

Metal-Free Photocatalytic Radical Trifluoromethylation Utilizing Methylene Blue and Visible Light Irradiation

Spencer P. Pitre, Christopher D. McTiernan, Hossein Ismaili, and Juan C. Scaiano*

Department of Chemistry and Centre for Catalysis Research and Innovation, University of Ottawa, 10 Marie Curie, Ottawa K1N 6N5, Canada

Supporting Information

ABSTRACT: The use of organofluorine compounds, especially those with an incorporated trifluoromethyl moiety, has increased dramatically in both the pharmaceutical and agrochemical industry. It has therefore become imperative to develop a mild and efficient synthetic technique for the inclusion of trifluoromethyl groups. Herein, we report the first use of methylene blue as a photosensitizer for the catalytic radical trifluoro- and hydrotrifluoromethylation of electron-rich heterocycles as well as terminal alkenes and alkynes under visible light irradiation. These reactions proceed with moderate to good yields at low catalyst concentrations; short irradiation times; and most importantly, without the need for potentially toxic transition-metal catalysts. In this work, considerable emphasis was also placed on understanding the kinetics of the mechanistically key steps through the use of laser flash photolysis techniques to more efficiently optimize the reaction conditions.

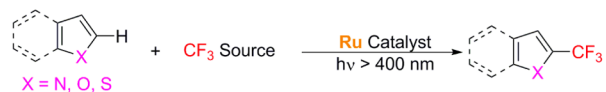
KEYWORDS: trifluoromethylation, metal-free, methylene blue, photoredox catalysis, laser flash photolysis

INTRODUCTION

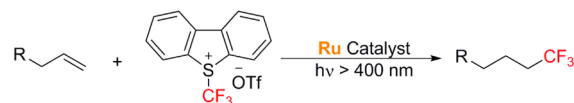
Over the years, the impact of organofluorine compounds on both the pharmaceutical and agrochemical industries has grown exponentially.^{1,2} In particular, the trifluoromethyl (CF₃) group is becoming one of the most structurally important moieties in these fields. Incorporation of fluorine atoms, in particular CF₃ moieties, can lead to an increase in bioavailability, lipophilicity, metabolic stability, and hydrolytic stability in compounds in comparison with their nonfluorinated counterparts.³ Considering that organofluorine compounds are virtually absent in nature, developing a mild, efficient synthetic method for the inclusion of a CF₃ group is of utmost importance.

In the past five years, the development of methods for the direct replacement of C–H bonds with C–CF₃ bonds has attracted a great deal of attention.⁴ For example, MacMillan and co-workers have developed a highly efficient photocatalytic technique for the trifluoromethylation of a variety of different substrates based on ruthenium and iridium complexes using various CF₃ precursors.^{5–8} Employing a similar system, Cho and co-workers have also demonstrated the trifluoromethylation of a variety of electron-rich heterocycles (see Figure 1A).⁹ Ruthenium complexes along with Umemoto's reagent have also been recently shown to catalyze the hydrotrifluoromethylation of a broad scope of unactivated terminal alkenes and alkynes (see Figure 1B).¹⁰ A major limitation of these methods is the use of precious metals as photocatalysts, which can exhibit high toxicity and thus limit their further applications in the pharmaceutical and agrochemical industries. Alternatively to these photochemical methods, these transformations can be achieved with the use of other transition-metal catalysts.¹¹ For

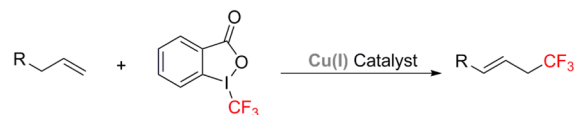
A. Previous Work: Trifluoromethylation of Heterocycles (MacMillan, Cho)



B. Previous Work: Hydrotrifluoromethylation of Unactivated Alkenes (Gouverneur)



C. Previous Work: Trifluoromethylation of Unactivated Alkenes (Buchwald, Wang)



D. This Work: Methylene Blue Catalyzed Radical Trifluoromethylation

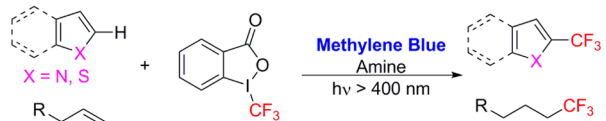


Figure 1. Trifluoromethylation of electron-rich heterocycles and unactivated alkenes.^{5,9,10,12,13}

example, Buchwald and Wang have independently developed efficient methods for the trifluoromethylation of unactivated

