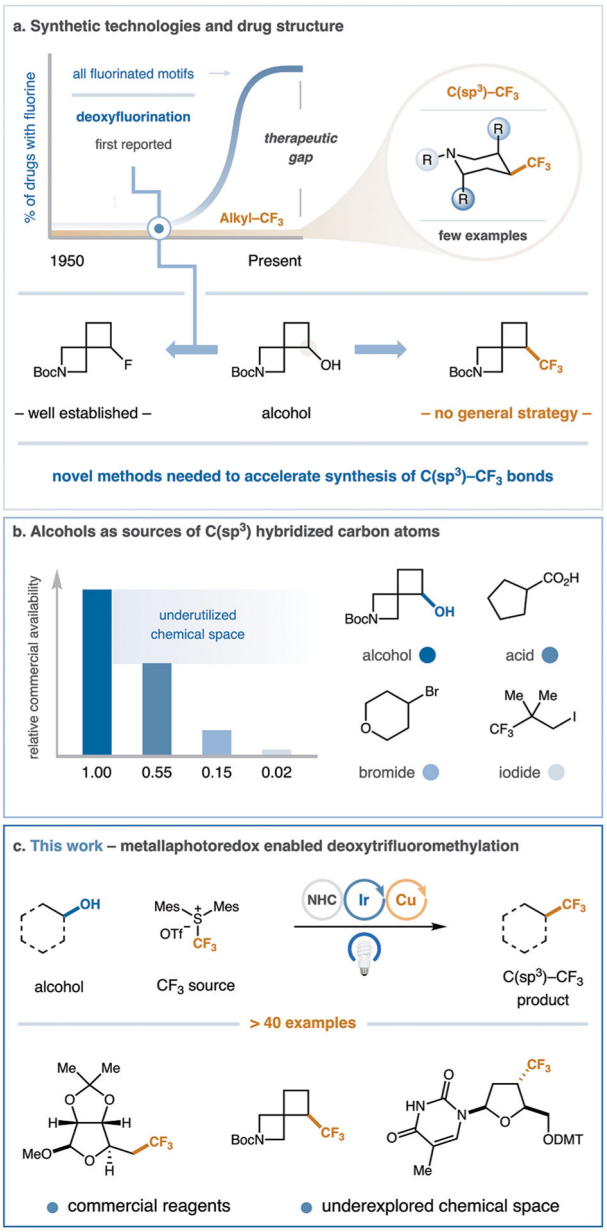


Figure 1.
Deoxytrifluoromethylation of alcohols.

