A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Direct C(sp3)–H Trifluoromethylation of Unactivated Alkanes Enabled by Multifunctional Trifluoromethyl Copper Complexes

Authors: Geunho Choi, Geun Seok Lee, Beomsoon Park, Dongwook Kim, and Soon Hyeok Hong

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202012263

Link to VoR: https://doi.org/10.1002/anie.202012263

WILEY-VCH

10.1002/anie.202012263

WILEY-VCH

RESEARCH ARTICLE

Direct C(sp^3)–H Trifluoromethylation of Unactivated Alkanes Enabled by Multifunctional Trifluoromethyl Copper Complexes

Geunho Choi[a],[c], Geun Seok Lee[a],[c], Beomsoon Park[a], Dongwook Kim[a],[b], and Soon Hyeok Hong*[a]

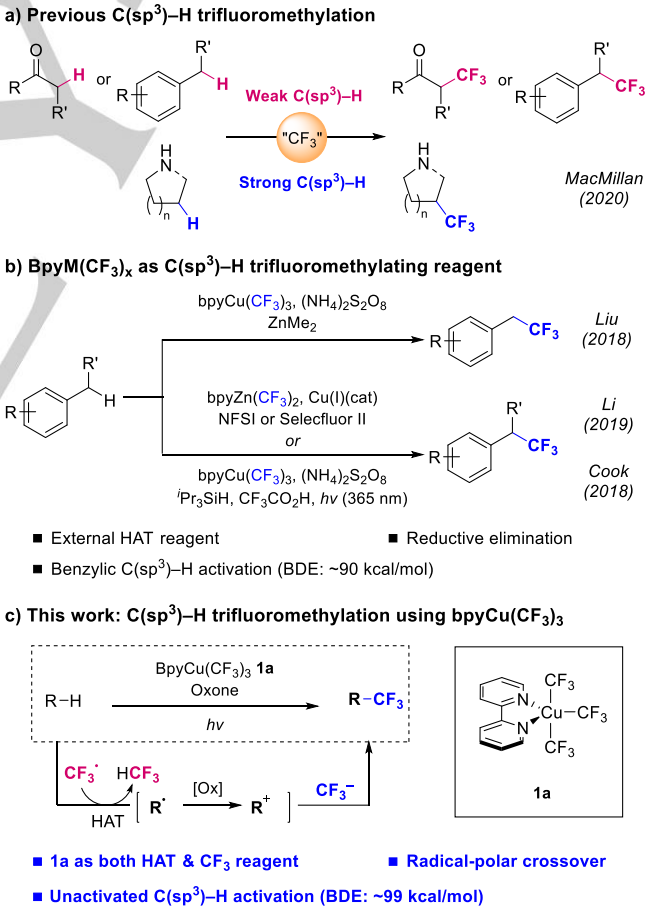
[a] G. Choi, G. S. Lee, B. Park, Dr. D. Kim, Prof. Dr. S. H. Hong
Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141 (Republic of Korea)
E-mail: soonhyeok.hong@kaist.ac.kr
[b] Dr. D. Kim
Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141 (Republic of Korea)
[c] G. Choi, G. S. Lee
Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 08826 (Republic of Korea)

Abstract: Despite the extensive development in trifluoromethylation, introduction of a trifluoromethyl group into an unactivated C(sp^3)–H bond is significantly challenging. Herein, we report the development of a mild and operationally simple C(sp^3)–H trifluoromethylation method for unactivated alkanes utilizing a bench-stable Cu(III) complex, bpyCu(CF$_3$)$_3$, as a visible-light photo-induced reaction initiator, a trifluoromethyl radical source as a hydrogen atom transfer reagent, and a trifluoromethyl anion source for functionalization. The reaction was initiated by reactive electrophilic carbon-centered CF$_3$ radical generation from photo-induced homolytic cleavage of bpyCu(CF$_3$)$_3$, which performs hydrogen abstraction from an unactivated C(sp^3)–H bond. Comprehensive mechanistic investigations based on a combination of experimental and computational methods suggested that C–CF$_3$ bond formation was enabled by radical-polar crossover and ionic coupling between the resulting carbocation intermediate and the anionic CF$_3$ source. The newly developed reaction can be applied to various methylene selective trifluoromethylation reactions including direct, late-stage trifluoromethylation of natural products and bioactive molecules.

Introduction

The introduction of a trifluoromethyl group to organic molecules is important for metabolic stability, lipophilicity, and hydrophobicity. Therefore, trifluoromethylation has attracted significant attention in the field of material, pharmaceutical, and agricultural chemistry to conveniently modulate the polarity, solubility, and chemical reactivity of desired compounds.[1] Various synthetic methods to form C–CF$_3$ bonds have been developed using nucleophilic,[2] electrophilic,[3] or radical[4] trifluoromethyl sources.

Direct formation of C–CF$_3$ bonds via C–H activation is ideal for trifluoromethylation in consideration of atom- and step-efficiencies. C(sp^2)–H trifluoromethylation reactions have been extensively developed to introduce trifluoromethyl groups on arenes,[5] heteroarenes,[6] olefins,[7] and aldehydes.[8] Although C(sp^2)–H trifluoromethylation has been significantly investigated, very few examples of C(sp^3)–H trifluoromethylation have been reported, employing a directing group,[9] and being only applicable to relatively more activated C(sp^3)–H bonds such as α-carbonyl,[10] α-nitrogen,[11] and benzylic C–H bonds (Scheme 1a).[12] Therefore, direct C(sp^3)–H trifluoromethylation of unactivated alkanes under mild conditions is highly desired to facilitate a streamlined synthesis of various trifluoromethylated compounds, obviating the need for pre-functionalization. During the preparation of this manuscript, MacMillan and co-workers reported trifluoromethylation of aliphatic C(sp^3)–H bonds combining decatungstate photocatalysis and copper catalysis by using the Togni reagent.[13] The elegant dual catalysis enabled the direct C–CF$_3$ bond formation at aliphatic and benzylic C(sp^3)–H bonds.



Scheme 1. Undirected C(sp^3)–CF$_3$ trifluoromethylation via C(sp^3)–H activation.

Considering a novel strategy for the direct trifluoromethylation of normal C(sp^3)–H bonds, we were inspired by the recently highlighted bpyM(CF$_3$)$_x$ (M = Cu, Zn; bpy = 2,2'-bipyridine) complexes[8, 9b, 14] due to their exceptional reactivity

10.1002/anie.202012263

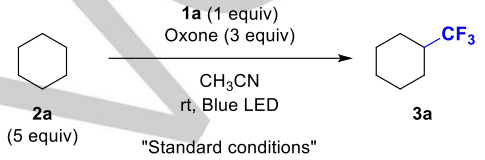
toward benzylic C(sp^3)–CF_3 trifluoromethylation (Scheme 1b). Li and co-workers introduced copper-catalyzed benzylic C(sp^3)–H trifluoromethylation using bpyZn$(CF_3)_2$ as the anionic trifluoromethyl source and *N*-fluorobenzenesulfonimide (NFSI) or Selectfluor as the oxidant and hydrogen atom transfer (HAT) reagent precursor.[12b] Liu and Cheng trifluoromethylated benzylic C(sp^3)–H bond by combining bpyCu$(CF_3)_3$ **1a** and Zn$(Me)_2$ to activate **1a** to bpyCu(II)$(CF_3)_2$ with the generation of $MeCF_3$.[12c] Cook and co-workers reported the trifluoromethylation of benzylic C(sp^3)–H with **1a** using persulfate, silane, and acid in acetone/water.[12a] UV-irradiation induces homolysis of **1a** to form the active bpyCu(II)$(CF_3)_2$ and CF_3 radical, while the sulfate radical anion performs the HAT from the benzylic C–H bond, generating the benzyl radical which is recombined with bpyCu(II)$(CF_3)_2$, followed by reductive elimination, for the desired trifluoromethylation. Especially, silane is required to capture the CF_3 radical to control the reactivity.

