catalysts

MDPI

Article

Cu(II)-Catalyzed Oxidative Trifluoromethylation of Indoles with KF as the Base

Xiaolin Shi [1,2,4], Xiaowei Li [1,2,4], Lina Ma [1,2,4] and Dayong Shi [1,2,3,4,*]

1 Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences, Qingdao 266071, China; shixiaolin16@mails.ucas.ac.cn (X.S.); lixiaowei17@mails.ucas.edu.cn (X.L.); nanjiluotuo@163.com (L.M.)
2 Laboratory for Marine Drugs and Bioproducts of Qingdao National Laboratory for Marine Science and Technology, Qingdao 266000, China
3 State Key Laboratory of Microbial Technology, Shandong University, No. 72 Binhai Road, Qingdao 266237, China
4 University of Chinese Academy of Sciences, Beijing 100049, China
* Correspondence: shidayong@qdio.ac.cn; Tel.: +86-532-8289-8719

Received: 28 February 2019; Accepted: 14 March 2019; Published: 19 March 2019

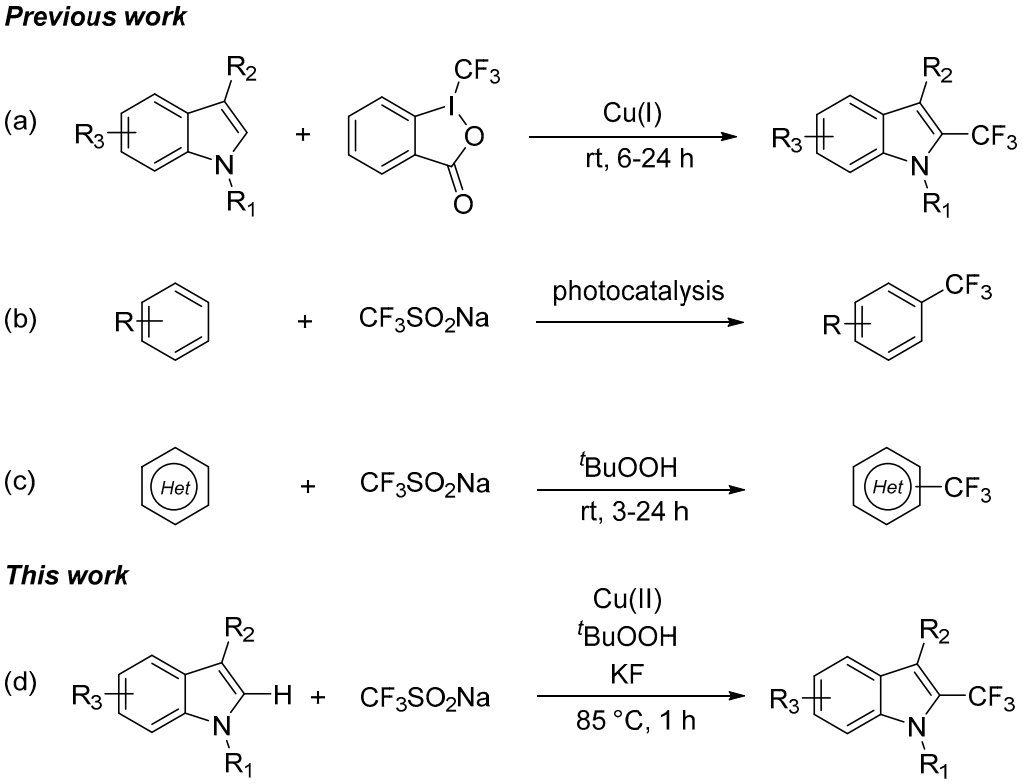
Abstract: This paper offers an efficient copper-catalyzed oxidative trifluoromethylation of indoles with low-cost CF_3SO_2Na via C–H activation. Notably, the use of a base is crucial for the trifluoromethylation of indoles. This reaction proceeds efficiently in good to excellent yields and is tolerance of a broad range of functional groups. Furthermore, melatonin, a medicine for sleep disorders, is converted to its 2-CF_3 analogue in 68% yield. Studies of possible reaction pathways suggest that this reaction proceeds through a radical process.