Received: April 30, 2014

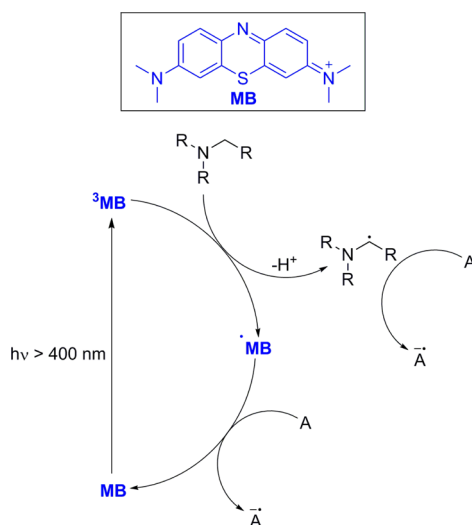
Revised: June 12, 2014

Published: June 13, 2014

alkenes employing different copper(I) catalysts and Togni's Reagent as the CF₃ source (see Figure 1C) and have provided experimental evidence that free CF₃ radicals were involved in these transformations.^{12,13} However, these transformations typically require a high concentration of the copper(I) catalyst (10–15 mol %), and the method developed by Wang and co-workers also requires the input of heat into the system to obtain high reaction efficiency.

In light of the disadvantages associated with these transition-metal catalyzed methods, there has been a recent push to develop a novel transition-metal-free catalytic system for these trifluoromethylation transformations.^{14–20} However, the use of metal-free systems in this field still remains rather underdeveloped. On the basis of our previous results for the oxidative hydroxylation of arylboronic acids using methylene blue (MB) as photosensitizer,²¹ we decided to test MB as a photosensitizer for the radical trifluoromethylation of various substrates. MB is a member of the thiazine dye family and, as previously demonstrated, has a triplet state that is readily quenched by aliphatic amines to form a semireduced MB radical and an amine-radical cation (Scheme 1). In this case, both the

Scheme 1. General Scheme for Photoredox Transformations Catalyzed by a Methylene Blue/Amine Photocatalytic System



semireduced MB and the amine-radical cation, which readily deprotonates to form an α -aminoalkyl radical under basic conditions, are capable of reducing numerous organic substrates.^{21,22} With this knowledge, we aimed to develop a mild trifluoromethylation method based on a system in which MB and the α -aminoalkyl radicals could be used to reduce several electrophilic CF₃ sources and thereby produce the required CF₃ radicals (see Figure 1D).

Herein, we report the first use of MB as a photocatalyst, coupled with Togni's reagent as the CF₃ source, for the radical trifluoromethylation of electron-rich heterocycles, as well as the hydrotrifluoromethylation of terminal alkenes and alkynes under visible light irradiation. In this work, considerable emphasis was placed on understanding the kinetics of the mechanistically relevant steps using laser flash photolysis techniques to more efficiently optimize our reaction conditions. Rate constants for these steps have also been determined.

RESULTS AND DISCUSSION

Because of the electrophilic nature of the CF₃ radical, we chose to begin our studies of radical trifluoromethylation employing MB as a photocatalyst for the trifluoromethylation of electron-rich substrates using 3-methylindole (3MI) as our model substrate. Recently, Cho and co-workers reported the trifluoromethylation of 3-methylindole with Ru(bpy)₃Cl₂ as the photosensitizer and CF₃I as the CF₃ radical source.⁹ One limitation of this method, however, is the use of CF₃I, which is a gas. This makes it difficult to know the exact concentration present in the reaction mixture, making it difficult to optimize the kinetics of key reaction steps, something we emphasize in this contribution. With this in mind, we decided to employ electrophilic CF₃ reagents, such as Togni's hypervalent-iodine compounds and Umemoto's reagent, for the trifluoromethylation of 3-methylindole.

