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Organic Photoredox-Catalyzed Synthesis of δ-Fluoromethylated Alcohols and Amines via 1,5-Hydrogen-Transfer Radical Relay

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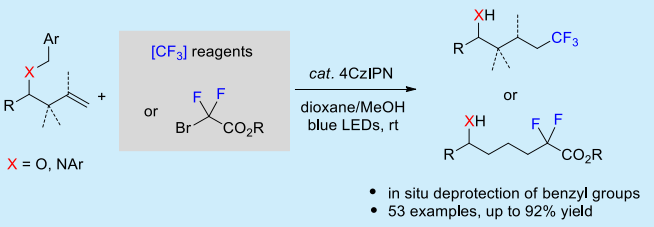
Supporting Information

ABSTRACT: The hydrotrifluoromethylation of benzyl-protected homoallylic alcohol and amine derivatives catalyzed by 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) was developed. This reaction delivered δ-fluoromethylated free alcohols and amines with in situ deprotection of benzyl protecting group under mild irradiation conditions. 4CzIPN was found to be a competent metal-free photoredox catalyst for activating several types of fluoromethylation reagents including CF_3SO_2Cl, Togni's reagent, and 2-bromo-2,2-difluoroacetate via oxidative quenching and also CF_3SO_2Na through reductive quenching to allow direct hydrotrifluoromethylation of simple alkenes and Michael acceptors.



Incorporation of trifluoromethyl group into small organic molecules significantly improves their metabolic stability and lipophilicity,[1] which are important biological properties of concern in medicinal chemistry. As it was discovered that increasing the saturation in small molecules improves the possibility of clinical success in discovering small molecules as effective drugs, synthetic methods that introduce a trifluoromethyl substituent onto an unsaturated carbon atom have received substantial interest from the synthetic community.[2,3] Among various methods to forge a $C(sp^3)-CF_3$ bond, radical hydrotrifluoromethylation is the most straightforward and efficient method due to its high regioselectivity and atom economy.[4] Considering the ubiquity of free alcohol and amine structures in bioactive compounds,[5] an efficient synthetic method that selectively delivers trifluoromethylated free alcohols and amines would be of importance in the pharmaceutical industry, especially an operationally simple method without recourse of expensive and toxic transition-metal catalysts or additives. Herein, we report that by applying an organic photoredox catalyst,[6] 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN),[7] hydrotrifluoromethylations of benzyl-protected homoallylic alcohol and amine derivatives using electrophilic trifluoromethylation reagent (trifluoromethyl sulfonyl chloride and Togni's reagent[8]) deliver δ-fluoromethylated free alcohols and amines with in situ deprotection of a benzyl protecting group under mild irradiation conditions. The reaction proceeds in a mixed methanol/dioxane solvent without use of any additives and exhibits excellent functional group compatibility. The reaction proceeds through an oxidative quenching process to deliver a trifluoromethyl radical followed by 1,5-hydrogen transfer relay with in situ removal of benzyl protecting group. During this study, we also discovered that photoexcited 4CzIPN catalyst can also be reductively quenched by nucleophilic trifluoromethyl reagent an sodium triflinate to allow hydrotrifluoromethylation of simple alkenes and Michael acceptors. These results reveal the general applicability of 4CzIPN photocatalyst for activation of various trifluoromethylation reagents through either oxidative quenching or reductive quenching due to its larger band gap (2.4 eV) and suitable HOMO/LUMO level to endow both strong reducing and oxidizing ability in a photoexcited state.[9]

Our working hypothesis is inspired by a copper-catalyzed anti-Markovnikov hydrofunctionalization of homoallylic alcohol reported by Chiba, Gagosz et al.[10,11] In this work, a wide variety of δ-fluoromethylated free alcohols were obtained through copper-catalyzed generation of trifluoromethyl radical following a 1,5-hydrogen transfer radical relay process. We conceive that a suitable organic dye 4CzIPN should be able to generate trifluoromethyl radical through oxidative quenching of its photoexcited triplet state ($E_{1/2}(PC^{\bullet+}/PC^*) = -1.18$ V. The generated trifluoromethyl radical can be trapped by benzyl-protected homoallylic alcohol followed by a 1,5-hydrogen-transfer process to generate more stable etheric benzylic radical.[12] The benzylic radical is supposed to be oxidized by the photoredox catalyst of its oxidation form to generate cationic intermediate ($(E_{1/2}(PC^{\bullet+}/PC) = +1.49$ V), which will be quenched by alcohol solvent to deliver acetal. After aqueous workup, δ-trifluoromethylated alcohol or amine will be delivered as the desired product (Scheme 1).