Keywords: Cu(II) catalyst; Langlois reagent; trifluoromethylation; indole; radical reaction

1. Introduction

The trifluoromethyl group is a privileged motif of medicinal chemistry, as it can dramatically improve the binding selectivity, solubility, lipophilicity, and catabolic stability of drug candidates [1–5]. As a consequence, the development of new methods for the synthesis of trifluoromethylated arenes and heteroarenes has received substantial attention [6–13]. In 2010, Sodeoka reported a Cu(OAc)-catalyzed trifluoromethylation of indoles using expensive and sensitive Togni reagent as the trifluoromethyl source (Scheme 1a) [14]. However, this method is limited to dry solvents and expensive trifluoromethyl sources, and it requires long reaction times. Therefore, the identification of an alternative inexpensive and readily available trifluoromethylation agent is actively being pursued in current research [15–21]. A seminal advance in this area was developed by Langlois who reported a novel trifluoromethyl source, CF_3SO_2Na (Langlois reagent). Although the study was restricted to electron-rich subtrates, it greatly extended the field of trifluoromethylation chemistry [22]. Subsequently, Li et al. described the photoinduced trifluoromethylation of arenes with CF_3SO_2Na as the trifluoromethyl source (Scheme 1b) [23]. Very recently, the Baran group also extended the substrate scope to heterocycles with the trifluoromethyl salt in the absence of a metal catalyst; however, the reaction took 3–24 h (Scheme 1c) [24].

Based on these procedures, we envisioned that CF_3SO_2Na is suitable for the trifluoromethylation of substituted indoles. Herein, we report an enhanced oxidative trifluoromethylation of unactivated indoles through a radical-mediated mechanism with commercially available CF_3SO_2Na as the trifluoromethyl source and KF as the base (Scheme 1d).



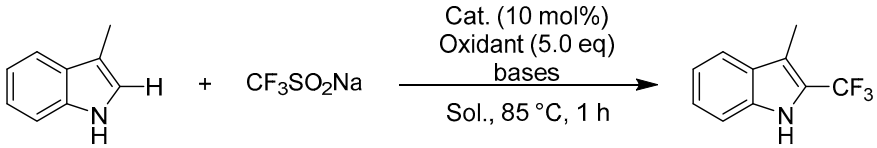
Scheme 1. Synthetic procedures for trifluoromethylation of arenes and heteroarenes.

2. Results

At the start of our work, the experiment of 3-methyl-1*H*-indole (**1a**) with CF_3SO_2Na (**2**) under various conditions was investigated (Table 1). To our delight, the C2-trifluoromethylated indole was obtained in a 39% yield with CuI as a catalyst and ^{t}BuOOH (*tert*-butyl hydroperoxide, 70% solution in H_2O) as the oxidant at 85 °C (Table 1, entry 1). Subsequently, we evaluated different catalyses, and Cu(II) appeared dramatically on the reaction, giving **3a** in 55% yield (entries 1–5). The screening of other oxidants revealed that ^{t}BuOOH was the best oxidant (entries 6–8). The effects of different solvents were compared, and the desired trifluoromethylated product was obtained in a 62% total yield in DMA (dimethylacetamide) (entries 9–15). Moreover, we were pleased to find that the presence of a base slightly improved the yield of this reaction, and KF provided a satisfying yield (entries 16–18). Additionally, by carefully adjusting the amount of KF, the yield was further improved, and the reaction gave desired product **3a** in 86% isolated yield (entry 19). Finally, performing the reaction at room temperature diminished the reaction rate and yield (entry 20).

With the optimized reaction conditions in hand, we explored the substrate scope. Our initial studies were focused on the reactions of 3-substituted and *N*-substituted indoles (Figure 1). To our satisfaction, a range of functional groups, such as linear alkyl groups, cyclic alkanes, esters, and amides, were tolerated in this reaction and provided the desired products in 47–86% (**3a**–**3j**). Notably, substrates with strong electron-withdrawing groups, such as halides and cyano, at the C3 position also reacted efficiently to give **3k** and **3l** in 45% and 58% yields respectively. Although the trifluoromethylation of *N*-benzyl indole required 12 h, it afforded the corresponding trifluoromethylated indole (**3o**) an excellent yield (70%).