The ingenious strategy developed by Cook led us to consider a different strategy to functionalize unactivated C(sp^3)–H bonds in order to expand the scope from benzylic C(sp^3)–H bonds. Instead of using an externally added persulfate as the HAT reagent and trapping the reactive CF_3 radical with a silane to control the reactivity, we envisioned direct utilization of the highly reactive CF_3 radical without using an external HAT reagent. Based on the bond-dissociation energy (BDE) of fluoroform (106 kcal/mol),[15] the CF_3 radical is hypothesized to perform the HAT from unactivated C(sp^3)–H bonds of alkanes to generate alkyl radicals, which can further undergo Cu-complex-mediated trifluoromethylation. Although the CF_3 radical has been reported to perform the HAT from C–H bonds of various hydrocarbons to generate fluoroform,[16] to the best of our knowledge, no C–H functionalization reaction utilizing the CF_3 radical as the HAT reagent has been reported. Herein, a novel trifluoromethylation of unactivated C(sp^3)–H bonds was achieved by photo-induced bpyCu$(CF_3)_3$ **1a** based on the newly designed strategy (Scheme 1c). A series of control experiments and computational studies suggested that the reaction occurs via an ionic pathway enabled by an oxidative radical-polar crossover with the aid of an Oxone additive. Notably, the bench-stable Cu complex **1a** plays multiple roles of the photo-induced reaction initiator, trifluoromethyl radical source for HAT, and trifluoromethyl anion source, thus enabling direct trifluoromethylation of strong C(sp^3)–H bonds under mild conditions.

Results and Discussion

Cyclohexane **2a** was chosen as a model hydrocarbon substrate to evaluate the feasibility of the designed strategy with **1a** (Table 1). When **2a** (5.0 equiv) was reacted with **1a** (1.0 equiv) in the presence of Oxone (3.0 equiv) in CH_3CN (0.5 mL), (trifluoromethyl)cyclohexane **3a** was produced in 93% yield under blue light irradiation for 3 h (entry 1). Reducing the amount of **2a** (1 or 3 equiv) resulted in diminished yield (50% and 73%, entries 2–3, respectively), and further increasing **2a** content showed quantitative yield (>96%, entries 4–5). Decreased yield was afforded without Oxone (16%, entry 6) and with less than 3.0 equiv of Oxone (39 or 70%, entries 7–8, respectively). Control experiments in the dark demonstrated the critical role of irradiation to produce **3a** (entry 9). Altering the light source to the near ultraviolet region (390 nm) was not effective (21%, entry 10). A lower yield was obtained when the reaction was conducted under air (63%, entry 11). Another oxidant including a persulfate salt, $(NH_4)_2S_2O_8$, resulted in a lower yield (60%, entry 12). Other solvents, except CH_3CN, afforded lower product yield (Table S1). The conditions reported by Cook were not effective to afford **3a** in good yield (14%, entry 13) likely because the HAT from silane to the generated sulfate radical anion is faster than that from a C(sp^3)–H bond of **1a**, which has a higher BDE than a benzylic C(sp^3)–H bond.[12a]

Table 1. Variation of the reaction conditions.[a]



Entry	Variation from the "standard conditions"	Yield **3a** [%]
1[b]	None	93
2	1.0 equiv **2a**	50
3	3.0 equiv **2a**	73
4	16.0 equiv **2a**	>96
5	32.0 equiv **2a**	>96
6[c]	No Oxone	16
7	1.0 equiv Oxone	39
8	2.0 equiv Oxone	70
9	No light	N. D.
10	390 nm, instead of blue light	21
11	Under air in a closed vial	63
12	$(NH_4)_2S_2O_8$, instead of Oxone	60
13[d]	Cook conditions[12a]	14

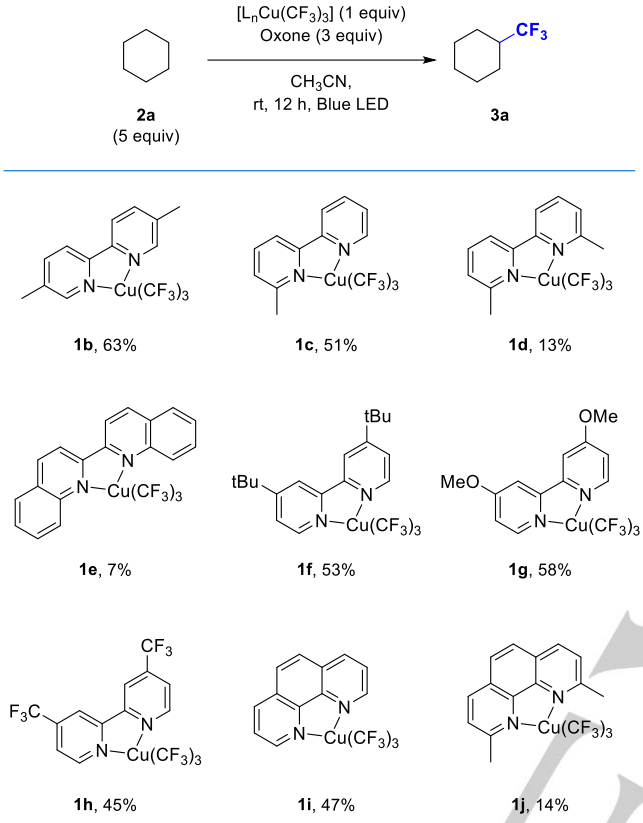
[a] Yields were determined by GC analysis using hexafluorobenzene as an internal standard. [b] Reaction conditions: **2a** (0.25 mmol, 5.0 equiv), **1a** (0.050 mmol, 1.0 equiv), Oxone (0.15 mmol, 3.0 equiv), and CH_3CN (0.5 mL) under 40 W blue LED irradiation with fan cooling (30±5 °C) for 3 h. [c] 12 h. [d] Reaction conditions: **2a** (0.10 mmol, 2.0 equiv), **1a** (0.05 mmol, 1.0 equiv), $(NH_4)_2S_2O_8$ (0.15 mmol, 3.0 equiv), $^iPr_3SiH$ (0.15 mmol, 3.0 equiv), trifluoroacetic acid (0.40 mmol, 8.0 equiv), acetone (0.3 mL), and water (0.3 mL) under 43 W 370 nm LED irradiation with fan cooling (30±5 °C) for 18 h. N. D. = not detected.