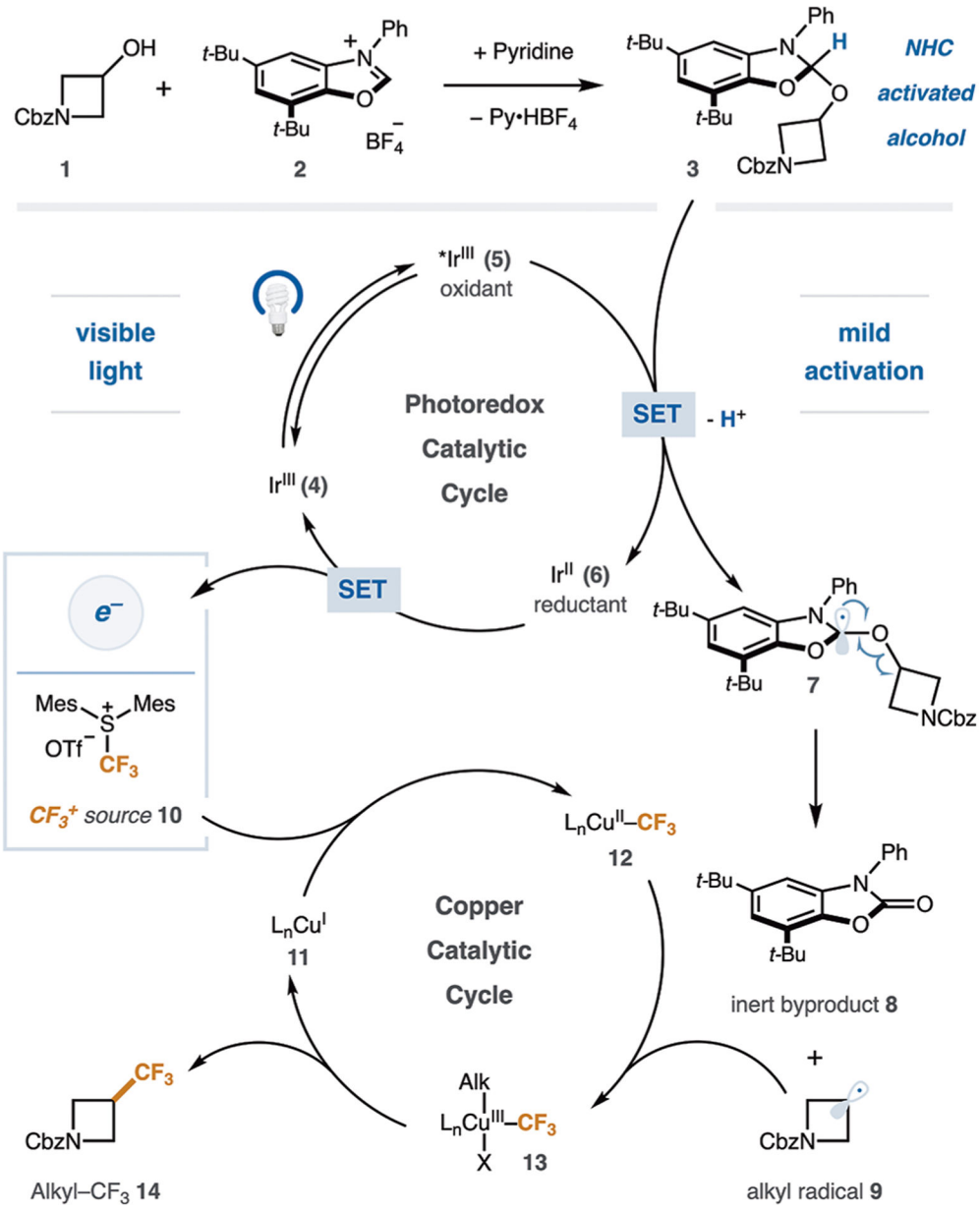
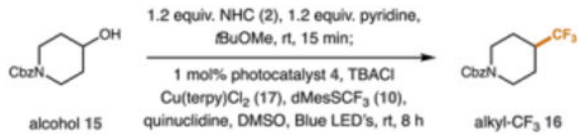


Figure 2.
Plausible mechanism for deoxytrifluoromethylation.

Table 1.

Control Reactions of Optimized Conditions[a]