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



1a **2** **3a**

Entry	Cat.	Oxidant	Solvent	Base	3a (Yield %) [b]
1	CuI	^{t}BuOOH	dioxane	-	39
2	-	^{t}BuOOH	dioxane	-	37
3	$FeCl_2$	^{t}BuOOH	dioxane	-	38
4	$CuSO_4$	^{t}BuOOH	dioxane	-	55
5	$Cu(OTf)_2$	^{t}BuOOH	dioxane	-	42
6	$CuSO_4$	air	dioxane	-	N.D.
7	$CuSO_4$	H_2O_2	dioxane	-	N.D.
8	$CuSO_4$	^{t}BuOOH [c]	dioxane	-	36
9	$CuSO_4$	^{t}BuOOH	DCM:H_2O [d]	-	58
10	$CuSO_4$	^{t}BuOOH	MeOH	-	34
11	$CuSO_4$	^{t}BuOOH	DCM	-	23
12	$CuSO_4$	^{t}BuOOH	MeCN	-	26
13	$CuSO_4$	^{t}BuOOH	PhMe	-	39
14	$CuSO_4$	^{t}BuOOH	DMF	-	49
15	$CuSO_4$	^{t}BuOOH	DMA	-	62
16	$CuSO_4$	^{t}BuOOH	DMA	CsF	69
17	$CuSO_4$	^{t}BuOOH	DMA	NH_4OH	68
18	$CuSO_4$	^{t}BuOOH	DMA	KF [e]	72
19	**$CuSO_4$**	**^{t}BuOOH**	**DMA**	**KF [f]**	**88(86)**
20	$CuSO_4$	^{t}BuOOH	DMA	KF [f,g]	72

[a] Conditions: **1a** (0.5 mmol), CF_3SO_2Na (1.5 mmol), catalyst (10 mol %), solvent (3.0 mL), 85 °C, 1 h, under Ar. [b] Reported yields were based on **3a** and determined by ^{1}H NMR using CH_2Br_2 as an internal standard. [c] ^{t}BuOOH-decane. [d] DCM:H_2O (1:1 ratio). [e] KF (100 mol%). [f] KF (50 mol%). [g] Room temperature, 12 h.

Furthermore, a variety of substrates with functional groups on the benzene ring were also screened (Figure 2). Generally, a wide range of functional groups, such as fluoro, chloro, bromo, and methoxy, were compatible with this protocol (**4a**–**4p**). In particular, halides, such as F, Cl, and Br, were well-tolerated, affording the C2-trifluoromethylated indoles in good to excellent yields (53–83%). Moreover, the newly developed protocol was successfully applied to the late-stage trifluoromethylation of complex or bioactive substances (**4q**–**4s**). Notably, melatonin, a medicine for sleep disorders, was directly converted to its 2-CF_3 analogue, **4s**, in 68% yield using the optimized conditions.

To elucidate the mechanism of this reaction, radical scavenger experiments were conducted (Scheme 2). When a radical inhibitor, including TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and BHT (butylated hydroxytoluene), was added, the reaction was dramatically suppressed, implying that a radical reaction pathway might be involved in the catalytic cycle.