Under optimized conditions, the reactivity of various Cu(III)–CF_3 complexes bearing other *N,N*-bidentate ligands, bipyridines, and phenanthrolines, were investigated (Table 2). Among the bipyridine ligands tested, the simplest bipyridine performed best. Introduction of any substituent on the *ortho*, *meta*, or *para* positions to modify the steric and electronic characters of the ligand resulted in lower product yield (**1b**–**1h**). No clear correlation between electronic and steric characters of the ligand

10.1002/anie.202012263

and reaction outcome were observed. The absorption of the Cu(III) complexes was also examined, but no specific correlations between the absorptions and λ_{max} of the screened Cu complexes and the reaction yields were observed (Figure S1–5).

Table 2. Reactivity of various copper complexes.[a]

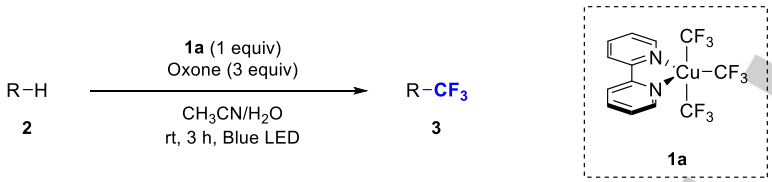


[a] Reaction conditions: **2a** (0.25 mmol, 5.0 equiv), **1** (0.050 mmol, 1.0 equiv), Oxone (0.15 mmol, 3.0 equiv), and CH_3CN (0.5 mL) under 40 W blue LED irradiation with fan cooling (30±5 °C) for 12 h; Yields were determined by GC analysis using hexafluorobenzene as an internal standard.

After investigating the reaction conditions, various hydrocarbon substrates were investigated to evaluate the generality of the newly developed photo-induced C–H trifluoromethylation protocol (Table 3). Although the conditions using anhydrous acetonitrile solvent performed best for **2a**, co-solvent conditions with water (CH_3CN/H_2O, 5:1 (v/v)) using 6.0 equiv hydrocarbon substrates were more effective for other C–H substrates, presumably due to increased solubility of Oxone. For instance, **2c** produced (trifluoromethyl)cycloheptane **3c** in 10% yield under the conditions without water. With the co-solvent conditions with water, the yield was dramatically increased to 84%, although 10% of cycloheptanone **4c** was observed as the by-product. Cyclic alkanes with varied ring sizes were efficiently converted to the corresponding trifluoromethylated products (**3a**–**3e**). The reactions with some substrates (**3e, 3j, 3l, 3m, 3q, 3u**) proceeded smoothly in hexafluoroisopropanol (HFIP) instead of CH_3CN. For example, cyclododecane **3e** furnished the desired product in 30% yield when HFIP was used as the solvent, whereas unidentified complex mixtures were obtained in CH_3CN solvent. Linear alkanes, including hexane (**2f**) and pentane (**2g**), readily underwent trifluoromethylation in very good yields with a preponderance on methylene positions (76 and 87% yields; 88 and 85% methylene selectivity, respectively), likely due to the enhanced stability of methylene radicals compared to primary methyl radicals. Benzylic C–H bonds in toluene could also be functionalized, but in a low yield (39%, **3h**) due to competing CF_3 radical addition to the aryl ring, which was suppressed when silane was used as a trapping reagent under Cook's conditions.[12a] Increased steric hindrance around the arene ring inhibited the undesired addition, affording the desired product in excellent yield (91%, **3i**). Carboxylic acids (**2j** and **2k**), an ester (**2l**), and an amide (**2m**) were also tolerated in this transformation. 1-Propanoic acid (**2j**) and methyl propanoate (**2l**) mostly underwent α-methylene C–H trifluoromethylation (47 and 71% yields; 85 and 82% α-selectivity, respectively), consistently demonstrating preference for the methylene C–H bond over terminal methyl C–H bond. Propanamide (**2m**) afforded the α-methylene C–H trifluoromethylated product (37%, **3m**) without significant byproduct formation. With 1-butanoic acid (**2k**), the more hydric β-methylene position was preferred over the α-methylene C–H bond (62% yield; 62% β-selectivity, **3k**). Other hydrocarbons containing a carbonyl group were trifluoromethylated with satisfactory yields, favoring functionalization on the more electron-rich C–H bonds due to the preference of the electrophilic CF_3 radical for HAT (**3n**–**3q**). Cyclic ketones including cyclopentanone (**2n**) and cyclohexanone (**2o**) afforded trifluoromethylated products favoring the β-methylene C–H position (58 and 80% yields; 79 and 73% β-selectivity, respectively). Especially, the linear carbonyl 4-heptanone (**2p**) was exclusively trifluoromethylated at the β-position of the carbonyl group rather than the α-methylene or γ-methyl position (88%, **3p**). The β-ketoester was also compatible with a major β-trifluoromethylation on the carbonyl group (48%, **3q**). Unfortunately, reactions using aliphatic amines such as *N*-Boc-pyrrolidine and *N*-acetylpyrrolidine were not compatible, producing messy unidentifiable compounds.

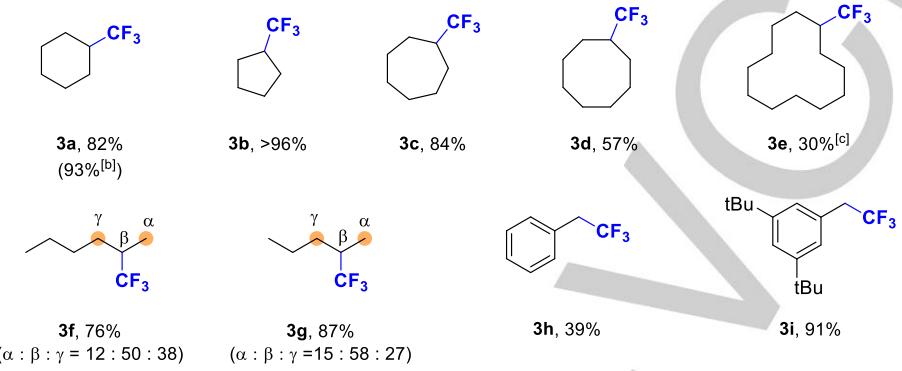
10.1002/anie.202012263

Table 3. Substrate scope of unactivated C(sp^3)–H trifluoromethylation.[a]



Substrate scopes

minor isomers



3a, 82% (93%[b])

3b, >96%

3c, 84%

3d, 57%

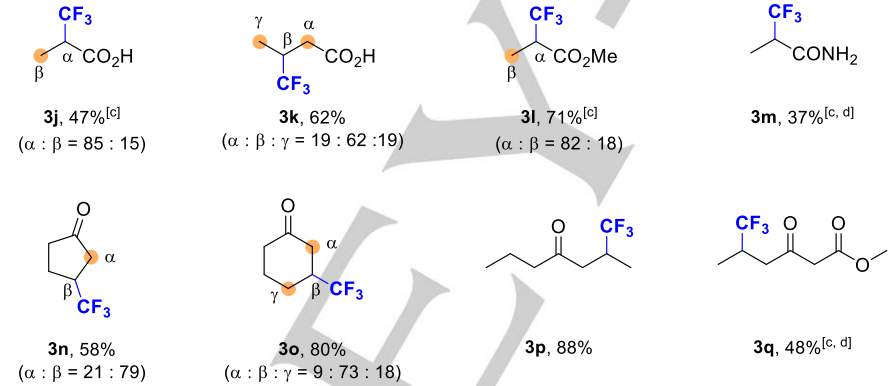
3e, 30%[c]