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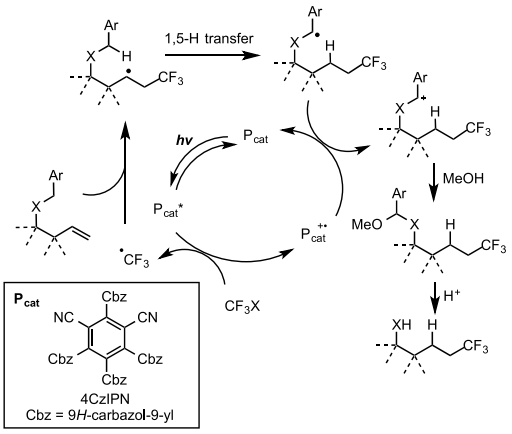
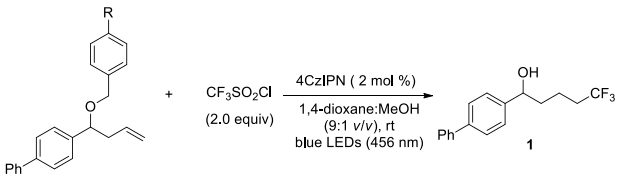
Scheme 1. Working Hypothesis of Organic Photoredox-Catalyzed Synthesis of δ-Trifluoromethylated Alcohols and Amines



Guided by this hypothesis, we report herein that 4CzIPN, a donor−acceptor-type organic dye, works as an effective catalyst for this reaction due to its suitable redox potential. According to the working hypothesis, a suitable benzyl protecting group is important because the benzyl moiety works as a hydrogen atom source and the substituent on benzyl affects the efficiency of the crucial 1,5-hydrogen-transfer process. Scheme 2 showed

Scheme 2. Investigation of Different Benzyl Protection Groups for 1,5-Hydrogen Transfer[a]



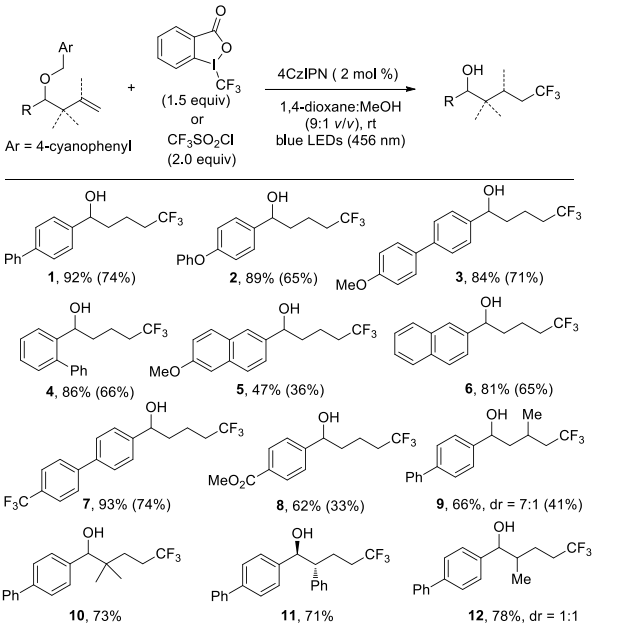
entry	R	isolated yield (%)	entry	R	isolated yield (%)
1	- H	53	5	- Me	41
2	- CF_3	59	6[b]	- CN	92
3	- CN	83	7[c]	- CN	63
4	- NO_2	75	8[b,d]	- CN	trace

