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Article

Trifluoromethylative and Pentafluoroethylative Heterofunctionalization (C−O, C−S, and C−N) of Alkenes Using Visible Light Photocatalysis

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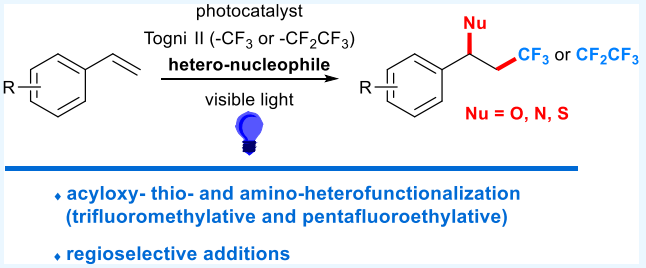
ABSTRACT: A mild and general method for photoredox-catalyzed trifluoromethylative and pentafluoroethylative heterofunctionalization of alkenes is proposed. In this reaction, the Togni reagent serves as a CF_3- or CF_2CF_3-radical source for the regioselective formation of the $C-CF_3$ and $C-CF_2CF_3$ bonds from alkenes, and additional nucleophiles (O, S, N) provide C−O, C−S, and C−N bonds, respectively. These reactions provide a common gateway to access the fluoroalkylative heterofunctionalization of alkenes.



INTRODUCTION

In the development of new synthetic methods, the incorporation of a trifluoromethyl group ($-CF_3$) into unsaturated C−C bonds has made notable progress. This is primarily due to its ability to simultaneously introduce other heteroatoms such as oxygen, sulfur, and nitrogen.[1] Specifically, the difunctionalization of alkenes allows the direct conversion of simple alkenes into complex organic molecules with a CF_3 attachment. The trifluoromethyl group offers several benefits in medicinal chemistry, precisely enhancing lipophilicity, permeability, bioactivity, and metabolic stability in pharmaceutical compounds.[2−5]

Over the past decade, significant advancements have been made in the direct transformation of alkenes. These include methods using transition metal catalysis, photoredox catalysis, electroorganic synthesis, and metal-free conditions. Namely, metal-catalyzed oxy-trifluoromethylation,[6−16] amino-trifluoromethylation,[17−23] thio-trifluoromethylation of alkenes[24,25] or photocatalyzed oxy-trifluoromethylation,[26−34] amino-trifluoromethylation,[26,31,35−37] cyclopropanation of alkynes and alkenes,[38,39] radical silyl transfer,[40,41] and thio-trifluoromethylation of alkenes[42−44] have been extensively reported (Scheme 1). These methods, utilizing either Togni or Umemoto reagents, enable the heterofunctionalization of alkenes and the formation of heterocyclic compounds. Recent advancements also include metal-free protocols.[44] However, most of these studies focus on a single functional transformation under standard conditions, with only a few examples demonstrating the potential for multiple heterofunctionalizations using the same reaction setup. Furthermore, the pentafluoroethylative difunctionalization of alkenes remains underexplored, in both transition metal and photoredox catalysis contexts.

In this study, we investigated both trifluoromethylative and pentafluoroethylative heterofunctionalizations of alkenes. We employed Togni reagents (**2a** and **2b**) in combination with photoredox catalysis using identical reaction conditions for each process.

RESULTS AND DISCUSSION

Our optimization process began with 4-methylstyrene **1a** and Togni II **2a** as the model substrates using 5 mol % of a photocatalyst in DCE. Initial tests with the $Ru(bpy)_3Cl_2{\cdot}6H_2O$ photocatalyst were promising, yielding the acyloxy trifluoromethylation adduct **3a** at 40% (Table 1, entry 1). The Ru-based catalyst $[Ru(Phen)_3](PF_6)_2$ produced a similar yield of 39% (Table 1, entry 2). In contrast, the *fac*-$Ir(ppy)_3$ catalyst resulted in a slightly lower yield of 28%, and the $[Ir[dF(CF_3)-ppy]_2(dtbpy)]PF_6$ catalyst achieved only a 19% yield of **3a** (Table 1, entries 3 and 4). The organic photocatalyst Acr^+-Mes, however, did not facilitate the desired transformation (Table 1, entry 5). Copper-based photocatalysts, $[Cu(dmp)_2Cl]Cl$ and $[Cu(dmp)_2]Cl$, were also ineffective (Table 1, entries 6 and 7).