3f, 76% (α : β : γ = 12 : 50 : 38)

3g, 87% (α : β : γ =15 : 58 : 27)

3h, 39%

3i, 91%

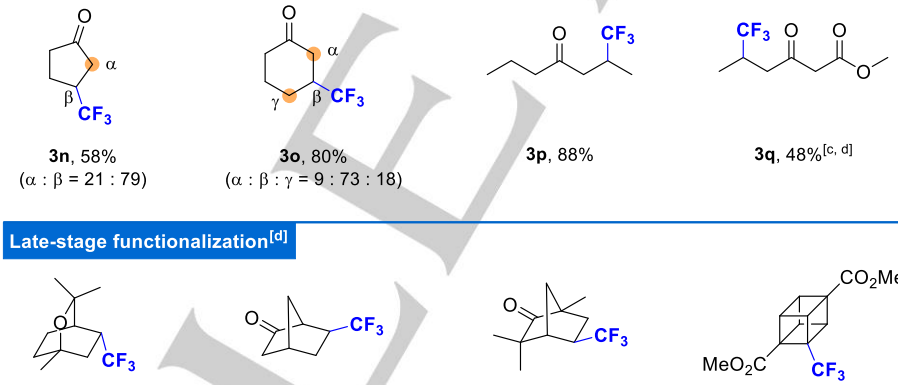


3j, 47%[c] (α : β = 85 : 15)

3k, 62% (α : β : γ = 19 : 62 :19)

3l, 71%[c] (α : β = 82 : 18)

3m, 37%[c, d]



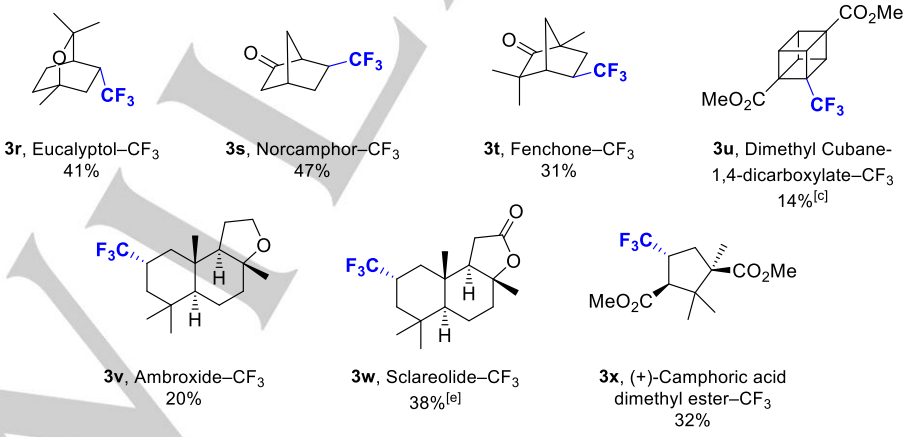
3n, 58% (α : β = 21 : 79)

3o, 80% (α : β : γ = 9 : 73 : 18)

3p, 88%

3q, 48%[c, d]

Late-stage functionalization[d]



3r, Eucalyptol–CF_3 41%

3s, Norcamphor–CF_3 47%

3t, Fenchone–CF_3 31%

3u, Dimethyl Cubane-1,4-dicarboxylate–CF_3 14%[c]

3v, Ambroxide–CF_3 20%

3w, Sclareolide–CF_3 38%[e]

3x, (+)-Camphoric acid dimethyl ester–CF_3 32%

[a] Reaction conditions: **2** (0.60 mmol, 6.0 equiv), **1a** (0.10 mmol, 1.0 equiv), Oxone (0.30 mmol, 3.0 equiv), CH_3CN (1.0 mL), and H_2O (0.2 mL) under 40 W blue LED irradiation with fan cooling (30±5 °C) for 3 h; Yields and selectivities (%) were determined by ^{19}F NMR using fluorobenzene as an internal standard unless otherwise noted. [b] Reaction conditions: **2a** (0.25 mmol, 5.0 equiv), **1a** (0.050 mmol, 1.0 equiv), Oxone (0.15 mmol, 3.0 equiv), and CH_3CN (0.5 mL) under 40 W blue LED irradiation with fan cooling (30±5 °C) for 3 h; Yields were determined by GC analysis using hexafluorobenzene as internal standard. [c] HFIP (2.0 mL) as a solvent. [d] Isolated yield. [e] **2w** (0.30 mmol, 3.0 equiv).

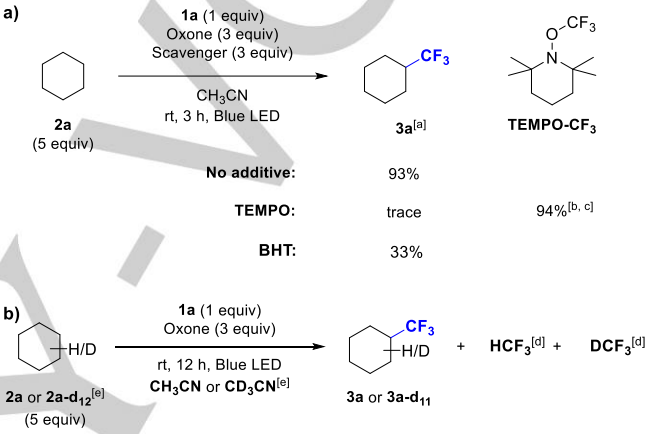
10.1002/anie.202012263

Trifluoromethyl group introduction can reportedly regulate bioactivity.[1b] Previously studied late-stage C–H trifluoromethylation mainly focused on C(sp^2)–H[6a, 17] and weak C(sp^3)–H bonds.[12a, 12b, 13] The applicability of the newly developed reaction was further examined with direct C(sp^3)–H trifluoromethylations of well-known natural products and bioactive molecule derivatives (Table 3). Eucalyptol, which has anti-inflammatory and antioxidant effects,[18] was smoothly trifluoromethylated with high regio- and diastereo-selectivities at the less sterically hindered position (41%, **3r**). Other bicyclic terpenoids such as norcamphor, the analog of the naturally occurring terpenoid camphor, and fenchone, which exhibits antifungal activity,[19] also delivered the desired C–H trifluoromethylated products (47%, **3s** and 31%, **3t**). Additionally, a cubane core, whose derivatives have not been trifluoromethylated, afforded **3u** in moderate yield (14%). Ambroxide, a naturally occurring terpenoid that is commonly used in the fragrance industry,[20] was trifluoromethylated to furnish a major 2-functionalized regioisomer albeit with low efficiency (20%, **3v**). It should be noted that trifluoromethylation was conducted in the sterically less-hindered cyclohexyl ring, but not at the α-oxy position, exhibiting an unusual trend compared to other radical-based C–H functionalization reactions.[21] Sclareolide, an antifungal plant compound,[22] showed a similar selectivity to ambroxide with higher yield (38%, **3w**). Finally, camphoric acid, which is often used as a precursor of bioactive molecules,[23] was used as a dimethyl ester derivative (**2x**) and was selectively trifluoromethylated at the least sterically hindered methylene position in a moderate yield (32%, **3x**). These results demonstrated the potential applicability of the developed reaction for late-stage, direct C–H trifluoromethylation of functional molecules with reasonable regio- and diastereo-selectivities favoring less-sterically hindered positions.

