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Terminal Trifluoromethylation of Ketones via Selective C−C Cleavage of Cycloalkanols Enabled by Hypervalent Iodine Reagents

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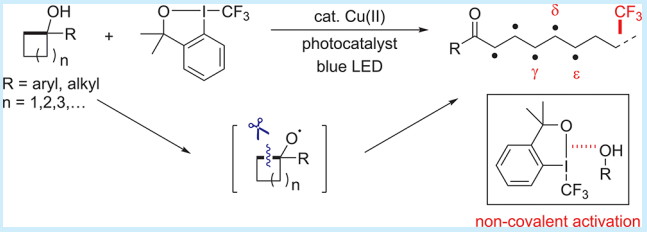
ABSTRACT: We report the first terminal trifluoromethylation at aryl and alkyl ketones' γ, δ, ε, or more remote sites via the selective C−C bond cleavage of cycloalkanols. The noncovalent interactions between alcohols and hypervalent iodines(III) reagents were disclosed to activate both alcohols and the Togni I reagent in the dual photoredox/copper catalysis for the transformation. This reaction was scalable to the gram-scale synthesis, applicable to the structurally complex steroid trifluoromethylation, and extendable to the pentafluoroethylation.



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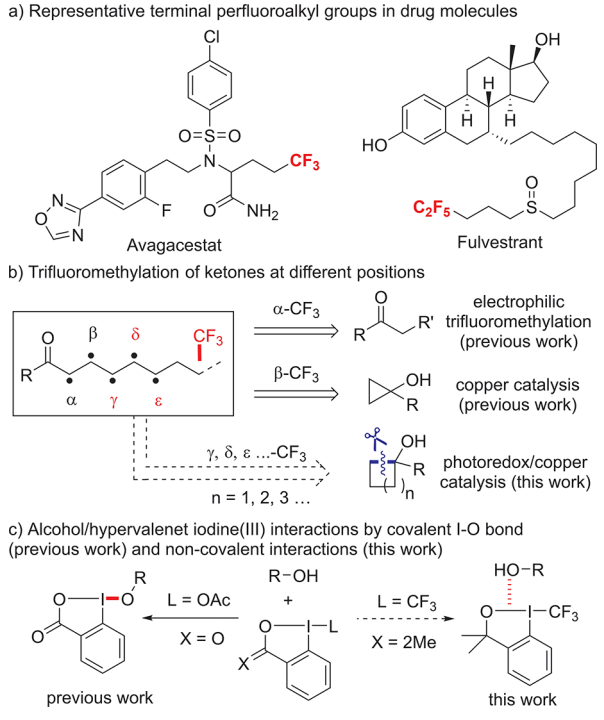
The perfluoroalkyl groups in the terminal positions of drug molecules increase their lipophilicity and metabolic stability.[1] These include Avagacestat as the γ-secretase inhibitor for the potential Alzheimer disease treatment and Fulvestrant as the steroidal antiestrogen for the hormone-receptor-positive metastatic breast cancer (Scheme 1a).[2] The ketone exists abundantly in natural products and drug molecules, and the site-specific introduction of the perfluoroalkyl group to ketones is beneficial for their pharmaceutical applications.[3] The inductive effect is critical for the proximal trifluoromethylation of ketones by the electrophilic α-trifluoromethylation on keto-esters and silyl enol ethers (Scheme 1b).[4] For the β-trifluoromethylation of ketones, the angle strains of the three-membered ring enabled the copper-catalyzed ring-opening trifluoromethylation of cyclopropanols.[5] However, the terminal trifluoromethylations at ketones' γ, δ, or more remote sites are chemically challenging and have not been reported.

Scheme 1. Ketone's Terminal Trifluoromethylation by the Selective C−C Bond Cleavage of Cycloalkanols



Compared to the well-established nucleophilic and electrophilic trifluoromethylation methods,[4b,6] the recently emerged radical trifluoromethylation has unique advantages and is suitable for constructing the alkyl-CF_3 bonds.[7] While the conversion of alkyl halides,[8] alkyl boronates,[9] or alkyl carboxylates[10] to alkyl CF_3 groups have been developed, the selective C(sp^3)−C(sp^3) bond cleavage for the new alkyl-CF_3 bond formation remains elusive. The alkoxyl radical β-fragmentation may selectively cleave the β-C−C bond of alcohols. However, the β-C−C bond cleavage/trifluoromethylation of cycloalkanols remains unaccomplished.