[a]Reaction conditions: alkene (0.2 mmol), CF_3SO_2Cl (0.4 mmol), 4CzIPN (0.004 mmol) in solvent (2.0 mL) irradiated by 40 W blue LEDs (456 nm) for 12 h under Ar. Isolated yields. [b]Togni's reagent (0.3 mmol) was used instead of CF_3SO_2Cl. [c]Umemoto's reagent was used. [d]TEMPO (0.3 mmol) was added.

the results of applying various substituted benzyls as hydrogen donating groups. 4-Cyanobenzyl appeared to be the optimal protecting group due to its easily installation and the appropriate electronic effect of cyano substituent to modulate the speed of 1,5-H transfer step for a productive process (entry 3). The yield of **1** was further improved by applying Togni's reagent instead of CF_3SO_2Cl (entry 6). The use of Umemoto's reagent (*S*-(trifluoromethyl)dibenzothiophenium triflate) as the CF_3 source led to a lower yield (entry 7). The reaction was inhibited by using TEMPO as the radical scavenger, which suggests a radical process was involved (entry 8).

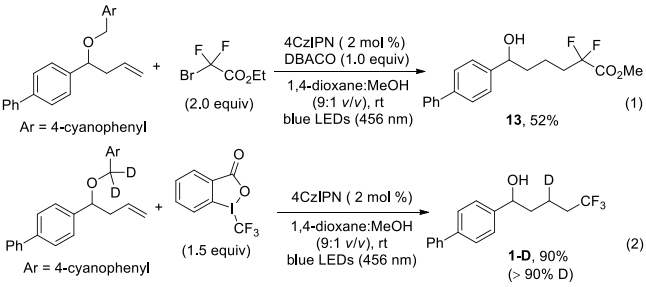
After determining 4-cyanobenzyl as the optimal protecting group, we examined the reaction scope with respect to various homoallylic alcohols (Scheme 3). The reaction conditions are very simple, and the product could be easily purified. Togni's reagent provided generally higher yield than trifluoromethanesulfonyl chloride, probably because of the competing alcoholysis of sulfonyl chloride. Besides linear α-substituted homoallylic alcohol derivatives (**1**−**8**), β- and γ-substituted homoallylic alcohol derivatives were also amenable substrates (**9**−**12**). It is notable that chirality on both the α- and β-carbon of homoallylic alcohol was fully retained after the reaction (**11**). However, tertiary and alkyl-substituted alcohol substrates did not work under the optimized conditions.

Scheme 3. Scope of δ-Trifluoromethylated Alcohols[a,b]



[a]Reaction conditions: 0.2 mmol scale in dioxane/MeOH (2.0 mL, v/v 9/1) irradiated by 40 W blue LEDs (456 nm) for 12 h under Ar. Isolated yields. [b]The yields in parentheses are yields obtained using CF_3SO_2Cl instead of Togni's reagent.

It was discovered that, besides trifluoromethylation, 6-hydroxy-2,2′-difluorocarboxylate (**13**) could also be synthesized by this method applying 2-bromo-2,2-difluoroacetate (eq 1).[13] However, transesterification was observed in this



reaction. An experiment using α-deuterated benzyl as the protecting group confirmed the 1,5-hydrogen-transfer process, as deuterium was incorporated (>90%) onto the γ-position of the trifluoromethylated alcohol product. The method offers a synthetic route to synthesize regioselectively deuterium-labeled trifluoromethylated alcohols, which will be useful in medicinal chemistry study.[14]

We were delighted to find that the same protocol was also applicable to hydrotrifluoromethylation of homoallylic amine derivatives. Various N-arylated homoallylic amines perform as amenable substrates to provide δ-trifluoromethylated N-

