Deoxytrifluoromethylation of Alcohols

Nicholas E. Intermaggio, † Agustin Millet, † Dali L. Davis, and David W. C. MacMillan*

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 (CF₃) 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 benzoazolium salts for C(sp³)–CF₃ bond formation.

The structural topology of drug candidates is inextricably linked to the state of the art of chemical synthesis. Consequently, novel synthetic methods that provide access to underexplored chemical space can enable the discovery of breakthrough therapeutics. 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, 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 diethyldiamino-sulfur trifluoride (DAST) (Figure 1a). 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. 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(sp³)−CF₃]. This discrepancy represents an opportunity for the development of novel C(sp³)−CF₃ bond forming reactions.

Among limited examples to date, copper has emerged as the metal of choice for catalytic C(sp³)−CF₃ 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, alkyl bromides, alkyl iodides, xanthate esters, and C−H bonds. At present, however, the largest reservoir of aliphatic building blocks—the alcohol—remains underutilized for the construction of C(sp³)−CF₃ bonds.

Alcohols are among the most abundant sources of functional C(sp³) carbon atoms (Figure 1b). 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 CF₃ sources or are limited in scope. Consequently, there remains no general method for the direct conversion of native alcohols to aliphatic trifluoromethyl groups.

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. 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 benzoazolium salt 2, forming NHCl–alcohol adduct 3. Excitation of photocatalyst 4 [Ir(dF(OMe)ppy)₂₅S(CF₃)bpy]PF₆ 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) that could be quenched by 3 via single-electron transfer (SET). Subsequent deprotonation of the now acidified methine C−H (pKₐ ~10)²⁵ would provide α-amino radical 7, which can

Received: May 5, 2022
Published: July 5, 2022

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undergo exothermic $\beta$-scission\textsuperscript{28} of the alcohol C–O bond to afford alkyl radical 9 and inert byproduct 8. Concurrently, formal reduction of electrophilic CF$_3$ source\textsuperscript{10} in the presence of Cu(I) is known to give rise to Cu(II)–CF$_3$ species\textsuperscript{19} \textsuperscript{12}, capable of trapping the newly generated alkyl radical 9 at near diffusion controlled rates.\textsuperscript{29} Reductive elimination from the resulting putative alkyl–Cu(III)–CF$_3$ complex\textsuperscript{13} would furnish the desired aliphatic trifluoromethylated product\textsuperscript{14}.\textsuperscript{30}

Following an extensive optimization campaign, we identified the conditions outlined in Table 1 as optimal. Alcohol 15 was condensed with NHC salt\textsuperscript{2} under mildly basic conditions, then subjected to irradiation with blue light, along with 1 mol % photocatalyst\textsuperscript{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.\textsuperscript{19} While the exact role of Cl$^-$ in the present transformation remains under investigation, prelimi-

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**Table 1. Control Reactions of Optimized Conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>NaCl instead of TBACl</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>CuCl$_2$ instead of Cu(terpy)Cl$_2$</td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>No TBACl</td>
<td>41%</td>
</tr>
<tr>
<td>5</td>
<td>No photocatalyst</td>
<td>27%</td>
</tr>
<tr>
<td>6</td>
<td>No copper catalyst</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>No photocatalyst, no TBACl</td>
<td>12%</td>
</tr>
<tr>
<td>8</td>
<td>No light</td>
<td>0%</td>
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\textsuperscript{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). \textsuperscript{b}Yields determined by $^{19}$F NMR analysis using 1,4-difluorobenzene as internal standard. See the SI for experimental details.
nary data suggest this X-type ligand is suppressing off-cycle reduction of dMesSCF₃ to fluoroform (CHF₃) by low-valent copper. This proposal is supported by four key observations: (1) in the absence of chloride anion, consumption of dMesSCF₃ is rapid and causes the reaction to stall; (2) unproductive consumption of dMesSCF₃ is mediated by both copper and light; (3) Cl⁻ modulates the ligand sphere of Cu₃(terpy)Cl as measured by UV–vis spectroscopy; (4) Cl⁻ suppresses reduction of dMesSCF₃ by Cu(terpy)Cl₂. 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