We hypothesize that using a dual photoredox/copper catalysis may enable both the alkoxyl radical generation for the C−C bond cleavage and the copper-catalyzed radical trifluoromethylation for the terminal trifluoromethylation.[11]

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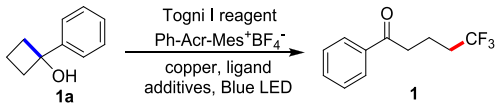
However, the compatibility of the alkoxyl radical generation with the copper-catalyzed trifluoromethylation has not been documented, and the compatibility of the photoredox catalysis with the stable hydroxyl-copper complex remains unknown. We previously discovered that hypervalent iodine(III) reagents BI-OAc activated the cycloalkanols and acyclic alcohols via the covalent iodine−oxygen bond formation to generate alkoxyl radicals (Scheme 1c).[12] We hypothesize that the alcohol-hypervalent iodine complex formation may outcompete the hydroxyl-copper complex for the dual catalysis. We serendipitously discovered instead that the noncovalent interactions between alcohols and hypervalent iodine are critical for the transformation.

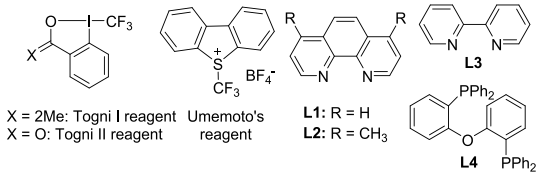
We started the investigations with Ph-Acr-Mes$^+$BF$_4^-$ (E^*_{red} = +2.08 V vs SCE in MeCN)[13] as the photocatalyst for the transformation of cyclobutanol **1a**. Different ligands were first screened with the Togni I reagent using Cu(OAc)$_2$ as the copper source.[14] The 1,10-phen **L1** as the ligand gave the desired γ-CF$_3$ ketone **1** in 25% yield. However, the conversion was low and did not proceed further with the prolonged reaction time (entry 1 in Table 1). The change to 4,7-dimethyl-1,10-phen **L2** or bipyridine **L3** gave decreased conversions, while bisphosphine **L4** was ineffective (entries 2−4).[11] We next tested the addition of different cyclic iodine reagents such as BI-OAc to facilitate the alkoxyl radical generation and found the reaction was not improved (Table S6).[12,15] The proton-coupled electron transfer (PCET) was critical in many biological processes, including photosynthesis and respiration, and recently found applications in photoredox catalysis for the concerted proton and electron transfer.[16] We then added different bases to promote the PCET and found the catalytic addition of ^{n}Bu$_4$P$^+$(OMe)$_2$POO$^-$ improved **1** to 60% yield in 69% conversion (entry 5). In contrast, the collidines were ineffective in giving a 32% yield of **1** (entry 6). The change to CuBr$_2$ as the copper source afforded **1** in the optimal 66% yield in 89% conversion (65% isolated yield, entry 7). The Togni II reagent only resulted in a 35% yield of **1**, and Umemoto's reagent was ineffective (entries 8−9). The photocatalyst Ir(dF(CF$_3$)ppy)$_2$(5,5′-dCF$_3$bpy)PF$_6$ (E^*_{red} = +1.68 V vs SCE in MeCN) with lower reduction potential afforded **1** in 40% yield with the extended 12 h reaction time (entry 10). In the absence of photocatalysts, light irradiation, or copper, there was no conversion of **1a** (entries 11−13).

Table 1. Reaction Discovery and Optimizations[a]



entry	conditions	conv (%)	yield (%)[b]
1	Cu(OAc)$_2$, **L1**	32[c]/35	24[c]/25
2[c]	Cu(OAc)$_2$, **L2**	18	16
3[c]	Cu(OAc)$_2$, **L3**	27	15
4[c]	Cu(OAc)$_2$, **L4**	<5	0
5	Cu(OAc)$_2$, **L1**, ^{n}Bu$_4$P$^+$(OMe)$_2$POO$^-$	69	60
6	Cu(OAc)$_2$, **L1**, collidines	38	32
7	CuBr$_2$, **L1**, ^{n}Bu$_4$P$^+$(OMe)$_2$POO$^-$	89	66(65)
8	entry 7, Togni II reagent	75	35
9	entry 7, Umemoto's reagent	116	<5
10[d]	entry 7, Ir(dF(CF$_3$)ppy)$_2$(5,5′-dCF$_3$bpy)PF$_6$	55	40
11	no photocatalyst	0	0
12	no light	0	0
13	no CuBr$_2$	11	0