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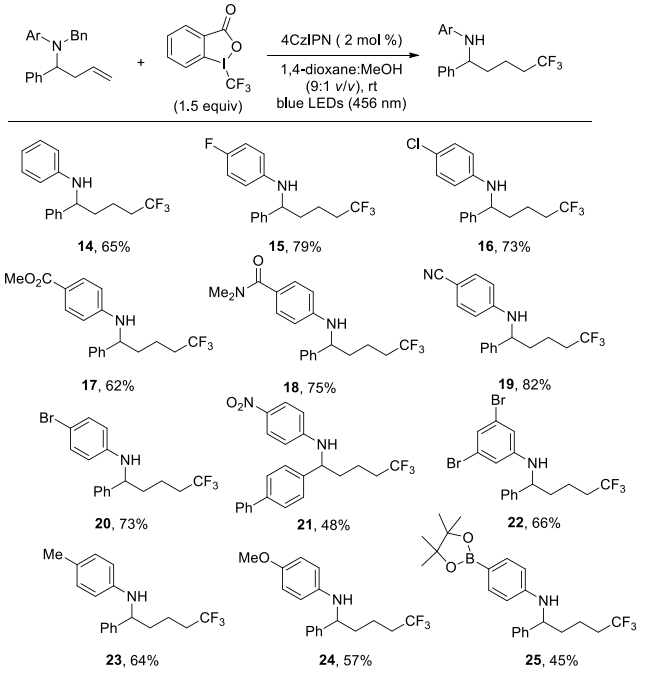
arylated secondary amines in good yields (Scheme 4). A variety of functional groups, such as bromo (**20**, **22**), fluoro

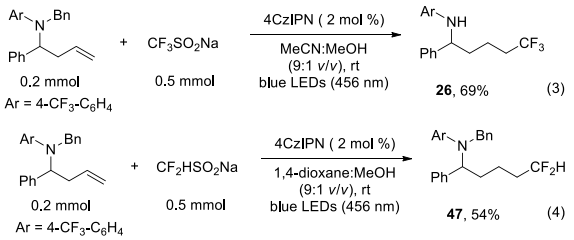
Scheme 4. Scope with Respect to *N*-Aryl Substituents on Amines[a]



[a]Reaction conditions: 0.2 mmol scale in dioxane/MeOH (2.0 mL, v/v 9/1) irradiated by 40 W blue LEDs (456 nm) for 12 h under Ar. Isolated yields.

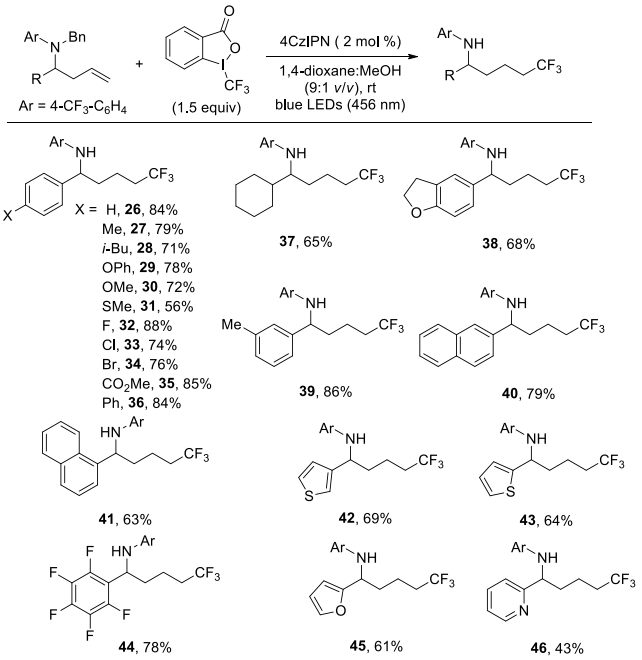
(**15**), chloro (**16**), ester (**17**), amide (**18**), cyano (**19**), nitro (**21**), ether (**24**), and even a pinacol boronate (**25**) substituent on aniline moiety, were well tolerated. Tolerance of the aryl pinacol boronate moiety shows the advantages of applying photoredox catalysis since aryl boronate is not well survivable in the presence of transition-metal catalyst and Togni's reagent. The reaction scope with respect to homoallylic amine derivatives is shown in Scheme 5. α-Heteroarylated δ-trifluoromethylated secondary amine could also be synthesized. Heteroarenes including thiophene (**42**, **43**), furan (**45**), and pyridine (**46**) were all tolerable.