Subsequent solvent screening showed that dioxane, THF, CH_3CN, and DMSO all resulted in lower yields of **3a** (Table 1, entries 9−12), and no reaction occurred with DMF (Table 1, entry 13). Attempts to improve yields with amine additives to

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Scheme 1. Trifluoromethylative and Pentafluoroethylative Difunctionalization of Alkene

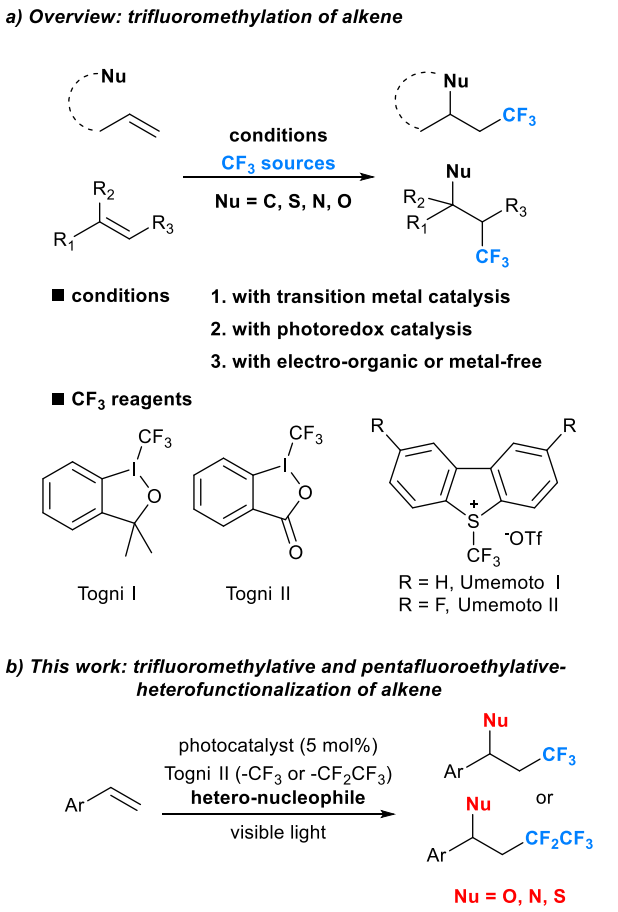
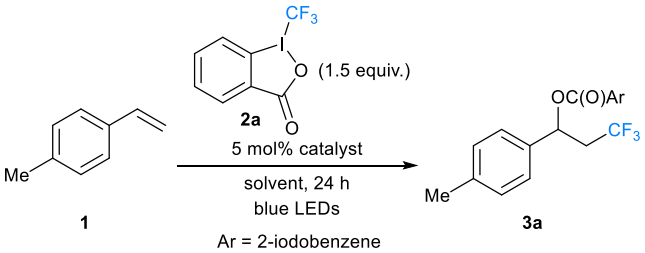


Table 1. Reaction Optimization[a]



entry	catalyst	additive	solvent	yield (%)[b]
1	$Ru(bpy)_3Cl_2·6H_2O$		DCE	40
2	$[Ru(Phen)_3](PF_6)_2$		DCE	39
3	*fac*-Ir(ppy)$_3$		DCE	28
4	$[Ir[dF(CF_3)ppy]_2(dtbpy)]PF_6$		DCE	19
5	Acr^+-Mes		DCE	<5
6	$[Cu(dmp)_2Cl]Cl$		DCE	7
7	$[Cu(dmp)_2]Cl$		DCE	<5
8	$Ru(bpy)_3Cl_2·6H_2O$		toluene	26
9	$Ru(bpy)_3Cl_2·6H_2O$		dioxane	30
10	$Ru(bpy)_3Cl_2·6H_2O$		THF	28
11	$Ru(bpy)_3Cl_2·6H_2O$		CH_3CN	39
12	$Ru(bpy)_3Cl_2·6H_2O$		DMSO	13
13	$Ru(bpy)_3Cl_2·6H_2O$		DMF	<5
14	$Ru(bpy)_3Cl_2·6H_2O$	Et_3N	DCE	<5
15	$Ru(bpy)_3Cl_2·6H_2O$	DIPEA	DCE	<5
16	$Ru(bpy)_3Cl_2·6H_2O$	K_3PO_4	DCE	13
17[d]	**$Ru(bpy)_3Cl_2·6H_2O$**		**DCE**	**54 (53)**[c]
18			DCE	<5
19[e]	$Ru(bpy)_3Cl_2·6H_2O$		DCE	<5