To determine the underlying reaction mechanism, several control experiments and computational studies were conducted. The intermediary of the CF_3 radical in the reaction was first examined (Table 4a). The liberation of the CF_3 radical from **1a** is experimentally and computationally well-documented.[12a, 14a, 14b] In agreement with the previous reports, introduction of a radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl radical) or BHT (2,6-di-*tert*-butyl-4-methylphenol), suppressed the trifluoromethylation of **2a**, with simultaneous formation of the **TEMPO–CF₃** adduct in 94% yield, clearly indicating that CF_3 radical formation is involved in the product-forming pathway.

Next, deuterium labelling experiments using deuterated cyclohexane (**2a-d₁₂**) and acetonitrile were conducted to determine the applicability of the generated CF_3 radical as the HAT reagent against the aliphatic C–H bonds (Table 4b). A sulfate radical, which can be generated from Oxone additive, was also reported as a HAT reagent that can activate C–H bonds.[8, 12a, 12c] However, as the reaction proceeded without Oxone, albeit in a lower yield (16%, Table 1, entry 6), it is unlikely that the HAT mediated by the sulfate radical is the major C–H activating process. With **2a** and **2a-d₁₂** as C–H substrates in a CD_3CN solvent, fluoroforms (HCF_3, >34% and DCF_3, >12%) were observed by ^{19}F NMR spectroscopy (entries 1–2). It should be noted that no DCF_3 was detected in the reaction with **2a** in CD_3CN indicating the reaction between a trifluoromethyl source and CD_3CN is not facile. Without cyclohexane, DCF_3 was not observed from the reaction between **1a** and CD_3CN, confirming that hydrogen or deuterium in the generated fluoroforms mainly originated from cyclohexane (entry 3). When the reaction was performed with **2a-d₁₂** in CH_3CN, DCF_3 (>8%) was observed along with a non-negligible amount of HCF_3 (>12%, entry 4). This may originate from HAT from CH_3CN because the reaction between **1a** and CH_3CN without cyclohexane generated HCF_3 (>40%, entry 5). These results clearly indicate that the trifluoromethyl radical serves as the HAT reagent in the reaction.

Table 4. Control experiments regarding the CF_3 radical as a HAT reagent.



Entry	**2a** or **2a-d₁₂**	Solvent	**3a** or **3a-d₁₁** [%]	HCF_3 [%]	DCF_3 [%]
1	**2a**	CD_3CN	35	>34	N. D.
2	**2a-d₁₂**	CD_3CN	17	>9	>12
3	-	CD_3CN	-	>5	N. D.
4	**2a-d₁₂**	CH_3CN	12	>12	>8
5	-	CH_3CN	-	>40	-

[a] Yields determined by GC analysis using hexafluorobenzene as an internal standard. [b] Yields determined by ^{19}F NMR analysis using fluorobenzene as an internal standard. [c] Product was confirmed by HRMS. [d] NMR tube reactions were performed. The amount of dissolved gaseous fluoroform was only determined by ^{19}F NMR analysis using fluorobenzene as an internal standard. [e] **2a-d₁₂** (99.5 D atom%); CD_3CN (99.8 D atom%). N. D. = not detected.

After identification of the CF_3 radical as the HAT reagent, three product forming pathways were proposed; (1) direct coupling between the alkyl and CF_3 radicals, (2) C–CF_3 reductive elimination via a Cu(III)–alkyl complex similar to recent reports on **1a**-mediated trifluoromethylation reactions,[12a, 12c, 14a, 14c] and (3) radical-polar crossover involving ionic coupling between an alkyl cation and trifluoromethyl anion. The first possibility, involving the selective coupling of two transient radical species, is unlikely because no homodimerization product was observed with or without Oxone. This indicates that the free alkyl radical species may not be sufficiently generated for the radical-radical coupling reaction. Secondly, reductive elimination is a viable pathway for C–CF_3 bond formation with **1a** as the trifluoromethylating reagent.

10.1002/anie.202012263

A Cu(II) complex has been proposed to trap a carbon-centered radical, subsequently forming the desired C–CF_3 bond via concerted reductive elimination.[12a, 12c, 14a, 14c] Recently, anionic or neutral alkyl-$Cu^{III}(CF_3)_x$ complexes were investigated to disclose that C(sp^3)–CF_3 bonds can be formed via concerted reductive elimination from a high-valent copper species.[24] Lastly, a radical-polar crossover pathway for the ionic coupling was proposed. In this case, alkyl radical, which has low oxidation potential (E^o_{calc}(**Cy-rad**/**Cy-cat**) = +0.46 V), is oxidized to generate an alkyl cation, followed by ionic coupling with a CF_3 anion for bond formation. C–X (X = F, CF_3) bonds can be formed via electron transfer from the alkyl radical to Cu^{II}–X.[14d, 25] We hypothesized that the oxidant can accelerate electron transfer from the alkyl radical, facilitating the radical-polar crossover pathway.

To determine the most viable pathway, density-functional theory (DFT) studies of the two proposed pathways were conducted with **2a** as model substrate at the B3LYP-D3/6-311++G**/SDD level of theory (Figure 1). Time-dependent density functional theory (TD-DFT) computations on complex **1a** revealed relevant singlet transitions in the blue light region, giving rise to **1a*** (Figure S15). This complex would then undergo intersystem crossing (ISC), traversing the triplet excited ^{3}**1a** to release CF_3 radical **CF_3-rad** and ^{2}**I**, as previously reported by the Cook group.[14a] Beginning with this species, HAT of **CF_3-rad** against cyclohexane **2a** is facile with a barrier of only 10.9 kcal/mol. This is reasonable considering the relative instability of the CF_3 radical and its electrophilic nature. After the HAT event, the reaction pathway could follow one of the two aforementioned mechanisms. The reductive elimination pathway (orange trace) involving the Cy–Cu(III) complex ^{1}**II** exhibited an overall barrier of 20.8 kcal/mol. All attempts to find alternative pathways of reductive elimination from ^{1}**II** with a lower energy barrier which can compete with the oxidative pathway (*vide infra*) were unsuccessful. The bisulfate ligand-assisted reductive elimination process, as proposed by the Cook group, has a computed activation barrier of 14.8 kcal/mol (Figure S14).[14a]