First, the role of the amine "electron-donor" was examined. The trifluoromethylation of 3-methylindole was attempted with MB and Togni's reagent (II) (see reaction 1 and Table 1) using



Table 1. Substrate Screening for the Trifluoromethylation of 3-Methylindole

	Umemoto	Togni (I)	Togni (II)
$E_{1/2}^{\text{red}}$ (V vs. SCE)	-0.75	-1.34	-1.49
³ MB k_q ($M^{-1} s^{-1}$)	4.75×10^9	4.83×10^7	2.33×10^8
Product Yield	35%	77%	47%

triethylamine (TEA), *N,N*-diisopropylethylamine (DIPEA), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, reaction 1) as the electron donors. We were pleased to observe the trifluoromethylated product in every case; however, when TMEDA was used as the electron donor, the highest yield was obtained (see S3 in the Supporting Information (SI)). This was, however, no surprise; we had found earlier that TMEDA has the highest rate constant for the quenching of MB's triplet state of the three amines chosen, which produces the semireduced MB radical, and an amine-radical cation.²¹

We then proceeded to screen which electrophilic CF₃ source would provide the most efficient generation of CF₃ radicals. We had initially hypothesized that Umemoto's reagent (Table 1, left) would be the most efficient source of CF₃ radicals because it has a much lower reduction potential than both analogues of Togni's reagent (Table 1).²³ However, after 24 h of irradiation, we observed that the reaction with Togni's reagent (I) was the most efficient at 77% yield, whereas the reaction with Umemoto's reagent was the least efficient of the three sources. Although this puzzled us initially, a detailed look at the kinetics for the triplet quenching of MB provided us with an answer.

Rather than provide extensive details for all the rates measured, we describe briefly below the type of measurements carried out by laser flash photolysis, and all other details (for other systems) are part of the Supporting Information.

Figure 2 shows the data used to determine the rate constant for TMEDA quenching of triplet MB. Because of the overlap in

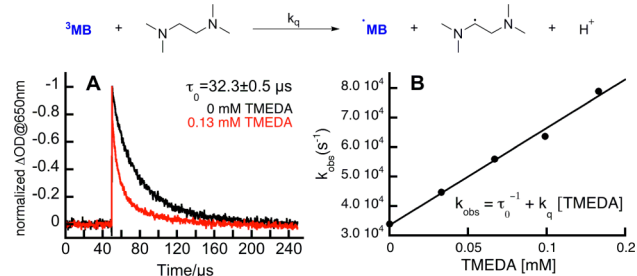


Figure 2. Kinetic analysis of the reaction between ^3MB and TMEDA. Because of overlap between signals corresponding to the triplet and reduced form of MB, the rate of ^3MB quenching was measured by monitoring the recovery of ground state MB at 650 nm. (A) Decay traces measured at 650 nm in the presence of 0 mM (black) and 0.13 mM (red) TMEDA after laser pulse excitation (308 nm, 10 mJ) of MB. Traces were normalized to account for permanent bleaching of the sample. (B) Kinetic plot showing the rate of ^3MB quenching as a function of [TMEDA]. The slope of this plot corresponds to the bimolecular rate constant for this reaction ($3.41 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$).

signals for triplet MB and its reduced form, we measured the rate by monitoring the recovery of the ground state band from MB at 650 nm following 308 nm laser excitation. The two traces shown correspond to the lowest (0 mM) and highest (0.13 mM) concentrations of TMEDA in the kinetic plot of panel B. From the slope in panel B, one derives the bimolecular quenching rate constant.

A procedure similar to that illustrated in Figure 2 was employed to determine various rate constants. As shown in Table 1, we also investigated the quenching constants (k_q) for all substrates and products in our model reaction. For this reaction to proceed efficiently, TMEDA must out-compete the other substrates for quenching of MB's triplet state so as to generate the active catalytic components.