[a]All reactions were performed using 0.25 mmol (0.1 M) and a standard 24 h reaction time. [b]^{1}H NMR yield. [c]Isolated yield. [d]1 equiv of Togni **2a** and 2 equiv of **1** were used. [e]Without blue LEDs.

facilitate photoexcitation were unsuccessful (Table 1, entries 14 and 15). The use of K_3PO_4 buffer was possibly improving the reaction system but only yielded 13% (Table 1, entry 16). To enhance the desired transformations, we then used Togni reagent **2a** as the limiting reagent, leading to improved outcomes (Table 1, entry 17). Notably, this condition provided trifluoromethylative acyloxylated adduct **3a** in 53% isolated yield. The reaction without a photocatalyst was completely inhibited (Table 1, entry 18). Additionally, irradiation with blue LEDs was confirmed to be crucial for the transformation (Table 1, entry 19).

With these optimized conditions, we expanded our study to various acyloxy trifluoromethylation reactions (Scheme 2). Para-substituted styrenes with electron-donating groups (**1b**–**1d**) yielded similar results. Specifically, 4-*tert*-butyl and 4-Ph-substituted styrenes (**1b** and **1c**) produced the desired adducts **3b** and **3c** with yields of 55% and 54%, respectively. The highest yield, 65%, was achieved with 4-MeO-styrene (**1d**). Conversely, styrenes with electron-withdrawing halogen substituents (4-Cl and 4-Br) resulted in lower yields of 24% (**1e**) and 22% (**1f**). Ortho-substituted (**1g**) and meta-substituted styrenes (**1h**) also exhibited slightly reduced yields of 44% each compared to those of the para-substituted counterparts. The reaction with 1-vinylnaphthalene (**1i**) yielded product **3i** at 40%. Applying the same conditions with the pentafluoro-substituted Togni-type reagent **2b**, we observed a smooth progression of acyloxy pentafluoroethylation reactions. Para-substituted styrenes with electron-donating groups (**1a**–**1d**) provided acceptable yields of the corresponding products (**3j**–**3m**), with 4-MeO-styrene (**1d**) showing the highest yield of 67% (**3m**), mirroring the acyloxy trifluoromethylation results. Notably, 4-Cl-substituted styrene (**1e**) was successfully transformed into product **3n** with an improved yield of 41% compared with its trifluoromethylated counterpart. The pentafluoroethylated adduct containing naphthalene (**3o**) was also produced in a 48% yield.

Next, we investigated the use of sulfur nucleophiles to assess the viability of this transformation (Scheme 3). Through a screening process detailed in the Supporting Information, potassium *O*,*O*-diethyl phosphorothioate (**4**) was identified as an effective sulfur source. This three-component difunctionalization protocol with styrene produced both thio-trifluoromethylation and thio-pentafluoroethylation adducts (**5**). Prominently, the phosphorothioate moiety, which has garnered attention in medicinal chemistry, particularly for oligonucleotide therapeutics,[45] was synthesized using this method. Our previous work detailed a two-step synthesis of this moiety involving thiocyanation followed by nucleophilic substitution of *H*-phosphine oxide.[46] Styrenes with electron-donating groups (4-Me and 4-MeO) led to the formation of products **5a** and **5b** in yields of 49% and 51%, respectively. Halogen-substituted variants (4-F and 4-Cl) produced **5c** and **5d** with yields of 45% and 50%. Ortho-methylstyrene yielded the desired product at a yield of 50%. Meta-substituted styrenes yielded **5f** and **5g** at 55% and 49%, respectively.