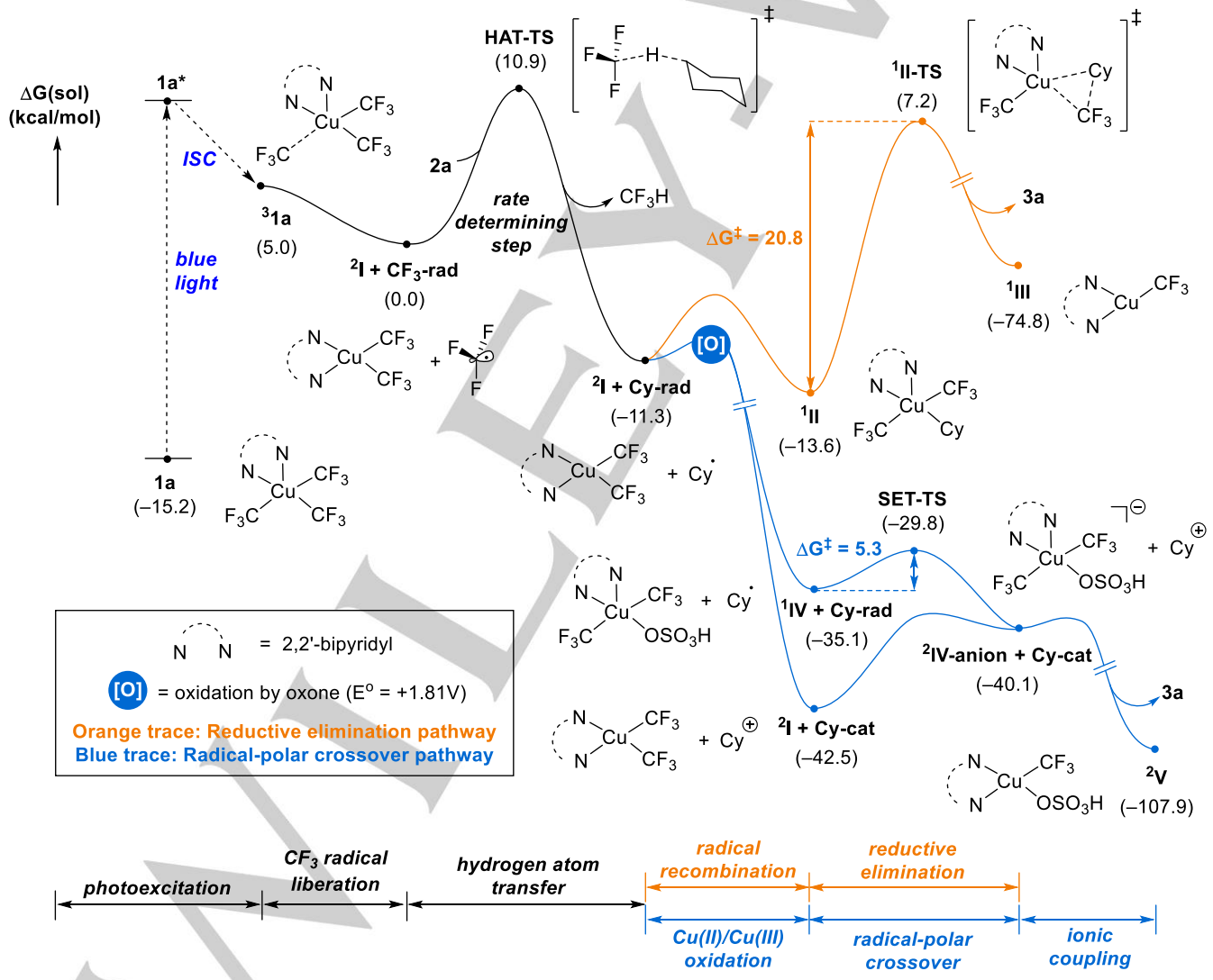
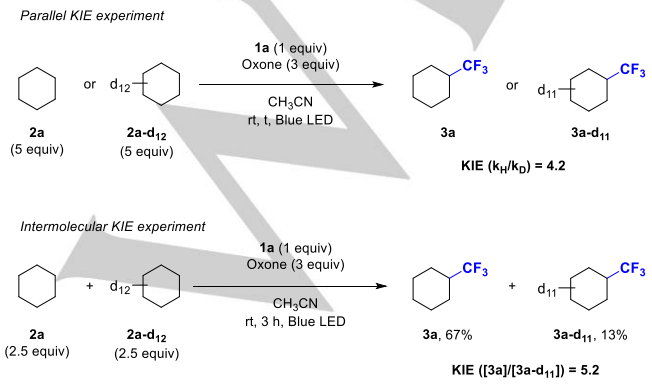


Figure 1. Computational results following the proposed reaction pathway.

10.1002/anie.202012263

In contrast, the DFT computation suggested that chemical oxidation of **^{2}I** with Oxone affords a Cu(III)–bisulfate species **^{1}IV** (blue trace), located at –35.1 kcal/mol. This is due to the strong oxidation power of Oxone, providing results analogous to previous work by the Cook group where persulfate served as the oxidant to produce the identical Cu species ($E°_{calc}$[**^{2}I**/**^{1}IV**] = +0.98 V, E°(Oxone) = +1.81 V).[14a] With this Cu species, single-electron oxidation of cyclohexyl radical was modeled using the Marcus theory, and the energy barrier of the electron transfer was 5.3 kcal/mol. The exotherm of the oxidation was –5.0 kcal/mol, indicating a good match in terms of redox potentials ($E°_{calc}$[**^{1}IV**/**^{2}IV-anion**] = +0.67 V, $E°_{calc}$(**Cy-rad**/**Cy-cat**) = +0.46 V). The generated transient Cu(II) complex **^{2}IV-anion** will undergo structural rearrangement to liberate a trifluoromethyl anion, which can spontaneously recombine with the cyclohexyl cation **Cy-cat** to furnish the desired product with a strong driving force of 67.8 kcal/mol. It should be noted that the oxidation of other Cu species, including **^{1}II**, could eventually generate the **^{2}IV-anion** and **Cy-cat**. Overall, for unactivated alkanes, the activation barrier was much lower for the radical-polar crossover pathway (5.3 kcal/mol) compared to the reductive elimination pathway (20.8 kcal/mol), accounting for the improved reaction efficiency with an oxidant. At the current stage, we cannot rule out another pathway leading to the key intermediates, **^{2}IV-anion** and **Cy-cat**, which is the direct single electron transfer between **Cy-rad** and Oxone to produce **Cy-cat**. Subsequent association of the bisulfate anion may lead to the formation of the identical key intermediates (blue trace via **^{2}I + Cy-cat**).

Based on the computational study, further experiments were performed to verify the proposed mechanism. First, the kinetic isotope effect (KIE) was measured using **2a** and **2a-d_{12}** to elucidate the rate-determining step (Scheme 2). Primary KIE values of 4.2 (parallel reaction) and 5.2 (intermolecular competition) were obtained, clearly indicating that the HAT step is rate-determining, in good accordance with the DFT studies. If the reductive elimination were the major product forming pathway, a primary KIE would not be observed as the reductive elimination should be the rate-determining step (Figure 1). Besides, as the only masses of the products obtained from the intermolecular competition experiment were *m/z* 152.1 (**3a**) and 163.2 (**3a-d_{11}**), we could conclude that the C–H cleavage is irreversible. This phenomenon is in good agreement with our DFT-computed energy profile where reverse hydrogen atom transfer possesses a higher barrier compared to the forward reactions.

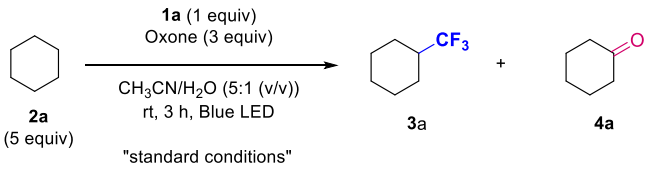


Scheme 2. H/D kinetic isotope effect.