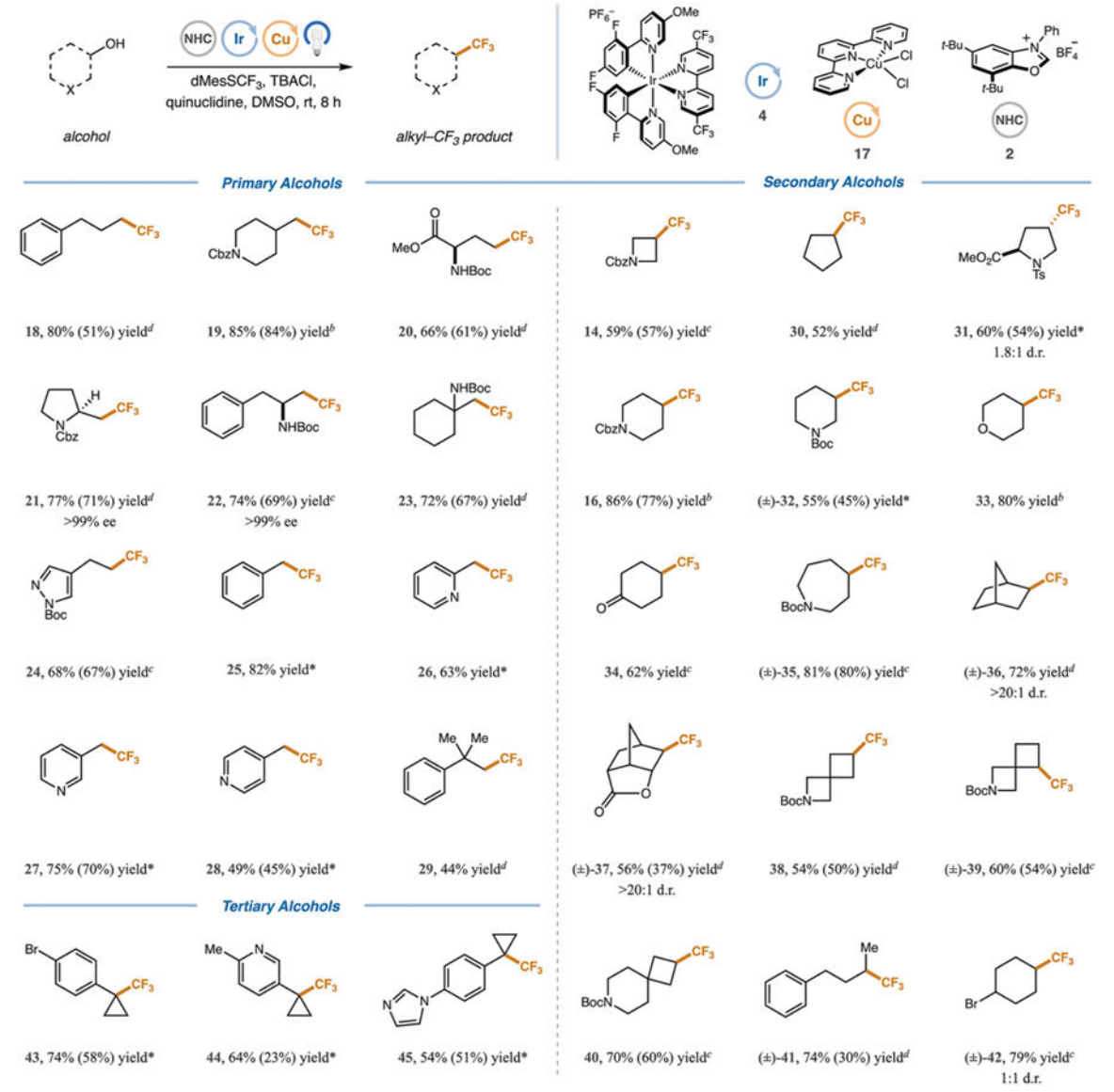
entry	deviation	yield[b]
1	none	84%
2	NaCl instead of TBACl	74%
3	$CuCl_2$ instead of Cu(terpy)Cl_2	80%
4	no TBACl	41%
5	no photocatalyst	27%
6	no copper catalyst	0%
7	no photocatalyst, no TBACl	12%
8	no light	0%

[a]Reactions performed with alcohol (1.0 equiv), Cu(terpy)Cl_2 (5 mol %), dMesSCF_3 (1.5 equiv), TBACl (2 equiv), quinuclidine (1.6 equiv), DMSO (0.025M), integrated photoreactor (450 nm, 100% light intensity).

[b]Yields determined by ^{19}F NMR analysis using 1,4-difluorobenzene as internal standard. See the SI for experimental details.

Table 2.

Scope of Metallaphotoredox-Enabled Deoxygenative Trifluoromethylation Reaction[a]



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[a]Performed on a 0.5 mmol scale with alcohol (1.0 equiv), **2** (1.2 equiv), pyridine (1.2 equiv), *t*BuOMe (0.1 M), $Ir(dF(OMe)ppy)_2(5,5'(CF_3)bpy)PF_6$ (1 mol %), $dMesSCF_3$ (1.5 equiv), TBACl (2 equiv), quinuclidine (1.6 equiv), DMSO (0.025 M), integrated photoreactor (450 nm, 100% light intensity). Due to volatility of products, yields were determined by ^{19}F NMR analysis of the crude reaction mixture using 1,4-difluorobenzene as an internal standard. Isolated yields are in parentheses.

[b]With $Cu(terpy)Cl_2$ (5 mol %).