We found that Umemoto's reagent quenches the triplet of MB 2 orders of magnitude faster than Togni's reagent (I), which probably accounts for the large difference in reactivity observed. To put this into perspective, we can formulate the following equation to determine the percentage of TMEDA quenching MB's triplet state at initial reaction conditions.

$$\% \text{TMEDA quenching} = \frac{100\% \times k_q^{\text{TMEDA}} [\text{TMEDA}]}{(\tau_0^{-1} + k_q^{\text{TMEDA}} [\text{TMEDA}] + k_q^{\text{3MI}} [\text{3MI}] + k_q^{\text{CF}_3\text{source}} [\text{CF}_3\text{source}] + k_q^{\text{O}_2} [\text{O}_2])}$$

By performing this calculation for both Umemoto's reagent and Togni's reagent (I) for a CF_3 source concentration of 45 mM, we determined that only 8% of the triplets are quenched by TMEDA for the reaction containing Umemoto's reagent, as compared with 51% of the triplets for the reaction containing Togni's reagent (I). Therefore, even though Umemoto's reagent has a much lower reduction potential than the hypervalent iodine compounds, it is still less efficient for radical trifluoromethylation with MB because it inhibits the quenching of the triplet by TMEDA. Note that this mechanistic

interpretation would not be possible without an in-depth kinetic analysis.

With the optimal substrates in hand, we then focused on optimizing the reaction conditions. As seen in Table 2, the rate

Table 2. Optimization of Reaction Conditions

MB, mM	TMEDA, mM	solvent	atm	time, h	isolated yield
0.3	60	CH_3CN	air	12	25%
0.3	60	DMF	air	6	23%
0.6	120	DMF	air	9	44%
1.2	120	DMF	air	6	59%
2	200	DMF	air	6	59%
2	200	DMF	argon	6	70%
	200	DMF	argon	6	trace
2		DMF	argon	6	35%
2	200	DMF	argon	6	no reaction ^a

^aReaction performed in the dark.

of the reaction was found to increase when the solvent was switched from CH_3CN to DMF. The reaction rate also increased proportionally when increasing the concentration of MB. Finally, removing O_2 from the reaction ($^3\text{MB } k_q = 2.46 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$)²¹ resulted in an 11% increase in yield as a result of the removal of this competing triplet quenching process. Control experiments also showed that both MB and visible light irradiation are required for the trifluoromethylation of 3-methylindole. Interestingly, trifluoromethylation was observed in the absence of TMEDA, yielding 35% of the trifluoromethylated indole. Upon further investigation, it was discovered that a single electron transfer from 3-methylindole ($E_{1/2}^{\text{ox}} = 1.12 \text{ V vs SCE}$)²⁴ to the triplet state of MB ($E_{1/2}^{\text{red}} = 0.011 \text{ V vs SCE}$ for ground-state MB)²⁵ is a thermodynamically favorable process when the triplet state energy of MB (33 kcal/mol)²⁶ is taken into account. The high triplet-quenching constant ($4.1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$) also makes it a kinetically favorable process upon removal of TMEDA. Therefore, upon removal of TMEDA, electron-transfer occurs to ^3MB from 3-methylindole, resulting in an oxidized indole and the semireduced form of MB. Because we do not isolate any other products after the reaction, we hypothesize that the oxidized indole could be reduced back to its original form by the trace amounts of amine impurities in the solvent.²⁷ In addition, we have previously observed that these amine impurities can also reduce ^3MB .²¹ This could explain why the percent yield is roughly half of that measured when our sacrificial amine is present in the reaction mixture.

With these final optimized conditions, we proceeded with the radical trifluoromethylation of various electron-rich heterocycles (Table 3) utilizing the same optimized conditions for the trifluoromethylation of 3-methylindole. The trifluoromethylation of various substituted indoles proceeded with high efficiency. No trifluoromethylation of the aromatic portion of the indole substrates was observed. The trifluoromethylation of pyrroles as well as a thiophene derivative also proceeded in moderate yields.