[a]Reaction conditions: cyclobutanol **1a** (0.15 mmol, 1.5 equiv), Togni reagent (0.10 mmol, 1.0 equiv), copper salt (0. 02 mmol, 0.2 equiv), ligand (0. 03 mmol, 0.3 equiv), additives (0.04 mmol, 0.4 equiv), and Ph-Acr-Mes$^+$BF$_4^-$ (0.002 mmol, 0.02 equiv) in 2.0 mL of DCM under nitrogen with 80 W blue LED irradiation at 25 °C for 2 h, unless otherwise noted. [b]Yields were determined by ^{1}H NMR analysis, and isolated yields were in parentheses. [c]4 W blue LED, 12 h. [d]12 h.



We next evaluated the γ-CF$_3$ ketone scopes with different cyclobutanols (Scheme 2a). The *para*-, *meta*-, or *ortho*- aryl substitutions on the cyclobutanols **2a**−**5a** did not affect the transformation to give γ-CF$_3$ ketones **2**−**5** in 61−71% yields. The *p*-tolyl or biphenyl substituted cyclobutanols **6a**−**7a** afforded **6**−**7** in 71−73% yields. The electron-withdrawing *p*-chlorophenyl or *p*-bromophenyl substituted cyclobutanols **8a**−**9a** gave **8**−**9** in 65−68% yields in 12 h. The heterocycles, including benzodioxan, benzodioxole, benzofurans, and thiophenes **10a**−**14a**, were tolerated to obtain **10**−**14** in 51−68% yields.[17] The cyclobutanols with fused naphthenes **15a**−**16a** afforded **15**−**16** in 48−58% yields.[18] Compared to the cyclobutanols with ring strains (26.5 kcal/mol), the less-strained inert C−C bonds in cyclopentanols and cyclohexanols (6.2 and 0 kcal/mol) were more challenging to cleave to synthesize δ-CF$_3$ and ε-CF$_3$ ketones.[19] With cyclopentanols **17a**−**20a**, the substituents ranging from electron-rich methoxyl to electron-deficient chloro groups were all tolerated to afford δ-CF$_3$ ketones **17**−**20** in 63−73% yields smoothly (Scheme 2b). The cyclohexanol **21a** without ring strains underwent selective C−C bond cleavage/trifluoromethylation to give the ε-CF$_3$ ketone **21** in 58% yield in 12 h. The medium- and large-sized cycloalkanols including 8-membered (**22a**−**23a**), 12-membered (**24a**−**25a**), and 15-membered rings (**26a**) all reacted to afford the remote η, λ, and ξ-CF$_3$ ketones **22**−**26** in 56−77% yields in 12 h, which were very difficult to synthesize by other methods. Notably, the ring-opening trifluoromethylation could be easily scaled up to 4 mmol to obtain the terminal-λ-CF$_3$ ketone **25** in 1.12 g in 70% yield (see Scheme S28 for details). We also found the acyclic benzyl alcohol **27a** afforded the trifluoromethylation adduct **27** in 58% yield, accompanied by the di-*p*-methoxyphenyl ketone elimination.

We next prepared the cyclopentanol **28a** and cyclohexanol **29a** with methyl substitutions at the β-position of cycloalkanols (Scheme 2c). The selective cleavage at the substituted C−C bond was observed to afford the secondary alkyl-CF$_3$ ketones **28**−**29** in 61−77% yields. The O-tethered 6-membered cycloalkanol **30a** yielded the ε-CF$_3$ ketone **30** in 62% yield, and the δ-phenyl substitution did not affect the reaction to obtain the ε-CF$_3$ ketone **31** in 61% yield. The bicyclic alcohol **32a** obtained the secondary alkyl-CF$_3$ ketone **32-1** and the primary alkyl-CF$_3$ ketone **32-2** in a combined 60% yield with an ∼2:1 ratio. This reaction was not limited to the trifluoromethylation of aryl ketones, and the alkyl-substituted alcohols **33a**−**34a** also yielded γ-CF$_3$ alkyl-substituted ketones **33**−**34** in 52−68% yields.[20] We also tested the steroid-derived cyclobutanol **35a**, and the desired γ-CF$_3$ ketone **35** was