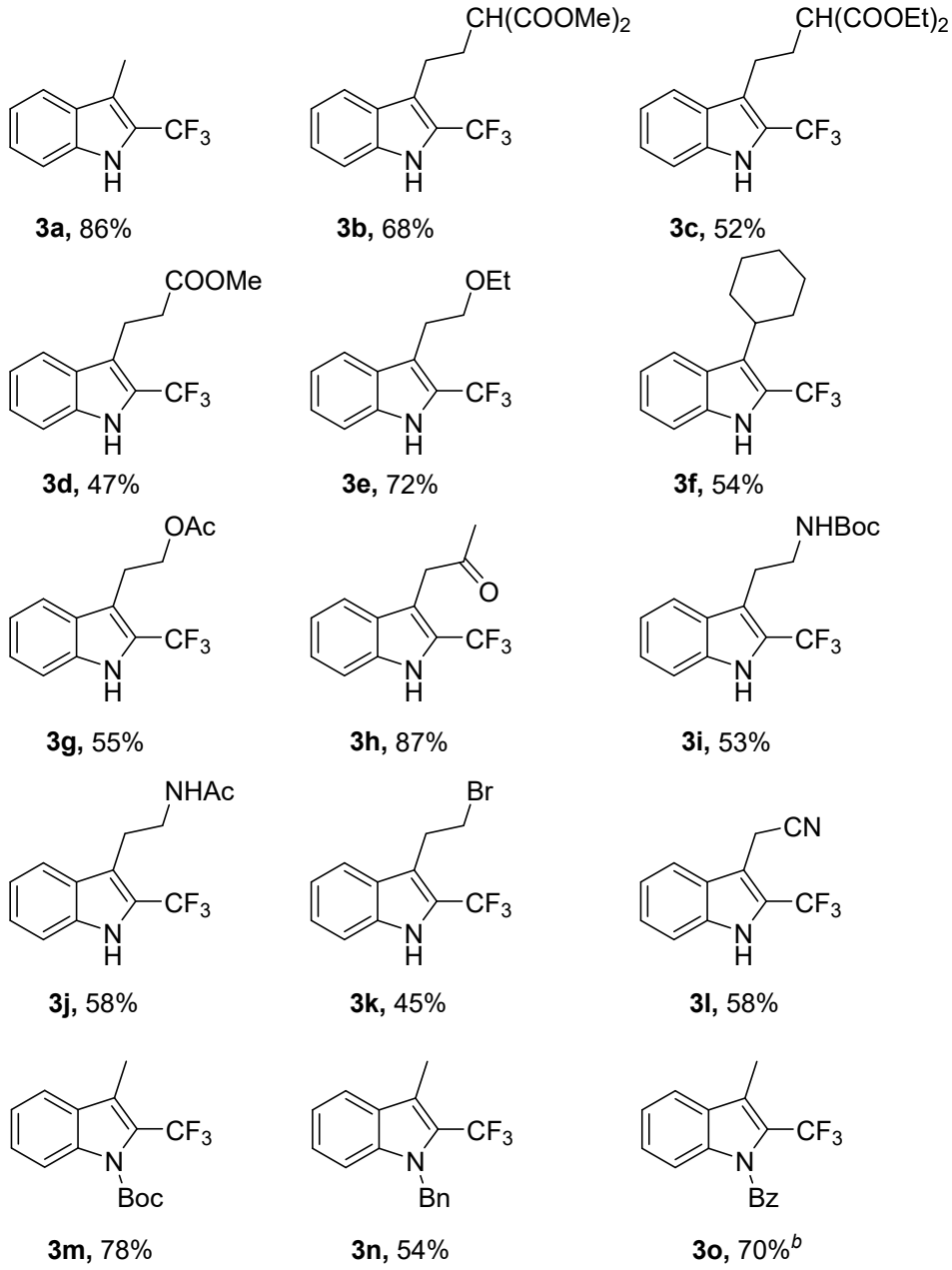


Figure 1. Reaction scope of the 3-indoles and the *N*-indoles [a]. [a] Conditions: **1** (0.5 mmol), **2** (1.5 mmol), $CuSO_4$ (10 mol %), ^{t}BuOOH (2.5 mmol), KF (50 mol%), DMA (3.0 mL), 85 °C, 1 h, under Ar. Isolated yield. [b] reaction time: 12 h.