We then shifted our attention to the trifluoromethylation of unactivated terminal alkenes. Currently, the methods available for alkenyl trifluoromethylation are limited to narrow substrate

Table 3. Trifluoromethylation of Electron-Rich Substrates

Substrate	Product	Yield
		70%
		79%
		52%
		42%
		44%
		63%

Conditions: substrate (100 mM), Togni's Reagent (1.5 equiv), MB (0.02 equiv), TMEDA (2 equiv) in DMF were irradiated with two warm white LEDs for 6 h.

scopes and the requirement of prefunctionalized substrates and transition-metal catalysts.¹ Because of recent work by Cho and co-workers in their development of a photoredox method for the trifluoromethylation of unactivated alkenes,²⁸ we decided to investigate the potential of our system for similar processes. 1-Dodecene was used as a model substrate, and the trifluoromethylation reaction was attempted under our predetermined optimized conditions. Interestingly, not only did we observe the product corresponding to the CF₃ radical addition to the double bond, but we also observed that the major product of the reaction corresponded to the addition of both a CF₃ radical and a hydrogen atom to the terminal double bond (see Table 4). Although this originally came as a surprise, multiple hydrogen sources are available in our reaction to promote such a transformation. For instance, it has been reported that oxidized amines are great hydrogen donors.²⁹ It has also been reported that the fully reduced form of MB, *leuco*-MB, can act as a hydrogen source.³⁰ In Cho's reported trifluoromethylation of terminal alkenes, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as the sacrificial electron donor for the Ru²⁺ excited state.²⁸ In an attempt to push the selectivity toward only CF₃ radical addition, we performed the reaction replacing TMEDA as the electron donor with DBU. Surprisingly, we observed the same distribution of the final products as the previous reaction with TMEDA; however, with an increased efficiency (Table 4).

Table 4. Trifluoromethylation of 1-Dodecene

Amine	Time	Major Product	Minor Product
	6 h		
$k_q^{3MB} = 3.41 \times 10^8$			
	3 h		
$k_q^{3MB} = 1.05 \times 10^7$			

Conditions: 1-dodecene (95 mM), Togni's Reagent (1.5 equiv), MB (0.02 equiv), amine (2 equiv) in DMF were irradiated with two warm white LEDs.

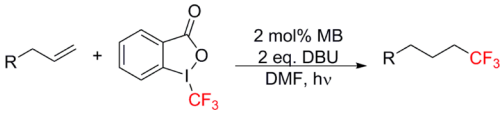
Notably, we were also able to complete the reaction in only 3 h using DBU. More interestingly, despite this increase in reaction efficiency, the ³MB quenching rate for DBU is actually a full order of magnitude less than that of TMEDA. However, it is important to note that these quenching constants take into account all forms of ³MB quenching because not all quenching events result in electron transfer. Therefore, although DBU may have a lower overall k_q compared with TMEDA, it is observed through absorption spectra that DBU forms a charge-transfer complex with MB, resulting in improved electron transfer (see Figure S1 in SI). To further investigate the nature of this charge-transfer complex, a Benesi–Hildebrand analysis was performed. From this, it was determined that a complex is formed with an association constant (K_A) of $2.5 \times 10^4 \text{ M}^{-1}$ (see section S6 in the SI).

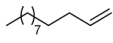
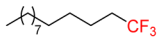
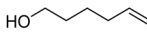
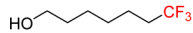
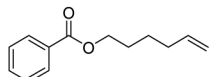
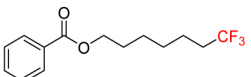
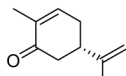
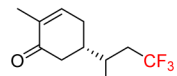
On the basis of these results, we decided to test our system in the hydrotrifluoromethylation of both a number of different terminal alkenes and alkynes. Gouverneur and co-workers reported a Ru(bpy)₃Cl₂ photoredox catalytic method for these transformations.¹⁰ More recently, Nicewicz and co-workers also developed an organocatalytic hydrotrifluoromethylation procedure based on an acridinium photocatalyst along with thiosalicylate or thiophenol as a substoichiometric H-donor.¹⁸ However, these methods require high catalyst concentrations and long irradiation times. Pleasingly, our system was able to catalyze many of these hydrotrifluoromethylation reactions for both terminal alkenes and alkynes (Tables 5 and 6). Importantly, our system required lower catalyst loading while providing improved efficiency, as well as an improved *E/Z* ratio for the hydrotrifluoromethylation of terminal alkynes as compared with the system developed by Gouverneur (Table 6).¹⁰

With efficient methods developed for both the trifluoromethylation of electron-rich heterocycles and for the hydrotrifluoromethylation of terminal alkenes and alkynes, we then decided to test the selectivity of our system by attempting the trifluoromethylation of 1-allyl-3-methylindole (Scheme 2).