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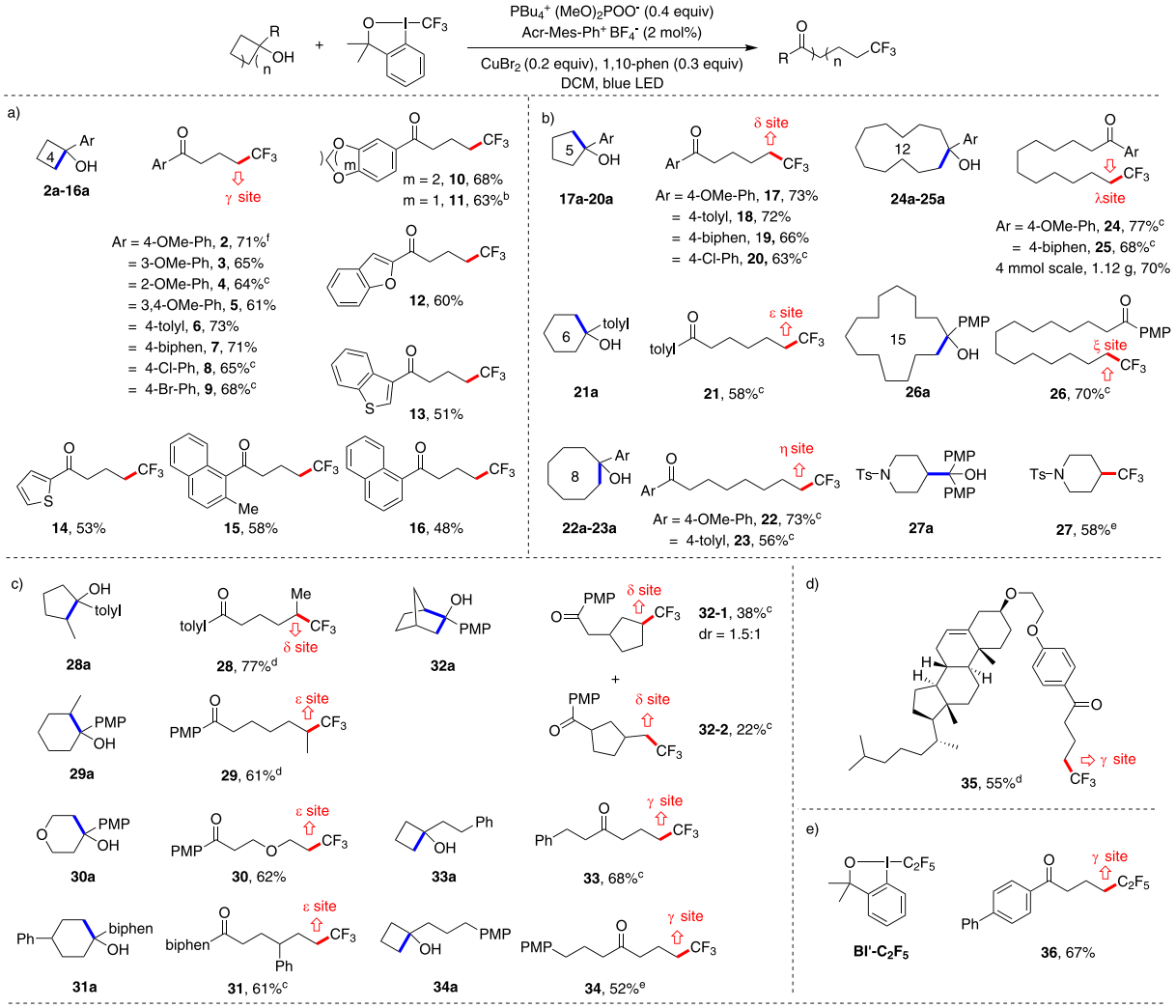
Scheme 2. Substrate Scopes of Cycloalkanols[a]



[a]Entry 7, Table 1. [b]$Cu(OAc)_2$ was used and no $^nBu_4P^+(OMe)_2POO^-$ addition. [c]Alcohol (0.30 mmol, 3.0 equiv), 12 h. [d]12 h. [e]Alcohol (0.30 mmol, 3.0 equiv) and $Cu(OAc)_2$ were used, and no $^nBu_4P^+(OMe)_2POO^-$ addition, 12 h. [f]No $^nBu_4P^+(OMe)_2POO^-$ addition.