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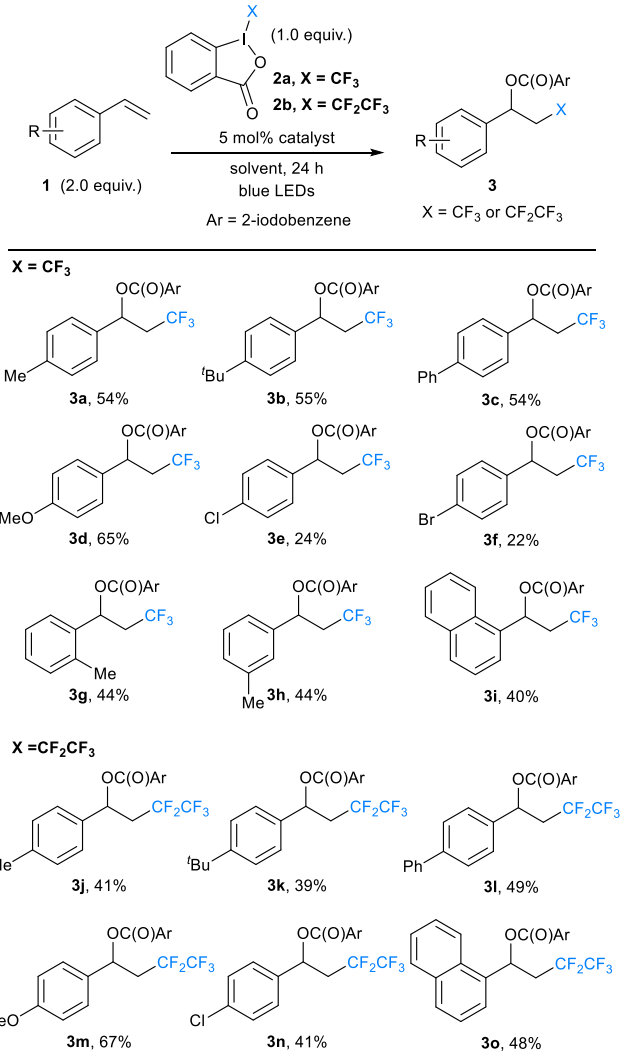
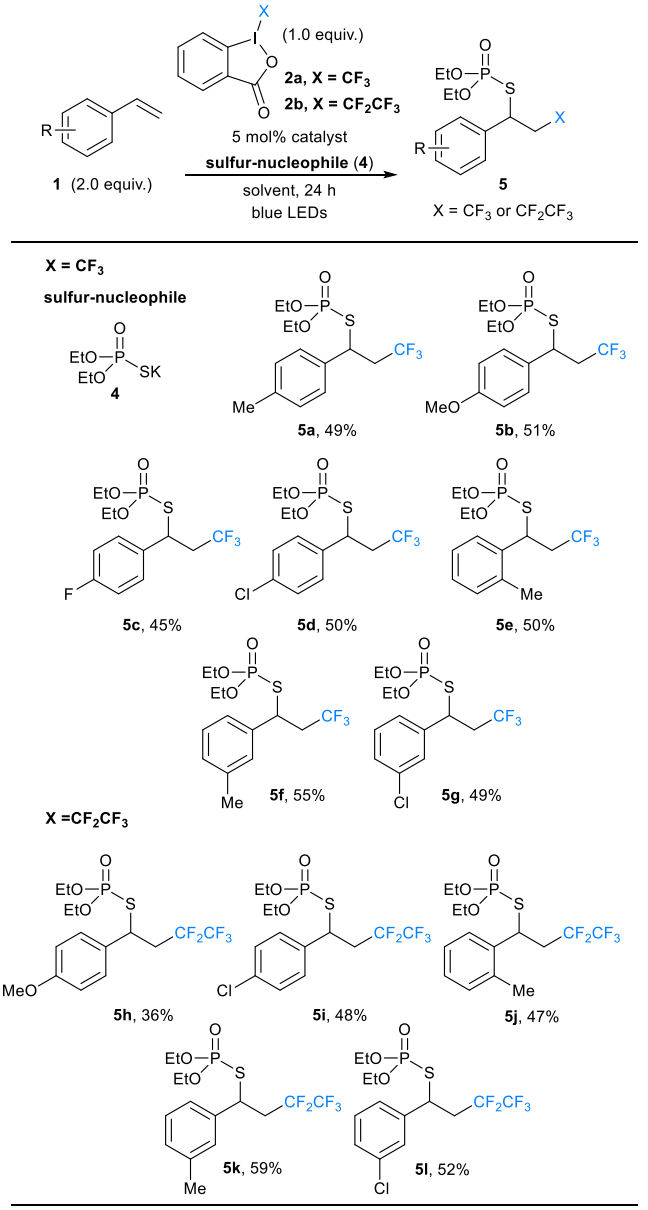
Scheme 2. Acyloxy Trifluoromethylation and Pentafluoroethylation of Alkene