Because of the electrophilic nature of the CF₃ radical, the radical should preferentially add to the electron-rich double bond of the alkene moiety over the terminal alkene moiety. Not surprisingly, we also observed minor products corresponding to the hydrotrifluoromethylation of the terminal alkene moiety, similarly to a recent report by Chu and Qing.³¹ However, from

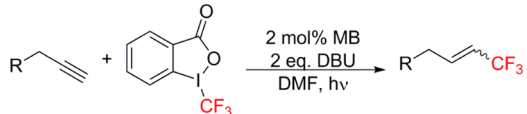
Table 5. Hydrotrifluoromethylation of Terminal Alkenes

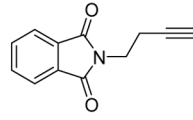
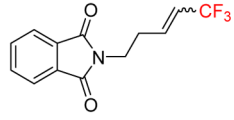
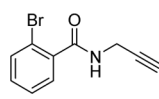
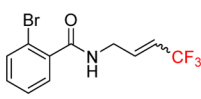
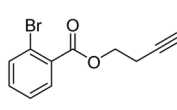
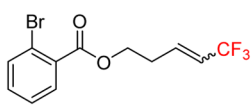


Substrate	Product	Yield
		67%
		48%
		83%
		40%

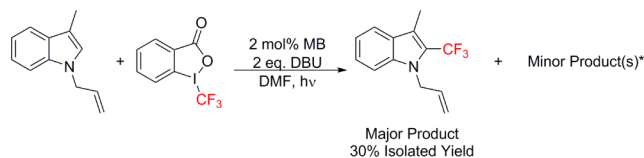
Conditions: substrate (100 mM), Togni's Reagent (1.5 equiv), MB (0.02 equiv), DBU (2 equiv) in DMF were irradiated with two warm white LEDs for 3 h.

Table 6. Hydrotrifluoromethylation of Terminal Alkynes



Substrate	Product	Yield
		70% (E:Z = 4:1)
		66% (E:Z = 10:1)
		79% (E:Z = 6:1)

Conditions: substrate (100 mM), Togni's Reagent (1.5 equiv), MB (0.02 equiv), DBU (2 equiv) in DMF were irradiated with two warm white LEDs for 3 h.

Scheme 2. Trifluoromethylation of 1-Allyl-3-methylindole^a

^aMinor products could not be isolated for further characterization.

these results, it is clear that the addition to the more electron-rich double bond happens before the addition to the terminal alkene. Note that by changing the reaction conditions, one could push the selectivity further, depending on whether the

hydrotrifluoromethylation of the terminal alkene is desired or not.

Finally, to establish if our reactions proceed with the addition of a CF₃ radical to our substrates, we added 4-hydroxy TEMPO to our reaction mixture to trap the CF₃ radical (Figure 3).

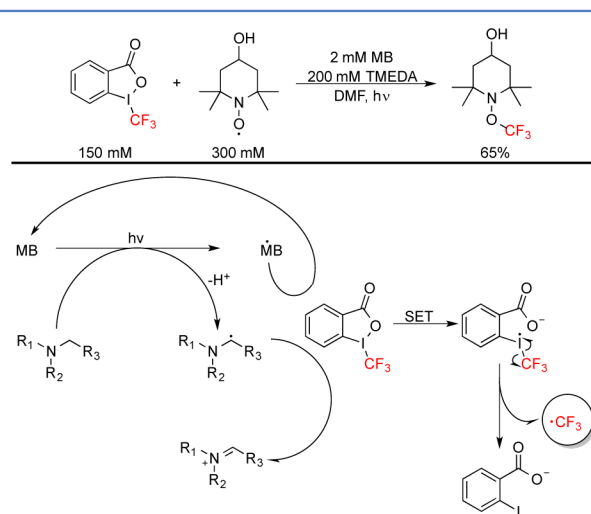


Figure 3. CF₃ radical trapping by TEMPO (top) and proposed mechanism for the formation of CF₃ radicals (bottom).