obtained in 55% yield without affecting other unsaturated C=C double bonds (Scheme 2d). We also found the ring-opening functionalization of cycloalkanols could easily extend to BI'-C_2F_5 to afford the γ-pentafluoroethylated ketone **36** from **7a** in 67% yield (Scheme 2e).[21]

We next probed the reaction mechanism by adding (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) to the **2a** reaction conditions (Scheme 3a). The inhibition of the product **2** formation was accompanied by the alkyl-TEMPO trapping adduct **37** in 19% yield. In addition, the CF_3-TEMPO trapping adduct **38** was obtained in 80% yield, confirmed by the ^{19}F NMR/HRMS-EI analysis. We also subjected tetrabromomethane to the **2a** reaction conditions and only observed the ring-opening bromination adduct **39** in 58% yield.[22] The fused cyclopropyl alkanol **40a** as the radical clock was next injected and the cyclopropyl ring-opening trifluoromethylation adduct **40** was observed in 28% yield, further suggesting the alkyl radical intermediate.[23] We next performed the fluorescence quenching experiments on $Ir(dF(CF_3)ppy)_2(5,5'\text{-}dCF_3bpy)\text{-}PF_6$ (Scheme 3b). While the excited photocatalyst was not quenched by cyclobutanol **1a**, the $^nBu_4P^+(OMe)_2POO^-$ addition significantly improved the fluorescence quenching by **1a** (red triangles). In contrast, the addition of copper salts or ligands had no effect. The oxidation potential of **1a** was also decreased by the $^nBu_4P^+(OMe)_2POO^-$ addition to E_p = +1.56 V vs SCE in MeCN from the original +1.90 V (Schemes S1, S3). We next performed the NMR titration of **1a** with $^nBu_4P^+(OMe)_2POO^-$ (Scheme 3c). The OH peak of **1a** shifted downfield with the $^nBu_4P^+(OMe)_2POO^-$ addition, while the aromatic/aliphatic C−H peaks of **1a** shifted upfield, which was consistent with the PCET mechanism.[16d,e,24]

Unexpectedly, mixing Togni I reagent with **1a** also resulted in the ^1H NMR peaks shifts of **1a** and the ^{19}F NMR peak shifts of Togni I reagent (Schemes S14, S17). Also, the Togni I reagent addition to **1a** improved the excited photocatalyst fluorescence quenching by **1a** (Scheme 3b, blue triangles). These results suggested both the phosphates and Togni I reagent accelerated the oxidative quenching of cycloalkanols on the excited photocatalysts. We next used the UV−vis absorption spectrometry to probe how the noncovalent interaction between Togni I reagent and **1a** affected the reactivity of the Togni I reagent. The CuBr/1,10-phen showed the 350−500 nm absorbance peak for Cu(I), and the Togni I reagent addition resulted in the oxidized copper intermediate