Secondly, we attempted to trap an alkyl cation intermediate that could arise from the radical-polar crossover pathway (Table 5). From Table 1, the standard reaction with **2a** under anhydrous conditions produced **3a** without significant by-product production (entry 1). Upon water addition, a significant amount of cyclohexanone **4a** (14%) was observed, which can be generated from the reaction between the cyclohexyl cation and water to furnish cyclohexanol, followed by subsequent oxidation to form the ketone (entry 2). Increased water contents facilitated the formation of **4a** (20%, entry 3). Without Oxone, no **4a** was generated despite the existence of water (entry 4). Cycloheptane **2c** also produced **3c** in a decreased yield (25%) with increased cycloheptanone by-product **4c** (16%) under the co-solvent conditions of increased amount of water (CH_3CN/H_2O, 1:1 (v/v)). This clearly suggested that a carbocation is generated under the reaction conditions. It has been reported that a persulfate can be homolytically cleaved via UV irradiation, acting as a HAT reagent.[12a, 26] However, under the reaction conditions without **1a**, neither oxidation nor dimerized products were observed, indicating that Oxone itself cannot perform the HAT from **2a** under the blue light irradiation conditions used herein (entry 5).

In summary, driven by the photo irradiation of **1a**, the homolytically cleaved CF_3 radical conducts the HAT from a C(sp^3)–H bond of alkane substrate, as experimentally supported by trapping CF_3 radical and detection of fluoroform HCF_3. Oxone dramatically increased the reaction efficiency by oxidizing the resulting Cu(II) complex **^{2}I** to Cu(III) **^{1}IV** which can oxidize the alkyl radical to form an alkyl cation. Formation of **4a** in presence of water supports the existence of an alkyl cation. The produced anionic Cu(II) complex **^{2}IV-anion** acts as a CF_3 anion source that undergoes ionic coupling with the alkyl cation to form the C(sp^3)–CF_3 bond.

Table 5. Oxidation product detection.[a]



Entry	Variation from the "standard conditions"	Yield **3a** [%]	Yield **4a** [%]
1	No water	93	N. D.
2	None	63	14
3	CH_3CN/H_2O (1:1 (v/v))	19	20
4	No Oxone	31	N. D.
5	No **1a**	-	N. D.

[a] Yields determined by GC analysis using hexafluorobenzene as an internal standard.

Conclusion

In conclusion, a novel C(sp^3)–H trifluoromethylation was developed using a photo-induced high-valent Cu–CF_3 complex. Diverse unactivated alkanes including bioactive molecules were trifluoromethylated using bench-stable bpyCu(CF_3)$_3$ **1a** under mild reaction conditions, favoring the methylene and less-sterically hindered C(sp^3)–H bonds. The experimental and computational mechanistic studies suggested that the reaction proceeds via the CF_3 radical-mediated HAT reaction to activate C(sp^3)–H bonds, followed by radical-polar crossover and ionic coupling. Notably, **1a** performs multiple roles as the photo-induced reaction initiator, precursor of the CF_3 radical as a unique HAT reagent, and trifluoromethylating source. It is anticipated that the developed operatively simple reaction will have wide-scale applications especially for late-stage, single-step trifluoromethylation of functional molecules.

Acknowledgements

Dr. Kicheol Kim is gratefully acknowledged for preliminary studies. We thank Sehye Min, Jinwoo Kim, and Jeonguk Kweon for the help with the spectroscopic measurements. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (NRF-2019R1A2C2086875; NRF-2014R1A5A1011165, Center for New Directions in Organic Synthesis).

Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H activation • copper • late-stage functionalization • radical-polar crossover • trifluoromethylation

[1] a) T. Fujiwara, D. O'Hagan, *J. Fluor. Chem.* **2014**, *167*, 16-29; b) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822-5880; c) Y. Zhao, M. G. Schwab, A. Kiersnowski, W. Pisula, M. Baumgarten, L. Chen, K. Müllen, C. Li, *J. Mater. Chem. C* **2016**, *4*, 4640-4646.

[2] a) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683-730; b) L. Chu, F.-L. Qing, *Acc. Chem. Res.* **2014**, *47*, 1513-1522.

[3] a) A. Prieto, O. Baudoin, D. Bouyssi, N. Monteiro, *Chem. Commun.* **2016**, *52*, 869-881; b) S. Barata-Vallejo, B. Lantaño, A. Postigo, *Chem. Eur. J.* **2014**, *20*, 16806-16829; c) J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650-682; d) R. Tomita, T. Koike, M. Akita, *Angew. Chem. Int. Ed.* **2015**, *54*, 12923-12927; *Angew. Chem.* **2015**, *127*, 13115-13119.

[4] a) T. Koike, M. Akita, *Acc. Chem. Res.* **2016**, *49*, 1937-1945; b) A. Studer, *Angew. Chem. Int. Ed.* **2012**, *51*, 8950-8958; *Angew. Chem.* **2012**, *124*, 9082-9090; c) A. Sato, J. Han, T. Ono, A. Wzorek, J. L. Aceña, V. A. Soloshonok, *Chem. Commun.* **2015**, *51*, 5967-5970.

[5] a) F. Sladojevich, E. McNeill, J. Börgel, S.-L. Zheng, T. Ritter, *Angew. Chem. Int. Ed.* **2015**, *54*, 3712-3716; *Angew. Chem.* **2015**, *127*, 3783-3787; b) X.-G. Zhang, H.-X. Dai, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 11948-11951; c) X. Wang, L. Truesdale, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648-3649; d) N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 536-539; *Angew. Chem.* 2012, 124, 551-554; e) M. Shang, S.-Z. Sun, H.-L. Wang, B. N. Laforteza, H.-X. Dai, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2014**, *53*, 10439-10442; *Angew. Chem.* **2014**, *126*, 10607-10610; f) L. Li, X. Mu, W. Liu, Y. Wang, Z. Mi, C.-J. Li, *J. Am. Chem. Soc.* **2016**, *138*, 5809-5812.

[6] a) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224-228; b) A. G. O'Brien, A. Maruyama, Y. Inokuma, M. Fujita, P. S. Baran, D. G. Blackmond, *Angew. Chem. Int. Ed.* **2014**, *53*, 11868-11871; *Angew. Chem.* **2014**, *126*, 12062-12065; c) T. Nishida, H. Ida, Y. Kuninobu, M. Kanai, *Nat. Commun.* **2014**, *5*, 3387; d) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95-99; e) L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 1298-1304; f) M. Nagase, Y. Kuninobu, M. Kanai, *J. Am. Chem. Soc.* **2016**, *138*, 6103-6106.

[7] a) C. Feng, T.-P. Loh, *Angew. Chem. Int. Ed.* **2013**, *52*, 12414-12417; *Angew. Chem.* **2013**, *125*, 12640-12643; b) N. J. W. Straathof, S. E. Cramer, V. Hessel, T. Noël, *Angew. Chem. Int. Ed.* **2016**, *55*, 15549-15553; *Angew. Chem.* **2016**, *128*, 15778-15782; c) C. Yang, A. Hassanpour, K. Ghorbanpour, S. Abdolmohammadi, E. Vessally, *RSC Adv.* **2019**, *9*, 27625-27639.

[8] P. Zhang, H. Shen, L. Zhu, W. Cao, C. Li, *Org. Lett.* **2018**, *20*, 7062-7065.