An interesting result was obtained when Langlois reagent was used in 2.5 equiv amount instead of Togni's reagent, as the desired product with deprotection of benzyl protecting group was also generated in 69% yield (eq 3). The yield of desired



product was significantly decreased when Langlois reagent was used in 1.5 equiv amount. Judged by redox potential, it is reasonable that Langlois reagent ($E_{1/2}$ = 1.05 V vs SCE) can reductively quench photoexcited 4CzIPN catalyst to generate trifluoromethyl radical ($E_{1/2}(PC^*/PC^{\bullet-})$ = +1.43 V), while

Scheme 5. Scope of Homoallylic Amine Derivatives[a]



[a]Reaction conditions: 0.2 mmol scale in dioxane/MeOH (2.0 mL, v/v 9/1) irradiated by 40 W blue LEDs (456 nm) for 12 h under Ar. Isolated yields.

this catalytic reaction requires an oxidant to proceed. We rationalize that excess amount of Langlois reagent acted as oxidant under photoredox condition for this reaction ($E_{1/2}(PC/PC^{\bullet-})$ = −1.24 V).

Further use of difluoromethylation using CF_2HSO_2Na produced unexpected hydrodifluoromethylation product without removal of benzyl protecting group (eq 4). We consider that the high reducing ability of 4CzIPN ($E_{1/2}(PC/PC^{\bullet-})$ = −1.24 V) allows reductive protonation of fluorinated alkyl radical without abstraction of hydrogen through 1,5-H transfer. Thus, we posited that the organic photoredox catalyst 4CzIPN could be competent to catalyze hydrotrifluoromethylation of simple alkene and Michael acceptors with CF_3SO_2Na, a process previously reported by using combination of acridinium photoredox catalyst and thiophenol hydrogen transfer catalyst[15] or iridium photoredox catalyst.[16] Simply applying 4CzIPN as photocatalyst is competent to catalyze hydrotrifluoromethylation of aliphatic alkenes (**49**, **50**) and Michael acceptors (**48**, **51**, **52**, **53**) with CF_3SO_2Na (Scheme 6). The hydride source for this hydrotrifluoromethylation reaction may come from the MeOH solvent.[16] These results above demonstrate that 4CzIPN is a competent catalyst for generation of trifluoromethyl radical from various trifluoromethylation reagents under simple irradiation conditions.

In conclusion, in this work we demonstrated an organic photoredox method using 4CzIPN as catalyst for hydrotrifluoromethylation without using any transition metal. Hydrotrifluoromethylation of benzyl-protected homoallylic alcohol and amine derivatives provides δ-fluoromethylated free alcohols and amines with in situ deprotection of the benzyl protecting group under mild irradiation conditions. The reaction exhibits excellent functional group compatibility and operational simplicity. 4CzIPN is a competent catalyst for trifluoromethyl radical generation via oxidative or reductive quenching of various trifluoromethylation reagents. We hope

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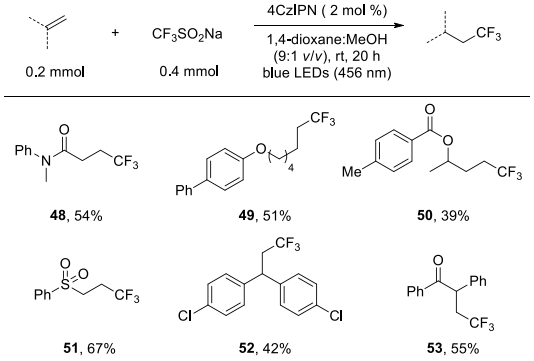
Scheme 6. Hydrotrifluoromethylation of Simple Alkenes and Michael Acceptors Using Langlois Reagent[a]



[a]Reaction conditions: 0.2 mmol scale in dioxane/MeOH (2 mL, v/v 9/1) irradiated by 40 W blue LEDs for 20 h under Ar. Isolated yields.

the method reported herein will find its use in pharmaceutical industry to synthesize important fluorinated intermediates or bioactive compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01714.

Experimental procedures, detailed optimization, mechanistic studies, compound characterization, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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