**Table 2. Scope of Metallaphotoredox-Enabled Deoxygenative Trifluoromethylation Reaction**

<table>
<thead>
<tr>
<th>Primary Alcohols</th>
<th>Secondary Alcohols</th>
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<tr>
<td>18, 80% (51%) yield</td>
<td>14, 59% (57%) yield</td>
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<tr>
<td>19, 85% (84%) yield</td>
<td>20, 66% (61%) yield</td>
</tr>
<tr>
<td>21, 77% (71%) yield</td>
<td>16, 86% (77%) yield</td>
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<tr>
<td>&gt;99% ee</td>
<td>(±)-32, 55% (45%) yield</td>
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<tr>
<td>24, 60% (67%) yield</td>
<td>33, 80% yield</td>
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<tr>
<td>25, 82% yield</td>
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<tr>
<td>26, 63% yield</td>
<td></td>
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<tr>
<td>27, 75% (70%) yield</td>
<td>38, 54% (50%) yield</td>
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<tr>
<td>28, 49% (45%) yield</td>
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<tr>
<td>29, 44% yield</td>
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<tr>
<td>30, 52% yield</td>
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<td>31, 66% (54%) yield</td>
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**Tertiary Alcohols**

| 43, 74% (58%) yield |
| 44, 64% (23%) yield |
| 45, 54% (51%) yield |
| 40, 70% (60%) yield |
| 48, 54% (30%) yield |
| 42, 79% yield |

**Notes:**
- 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′-(CF₃)-bpy)PF₆ (1 mol %), dMesSCF₃ (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 ¹⁹F NMR analysis of the crude reaction mixture using 1,4-difluorobenzene as an internal standard. Isolated yields are in parentheses. ³With Cu(terpy)Cl₂ (5 mol %). ²With Cu(terpy)Cl₂ (7.5 mol %). ³With Cu(terpy)Cl₂ (10 mol %). ⁴Reaction performed under modified conditions; see the SI for details.
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 deliver 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(sp3)−CF3 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, 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.

Quaternary triﬂuoromethylaryl cyclopropanes are of particular interest to medicinal chemists for their ability to function as bioisosteres for aryl tert-butyl groups. Traditionally, these motifs are prepared through a multistep synthetic sequence requiring the use of hazardous reagents and forcing temperatures. Although signiﬁcant progress has been made in the last 5 years, 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.

Table 3. Application of Deoxygenative Triﬂuoromethylation to Complex Heterocyclic Alcohols

| Complex Heterocyclic Alcohols | 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(S,S′(CF3)-bpy)PF6 (1 mol %), dMesSCF3 (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 19F NMR analysis of the crude reaction mixture using 1,4-diﬂuorobenzene as an internal standard. Isolated yields are in parentheses. | Performing under modified conditions, see the SI for details. | Cu(terpy)Cl2 (10 mol %). | Cu(terpy)Cl2 (7.5 mol %). | Reaction performed under modified conditions, see the SI for details. |

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**Iterative Functionalization of Diols**

52

[Chemical structure]

53, 47% yield

54, 68% (63%) yield

51, 50% (49%) yield

50, 62% (58%) yield

48, 44% (36%) yield

46, 86% (78%) yield

47, 72% (64%) yield

[Chemical structure]

[Chemical structure]

[Chemical structure]

[Chemical structure]

[Chemical structure]
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. 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. By simply changing to a less oxidizing photocatalyst ([Ir(F(Me)ppy)2(dtbbpy)PF6] (1 mol%), DMeSCF3 (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 19F NMR analysis of the crude reaction mixture using 1,4-difluorobenzene as an internal standard. Isolated yields are in parentheses. With Cu(terpy)Cl2 (10 mol %). With Cu(terpy)Cl2 (5 mol %). Reaction performed under modified conditions, see the SI for details.

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Installation of small trifluoromethylated alkyl groups on complex heteroarenes is often accomplished through Negishi coupling. 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 group37 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. As shown in Table 4, protected glucose 55 and furanose 56 were obtained via deoxy trifluoromethylation 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. Recently, Cook et al. reported a two-step approach to a 3’-(CF₃)-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 deoxy trifluoromethylation 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 deoxy trifluoromethylation 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 deoxy trifluoromethylation 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.

**ASSOCIATED CONTENT**

® 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)

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**Author Contributions**

†N.E.I. and A.M. 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.

**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 University, 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. Bacauan for helpful scientific discussions, B. Li and H. Sakai for graphic design support, and R. Lambert for assistance in preparing the manuscript.

**REFERENCES**

(9) Furet, P.; Guagnano, V.; Fairhurst, R. A.; Imbach-Weese, P.; Bruce, I.; Knapp, M.; Fritsch, C.; Blasco, F.; Blanz, J.; Aichholz, R.; Hamon, J.; Fabbro, D.; Caravatti, G. Discovery of NVP-BYL719 a Potent and Selective Phosphatidylinositol-3 Kinase Alpha Inhibitor


(21) SciFinder search from April 2022. "Prohibitive expensive" defined as >5× the cost of alcohol building block per 1 g of material.