[9] a) T. Ide, S. Masuda, Y. Kawato, H. Egami, Y. Hamashima, *Org. Lett.* **2017**, *19*, 4452-4455; b) Z. Liu, H. Xiao, B. Zhang, H. Shen, L. Zhu, C. Li, *Angew. Chem. Int. Ed.* **2019**, *58*, 2510-2513; *Angew. Chem.* **2019**, *131*, 2532-2535.

[10] a) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 4986-4987; b) A. T. Herrmann, L. L. Smith, A. Zakarian, *J. Am. Chem. Soc.* **2012**, *134*, 6976-6979; c) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875-10877; d) Q.-H. Deng, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2012**, *134*, 10769-10772; e) V. Matoušek, A. Togni, V. Bizet, D. Cahard, *Org. Lett.* **2011**, *13*, 5762-5765.

[11] a) A. A. S. Gietter-Burch, V. Devannah, D. A. Watson, *Org. Lett.* **2017**, *19*, 2957-2960; b) L. Chu, F.-L. Qing, *Chem. Commun.* **2010**, *46*, 6285-6287; c) H. Mitsudera, C.-J. Li, *Tetrahedron Lett.* **2011**, *52*, 1898-1900.

[12] a) S. Guo, D. I. AbuSalim, S. P. Cook, *J. Am. Chem. Soc.* **2018**, *140*, 12378-12382; b) H. Xiao, Z. Liu, H. Shen, B. Zhang, L. Zhu, C. Li, *Chem* **2019**, *5*, 940-949; c) M. Paeth, W. Carson, J.-H. Luo, D. Tierney, Z. Cao, M.-J. Cheng, W. Liu, *Chem. Eur. J.* **2018**, *24*, 11559-11563; d) H. Egami, T. Ide, Y. Kawato, Y. Hamashima, *Chem. Commun.* **2015**, *51*, 16675-16678.

[13] P. J. Sarver, V. Bacauanu, D. M. Schultz, D. A. DiRocco, Y.-H. Lam, E. C. Sherer, D. W. C. MacMillan, *Nat. Chem.* **2020**, *12*, 459-467.

[14] a) S. Guo, D. I. AbuSalim, S. P. Cook, *Angew. Chem. Int. Ed.* **2019**, *58*, 11704-11708; *Angew. Chem.* **2019**, *131*, 11830-11834; b) H. Shen, Z. Liu, P. Zhang, X. Tan, Z. Zhang, C. Li, *J. Am. Chem. Soc.* **2017**, *139*, 9843-9846; c) X. Tan, Z. Liu, H. Shen, P. Zhang, Z. Zhang, C. Li, *J. Am. Chem. Soc.* **2017**, *139*, 12430-12433; d) H. Xiao, H. Shen, L. Zhu, C. Li, *J. Am. Chem. Soc.* **2019**, *141*, 11440-11445; e) A. M. Romine, N. Nebra, A. I. Konovalov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *Angew. Chem. Int. Ed.* **2015**, *54*, 2745-2749; *Angew. Chem.* **2015**, *127*, 2783-2787.

[15] J. C. Amphlett, J. W. Coomber, E. Whittle, *J. Phys. Chem.* **1966**, *70*, 593-594.

[16] a) P. Gray, A. A. Herod, A. Jones, *Chem. Rev.* **1971**, *71*, 247-294; b) G. Bullock, R. Cooper, *Trans. Faraday Soc.* **1970**, *66*, 2055-2064; c) T. N. Bell, U. F. Zucker, *Can. J. Chem.* **1970**, *48*, 1209-1213; d) R. A. Fass, J. E. Willard, *J. Chem. Phys.* **1970**, *52*, 1874-1882.

[17] F. Ye, F. Berger, H. Jia, J. Ford, A. Wortman, J. Börgel, C. Genicot, T. Ritter, *Angew. Chem. Int. Ed.* **2019**, *58*, 14615-14619; *Angew. Chem.* **2019**, *131*, 14757-14761.

[18] G. H. Seol, K. Y. Kim, in *Drug Discovery from Mother Nature* (Eds.: S. C. Gupta, S. Prasad, B. B. Aggarwal), Springer International Publishing, Cham, **2016**, pp. 389-398.

[19] S. Sukhchain, G. Pawan, G. Jeena, *Curr. Drug Discov. Technol.* **2019**, *16*, 1-12.

[20] P. Zerbe, J. Bohlmann, in *Biotechnology of Isoprenoids* (Eds.: J. Schrader, J. Bohlmann), Springer International Publishing, Cham, **2015**, pp. 427-447.

[21] a) C. M. Morton, Q. Zhu, H. Ripberger, L. Troian-Gautier, Z. S. D. Toa, R. R. Knowles, E. J. Alexanian, *J. Am. Chem. Soc.* **2019**, *141*, 13253-13260; b) S. Mukherjee, B. Maji, A. Tlahuext-Aca, F. Glorius, *J. Am. Chem. Soc.* **2016**, *138*, 16200-16203.

[22] M. Jasiński, Y. Stukkens, H. Degand, B. Purnelle, J. Marchand-Brynaert, M. Boutry, *Plant Cell* **2001**, *13*, 1095-1107.

[23] V. V. Chernyshov, O. I. Yarovaya, D. S. Fadeev, Y. V. Gatilov, Y. L. Esaulkova, A. S. Muryleva, K. O. Sinegubova, V. V. Zarubaev, N. F. Salakhutdinov, *Mol. Divers.* **2020**, *24*, 61-67.

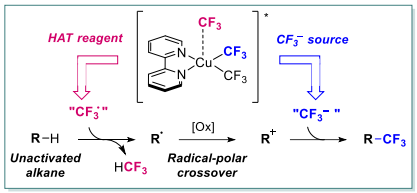
[24] a) M. Paeth, S. B. Tyndall, L.-Y. Chen, J.-C. Hong, W. P. Carson, X. Liu, X. Sun, J. Liu, K. Yang, E. M. Hale, D. L. Tierney, B. Liu, Z. Cao, M.-J. Cheng, W. A. Goddard, 3rd, W. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 3153-3159; b) S. Liu, H. Liu, S. Liu, Z. Lu, C. Lu, X. Leng, Y. Lan, Q. Shen, *J. Am. Chem. Soc.* **2020**, *142*, 9785-9791.

[25] Z. Liu, H. Chen, Y. Lv, X. Tan, H. Shen, H.-Z. Yu, C. Li, *J. Am. Chem. Soc.* **2018**, *140*, 6169-6175.

[26] a) Y. Liu, Y. Wang, Y. Yin, J. Pan, J. Zhang, *Energy Fuels* **2018**, *32*, 1999-2008; b) Y. Wang, Y. Wang, Y. Liu, *Chem. Eng. J.* **2020**, *393*, 124740.

10.1002/anie.202012263

Table of Contents



A photo-induced C(sp^3)–H trifluoromethylation of alkanes is developed by employing bpyCu(CF_3)$_3$ as a multifunctional reagent; photo-induced reaction initiator, the precursor of hydrogen atom transfer reagent, and trifluoromethylating source. The operatively simple reaction enables the direct, late-stage trifluoromethylation of complex molecules under mild reaction conditions.