Scheme 3. Thio-trifluoromethylation and Pentafluoroethylation of Alkene



This protocol was also effective for synthesizing thio-pentafluoroethylative adducts. The 4-methoxystyrene yield was slightly lower at 36% (**5h**) compared to other examples. The *para*-chloro-substituted styrene (**1e**) showed an increased yield of 48%, surpassing the yield with oxygen nucleophiles. The 2-Cl-styrene displayed a similar chemical yield. Styrenes with two meta substituents (3-Me and 3-Cl) produced thio-pentafluoroethylative adducts at higher yields of 59% (**5k**) and 52% (**5l**), respectively, exceeding the yields of their thio-trifluoromethylative counterparts.

We then extended our research to include nitrogen nucleophiles, aiming to produce trifluoromethylative difunctionalized alkenes (Scheme 4). *N*-Aminophthalimide was effectively incorporated at the benzylic position in styrenes with a methyl substituent at the ortho, meta, and para positions (**1a**, **1g**, and **1h**), achieving nearly identical yields of around 40%. Additionally, 2-bromostyrene (**1l**) underwent transformation, yielding the corresponding adduct in a 33% yield. In a further application, we used 2-fluoro-4-methoxyaniline as a nitrogen nucleophile, successfully obtaining the desired product (**6e**) in a yield of 37%. Overall, the yields are usually moderate to good and use excess styrenes, allowing expedient entry into different classes of fluorinated molecules using a unified system.

A plausible reaction mechanism for the heterotrifluoromethylation and pentafluoroethylation of styrene is depicted in Scheme 5 based on our findings and existing literature. Upon irradiation with visible light, Ru(II) transitions to a photoexcited state, initiating the production of CF_3 radical **7** and 2-iodobenzoate from Togni reagent **2a**. Styrene **1** captures radical **7**, forming benzylic radical **8**, which subsequently oxidizes to yield cation **9**. This cationic intermediate **9** then reacts with 2-iodobenzoate, resulting in product **3**. Alternatively, other nucleophiles can react with cationic intermediate **9**, forming the corresponding adducts **5** and **6**.

CONCLUSIONS

In summary, we developed a photocatalytic protocol for the heterotrifluoromethylation and heteropentafluoroethylation of styrene using a range of nucleophiles, including oxygen, sulfur,

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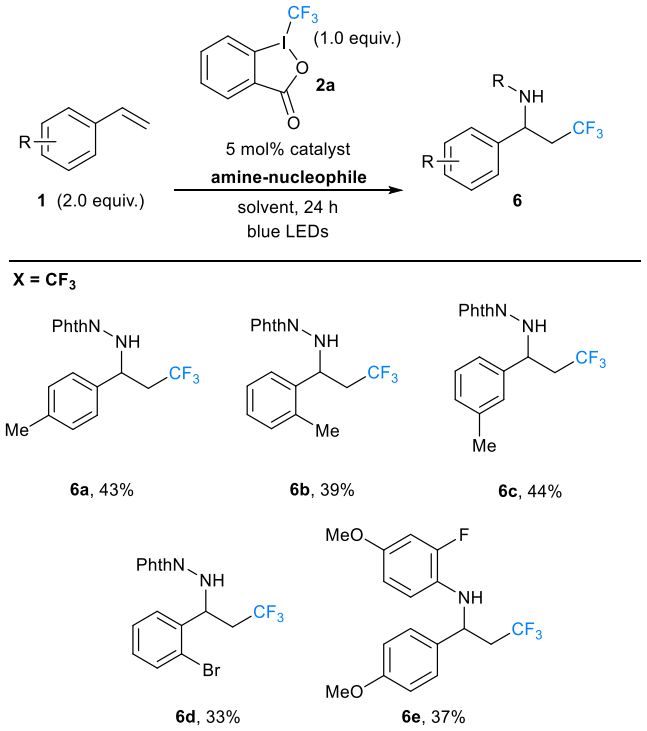
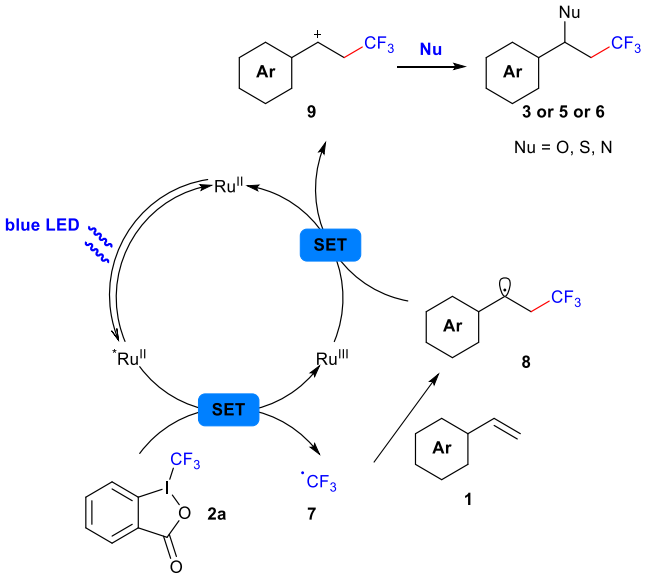
Scheme 4. Amino-trifluoromethylation of Alkene