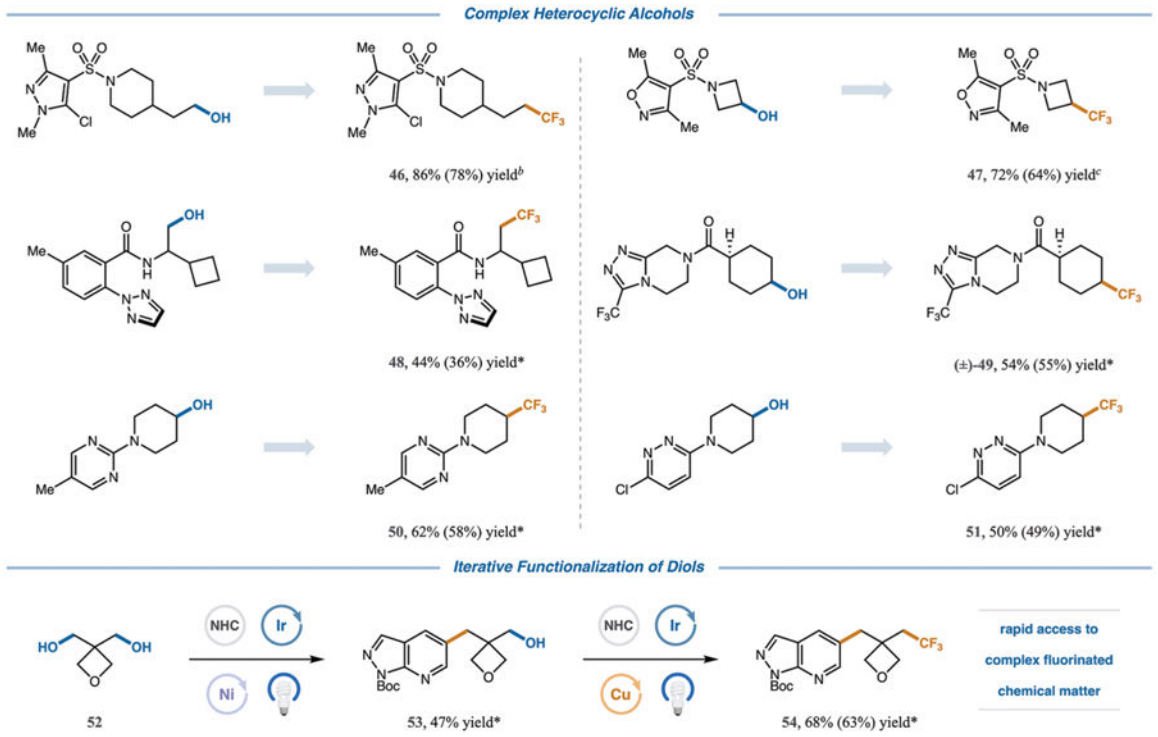
[c]With $Cu(terpy)Cl_2$ (7.5 mol %).

[d]With $Cu(terpy)Cl_2$ (10 mol %).

[*]Reaction performed under modified conditions; see the SI for details.

Table 3.

Application of Deoxygenative Trifluoromethylation to Complex Heterocyclic Alcohols[a]



[a]Performed on a 0.5 mmol scale with alcohol (1.0 equiv), **2** (1.2 equiv), pyridine (1.2 equiv), tBuOMe (0.1 M), $Ir(dF(OMe)ppy)_2(5,5'(CF_3)\text{-}bpy)PF_6$ (1 mol %), $dMesSCF_3$ (1.5 equiv), TBACl (2 equiv), quinuclidine (1.6 equiv), DMSO (0.025 M), integrated photoreactor (450 nm, 100% light intensity). Assay yields were determined by ^{19}F NMR analysis of the crude reaction mixture using 1,4-difluorobenzene as an internal standard. Isolated yields are in parentheses.

[b]With $Cu(terpy)Cl_2$ (10 mol %).

[c]With $Cu(terpy)Cl_2$ (7.5 mol %).

*Reaction performed under modified conditions, see the SI for details.