When the reaction was performed with 2 equiv of TEMPO with respect to Togni's reagent (1), we observed the trifluoromethylated TEMPO in 65% yield by ¹⁹F NMR, thus confirming the formation of CF₃ radicals. A possible mechanism for the catalytic formation of CF₃ radicals is shown in Figure 3, where upon visible light irradiation, the triplet state of MB can be quenched by either TMEDA or DBU to form the semireduced MB radical and an α -amino radical. Both of these species can in turn reduce Togni's reagent, resulting in the release of a CF₃ radical and the formation of 2-iodobenzoate.

CONCLUSION

We have demonstrated for the first time the use of methylene blue as a photosensitizer for the catalytic generation of CF₃ radicals. Using this system, we have demonstrated the trifluoromethylation of electron-rich heterocycles, which proceeded in moderate to good yield, as well as the hydrotrifluoromethylation of terminal alkenes and alkynes, which proceeded with high efficiency. Our method avoids the use of potentially toxic and expensive transition-metal catalysts while also providing improved reaction efficiency with lower catalyst loadings.

Once again, an understanding of the rate constants of the mechanistically key steps aided in the overall optimization and improved efficiency of our reaction conditions.

EXPERIMENTAL SECTION

General Information. Substrates, methylene blue, triethylamine (TEA), *N,N*-diisopropylethylamine (DIPEA), *N,N,N',N'*-tetramethylethylenediamine (TMEDA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and DMF were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar, TCI America, and Fisher) and used with no further purification unless otherwise noted. The light source, unless otherwise noted, was two warm white 90 W LEDs, which were

purchased from LedEngin. Flash column chromatography was performed using 230–400 mesh silica gel. Preparatory thin layer chromatography (PTLC) was performed using 1000- μm -thick glass baked TLC plates purchased from Silicycle. All ^1H and proton-decoupled ^{19}F NMR spectra were recorded on a Bruker Avance 400 spectrometer. Chemical shifts (δ) for ^1H NMR are reported in parts per million from the solvent resonance as the internal standard (CDCl_3 ; δ 7.26 ppm), and all proton-decoupled ^{19}F NMR were referenced versus CFCl_3 in CDCl_3 .

General Procedure for the Trifluoromethylation of Electron-Rich Heteroarenes. Heteroarene (0.3 mmol), methylene blue (2.2 mg, 0.006 mmol), Togni's Reagent (142 mg, 0.45 mmol), and DMF (3 mL) were added to a 10 mL Schlenk tube. The reaction mixture was then degassed using argon for 10–15 min, and TMEDA (90 μL , 0.6 mmol) was added under argon. The reaction mixture was then irradiated for 6 h. After irradiation, the mixture was extracted with ether ($\times 3$) and washed with brine ($\times 5$), and the ether layer was dried with MgSO_4 before being concentrated with a rotovap. The crude was purified by either flash column chromatography or PTLC.

General Procedure for the Trifluoromethylation of Terminal Alkenes and Alkynes. Substrate (0.3 mmol), methylene blue (2.2 mg, 0.006 mmol), Togni's Reagent (142 mg, 0.45 mmol), and DMF (3 mL) were added to a 10 mL Schlenk tube. The reaction mixture was degassed with argon, and DBU (90 μL , 0.6 mmol) was added under argon. The reaction mixture was then irradiated for 3 h. After irradiation, the reaction mixture was diluted with ether (30 mL) and washed with brine ($\times 5$), and the ether layer was dried with MgSO_4 before being concentrated with a rotovap. The crude was purified by either flash column chromatography or PTLC.

General Procedure for the Triplet Quenching Experiments of Methylene Blue. The triplet-quenching experiments of MB were performed using an excimer laser (308 nm, 10 mJ/pulse) in a LFP-111 laser-flash photolysis (LFP) system (Luzchem Inc., Ottawa, Canada) and 1×1 cm LFP-Luzchem cuvettes or 1×1 cm flow system. Samples of MB were prepared in solutions of 4:1 MeCN/ H_2O with a total volume of 3 mL and an absorbance of ~ 0.1 at 308 nm. The samples were degassed with N_2 for 30 min prior to use. The substrates used in the quenching studies were also prepared in solutions of 4:1 MeCN/ H_2O and degassed for the duration of the experiment.