Scheme 5. Proposed Mechanism



and nitrogen. This method stands apart from previous literature as it is universally applicable to the acyloxy-, thio-, and aminofunctionalization of styrenes.

EXPERIMENTAL SECTION

Unless otherwise noted, all solvents and reagents were purchased from commercial suppliers (Sigma-Aldrich, TCI, Alfa-Aesar, and Angene) and used without further purification. Togni-type reagents **2a** and **2b** were purchased from Jhchem (JH539350) and Sigma-Aldrich (CF0013), respectively. All reactions were performed under an atmosphere of dry argon. Thin-layer chromatography was performed on Merck (Silica gel 60, F-254, 0.25 mm). Chromatographic purifications were performed under gradient using a CombiFlash system and prepacked disposable silica cartridges using commercial 60 Å silica gel. NMR spectra were recorded on a Bruker AVANCE III HD (400, 100, and 376 MHz for ^{1}H, ^{13}C, and ^{19}F NMR, respectively) spectrometer. Chemical shifts are reported as δ values in parts per million downfield from solvents as internal standards ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.04 ppm for ^{13}C NMR). High-resolution mass spectra were obtained by electron impact and fast atom bombardment ionization technique (JMS 700, Joel, Japan, magnetic sector−electric sector double focusing mass analyzer) from the KBSI (Korea Basic Science Institute Daegu Center).

General Procedure of Acyloxy Trifluoromethylation and Pentafluoroethylation of Alkene. To a vial equipped with a stir bar were added styrene (0.5 mmol, 2 equiv), Togni-type reagent **2a** (79 mg, 0.25 mmol, 1 equiv) or **2b** (92 mg, 0.25 mmol, 1 equiv), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (9.4 mg, 0.013 mmol, 0.05 equiv), and 1,2-dichloroethane (1 mL, 0.25 M). The resulting solution was irradiated with blue LED light for 24 h. The reaction mixture was then diluted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by MPLC to give the final product.

General Procedure of Thio-trifluoromethylation and Pentafluoroethylation of Alkene. To a vial equipped with a stir bar were added styrene (0.5 mmol, 2 equiv), Togni-type reagent **2a** (79 mg, 0.25 mmol, 1 equiv) or **2b** (92 mg, 0.25 mmol, 1 equiv), sulfur nucleophile **4** (104 mg, 0.5 mmol, 2 equiv), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (9.4 mg, 0.013 mmol, 0.05 equiv), and dichloroethane (1 mL, 0.25 M). The resulting solution was irradiated with blue LEDs for 24 h. The reaction mixture was then diluted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by MPLC to give the final product.

General Procedure of Amino-trifluoromethylation of Alkene. To a vial equipped with a stir bar were added styrene (0.5 mmol, 2 equiv), Togni-type reagent **2a** (79 mg, 0.25 mmol, 1 equiv), amine nucleophile (0.5 mmol, 2 equiv), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (9.4 mg, 0.013 mmol, 0.05 equiv), and dichloroethane (1 mL, 0.25 M). The resulting solution was irradiated with blue LEDs for 24 h. The reaction mixture was then diluted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by MPLC to give the final product.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c06017.

Experimental procedures and ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra (PDF)

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Author Contributions

§Y.R.C., S.K., and J.H. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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