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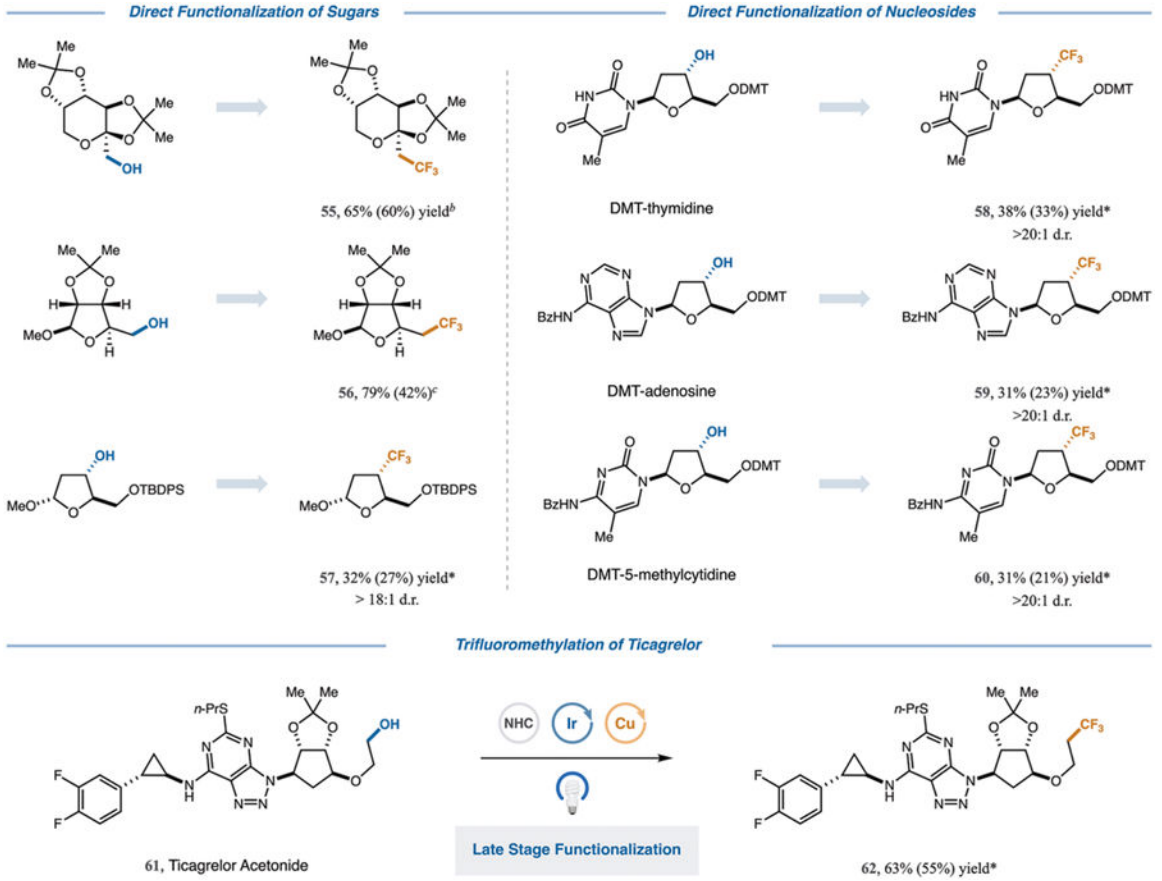
Table 4.

Direct Functionalization of Monosaccharides and Nucleosides[a]



[a]Performed on a 0.5 mmol scale with alcohol (1.0 equiv), **2** (1.2 equiv), pyridine (1.2 equiv), tBuOMe (0.1 M); $Ir(dF(OMe)ppy)_2(5,5'(CF_3)\text{-}bpy)PF_6$ (1 mol %), $dMesSCF_3$ (1.5 equiv), TBACl (2 equiv), quinuclidine (1.6 equiv), DMSO (0.025 M), integrated photoreactor (450 nm, 100% light intensity). Assay yields were determined by ^{19}F NMR analysis of the crude reaction mixture using 1,4-difluorobenzene as an internal standard. Isolated yields are in parentheses.

[b]With $Cu(terpy)Cl_2$ (10 mol %).

[c] With Cu(terpy)Cl_2 (5 mol %).

[*] Reaction performed under modified conditions, see the SI for details.