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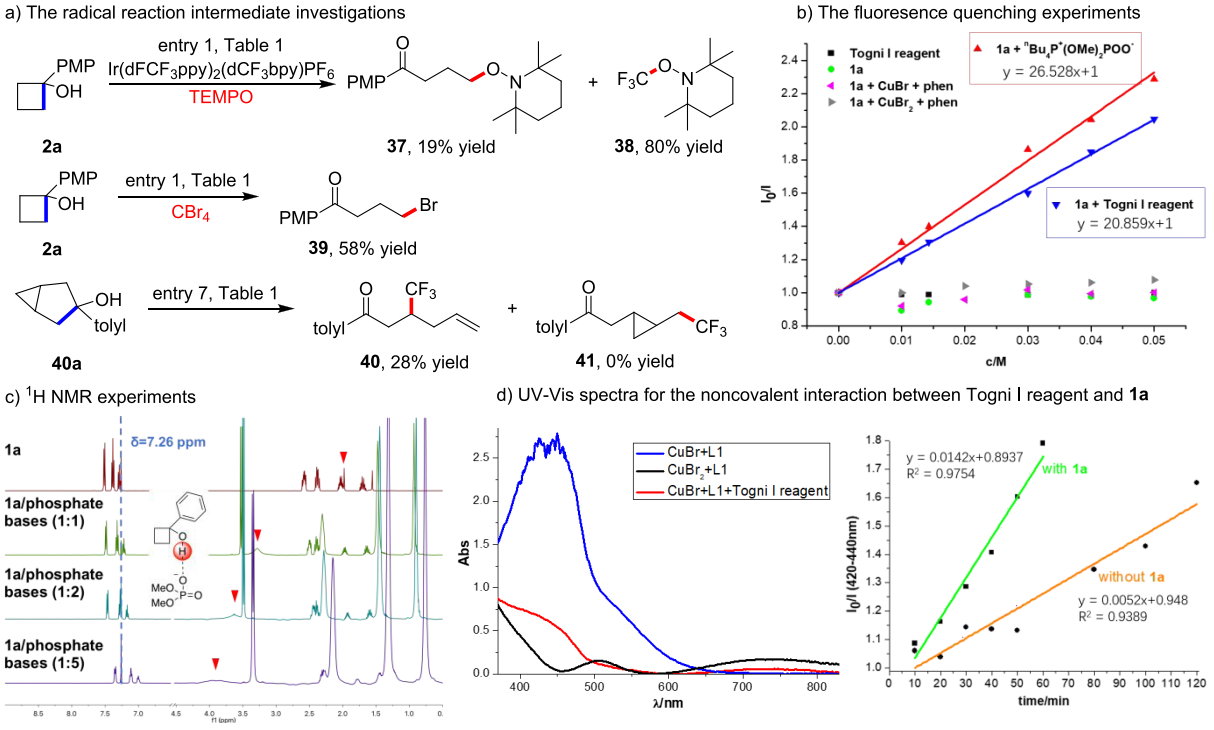
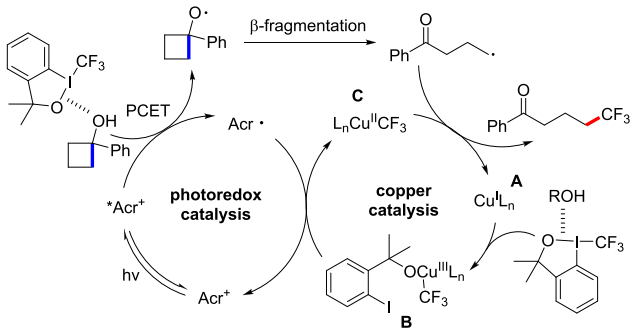
Scheme 3. Mechanistic Investigations



with the 650−800 nm absorption (Scheme 3d).[25] With the **1a** addition, the appearance of the oxidized copper signal and the disappearance of the Cu(I) signal (2.7 times) were greatly accelerated, suggesting the noncovalent interaction between Togni I reagent and **1a** facilitated the CF_3 oxidative addition on the copper center (Scheme S21 for details).

From the mechanistic investigations above, the photoredox catalysis starts with the visible light irradiation on Acr^+ to afford the excited-state $*Acr^+$ as the single-electron oxidant (Scheme 4). The cycloalkanol forms the noncovalent interaction with the hypervalent iodine(III) Togni I reagent, which facilitates its single-electron oxidization to the alkoxyl radical via the PCET mechanism. The *β*-fragmentation of the alkoxyl radical yields the ketone connecting the terminal alkyl radical to enter the copper catalysis. The cycloalkanol interaction with the Togni I reagent accelerates its oxidation of Cu(I) **A** to form the Cu(III)-CF_3 intermediate **B**.[5e] The Cu(III)-CF_3 **B** then oxidizes Acr· to release the Cu(II)-CF_3 intermediate **C**, which further reacts with the alkyl radical to afford the trifluoromethylation adduct and turns over Cu(I) **A**.[10a,26]

Scheme 4. Mechanistic Proposals



In conclusion, we have reported the first terminal trifluoromethylation at aryl and alkyl ketones' *γ*, *δ*, *ε*, or more remote sites from cycloalkanols with various ring sizes. The dual photoredox/copper catalysis enabled the alkoxyl radical generation, the C−C bond cleavage, and the copper-catalyzed radical trifluoromethylation under mild conditions. This reaction was easily scaled up to the gram-scale reaction, applicable to the structurally complex steroid modification, and extendable to the pentafluoroethylation. The noncovalent interactions between hypervalent iodine(III) reagents and alcohols were disclosed for the first time, which both activated the alcohols for the alkoxyl radical generation and activated the Togni I reagent for the essential Cu(III)-CF_3 complex formation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03526.

Experimental procedures, reaction optimizations, detailed mechanistic investigations, and new compounds characterizations (PDF)

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Notes

The authors declare no competing financial interest.

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