Because of the overlap of the methylene blue triplet (420 nm) and the semireduced form (430 nm), it was necessary to use the recovery of ground-state methylene blue (650 nm) to measure the triplet quenching.

■ ASSOCIATED CONTENT

● Supporting Information

Details on the synthesis of Togni's reagent and other substrates, laser flash photolysis data, quenching plots, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: scaiano@photo.chem.uottawa.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Canadian Foundation for Innovation, and the Canada Research Chairs program.

■ REFERENCES

- (1) Studer, A. *Agnew. Chem. Int. Ed.* **2012**, *51* (36), 8950–8958.
- (2) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2013**, *114* (4), 2432–2506.
- (3) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37* (2), 320–330.
- (4) Koike, T.; Akita, M. *Top. Catal.* **2014**, *57*, 967–974.
- (5) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224–228.
- (6) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132* (14), 4986–4987.
- (7) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131* (31), 10875–10877.
- (8) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem.* **2011**, *123* (27), 6243–6246.
- (9) Iqbal, N.; Choi, S.; Ko, E.; Cho, E. J. *Tetrahedron Lett.* **2012**, *53* (15), 2005–2008.
- (10) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135* (7), 2505–2508.
- (11) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111* (8), 4475–4521.
- (12) Parsons, A. T.; Buchwald, S. L. *Agnew. Chem. Int. Ed.* **2011**, *50* (39), 9120–9123.
- (13) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133* (41), 16410–16413.
- (14) Cui, L.; Matusaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoh, A. *Adv. Synth. Catal.* **2013**, *355* (11–12), 2203–2207.
- (15) Fu, W.; Guo, W.; Zou, G.; Xu, C. *J. Fluorine Chem.* **2012**, *140* (0), 88–94.
- (16) Yang, Y.-D.; Iwamoto, K.; Tokunaga, E.; Shibata, N. *Chem. Commun.* **2013**, *49* (48), 5510–5512.
- (17) Wu, X.; Chu, L.; Qing, F.-L. *Tetrahedron Lett.* **2013**, *54* (3), 249–251.
- (18) Wilger, D. J.; Gesmundo, N. J.; Nicewicz, D. A. *Chem. Sci.* **2013**, *4* (8), 3160–3165.
- (19) Cantillo, D.; de Frutos, O.; Rincón, J. A.; Mateos, C.; Kappe, C. O. *Org. Lett.* **2014**, *16* (3), 896–899.
- (20) Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16* (4), 1216–1219.
- (21) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. *J. Am. Chem. Soc.* **2013**, *135* (36), 13286–13289.
- (22) Ismaili, H.; Pitre, S. P.; Scaiano, J. C. *Catal. Sci. Technol.* **2013**, *3* (4), 935–937.
- (23) Yasu, Y.; Koike, T.; Akita, M. *Agnew. Chem. Int. Ed.* **2012**, *51* (38), 9567–9571.
- (24) Yin, B.; Wang, L.; Inagi, S.; Fuchigami, T. *Tetrahedron* **2010**, *66* (34), 6820–6825.
- (25) Rao, P. S.; Hayon, E. *J. Am. Chem. Soc.* **1974**, *96* (5), 1287–1294.
- (26) Murov, S. L.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*. MerceL Decker Inc: New York, 1993.
- (27) Juillard, J. *Pure Appl. Chem.* **1977**, *49*, 885–892.
- (28) Iqbal, N.; Choi, S.; Kim, E.; Cho, E. J. *J. Org. Chem.* **2012**, *77* (24), 11383–11387.
- (29) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131* (25), 8756–8757.
- (30) Yamamoto, S.; Fujiyama, Y.; Shiozaki, M.; Sueishi, Y.; Nishimura, N. *J. Phys. Org. Chem.* **1995**, *8* (12), 805–809.
- (31) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2011**, *134* (2), 1298–1304.