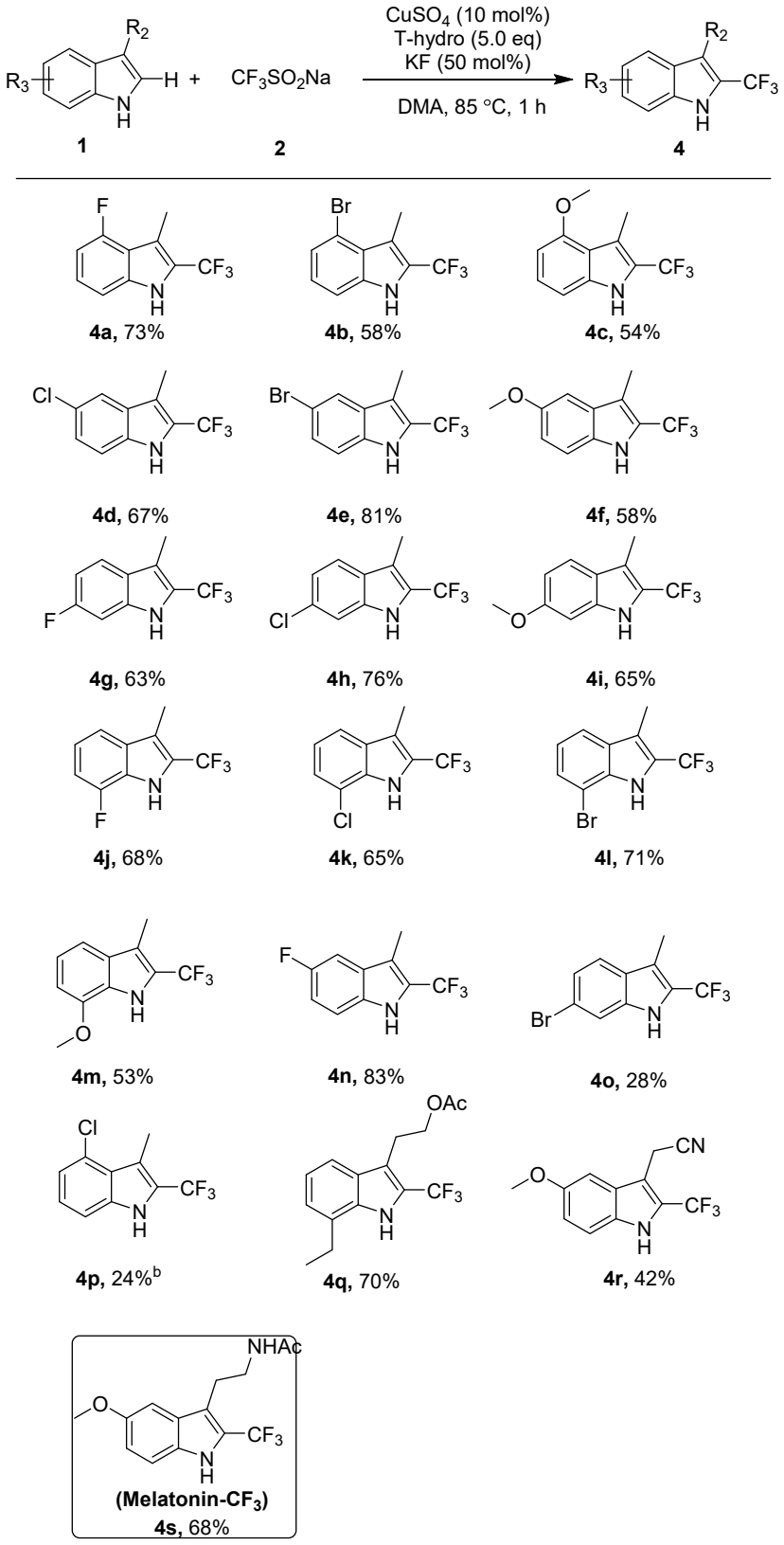
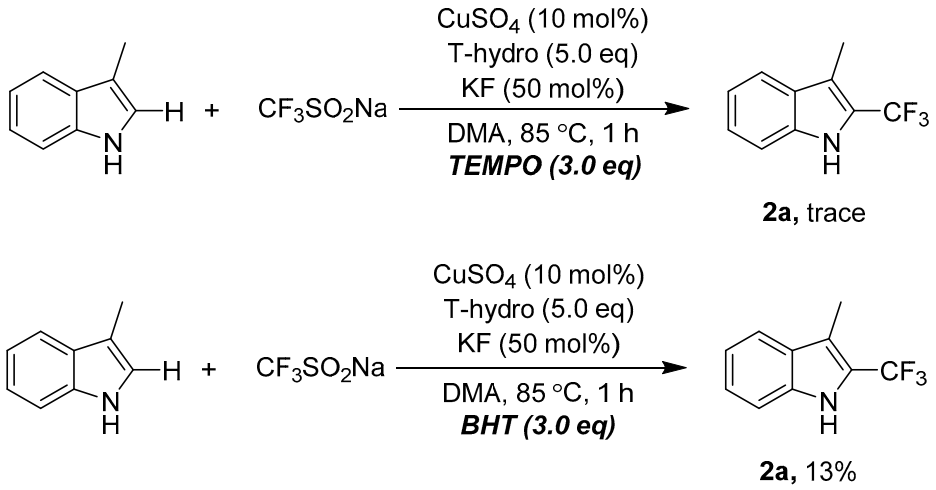
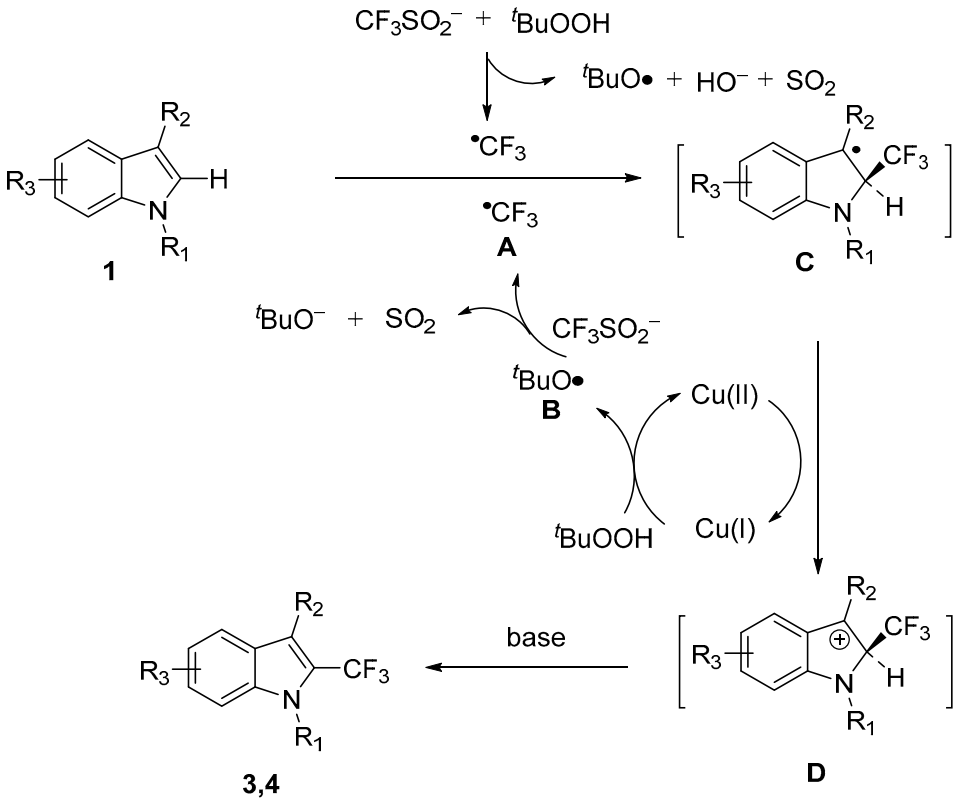


Figure 2. Reaction scope of functional indoles [a]. [a] Conditions: **1** (0.5 mmol), **2** (1.5 mmol), $CuSO_4$ (10 mol %), ^{t}BuOOH (2.5 mmol), KF (50 mol%), dimethylacetamide (DMA) (3.0 mL), 85 °C, 1 h, under Ar. Isolated yield. [b] Yield based on ^{1}H NMR.



Scheme 2. Mechanistic study. BHT: butylated hydroxytoluene; TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy.

Based on the above results and previous literature, a plausible mechanistic interpretation is depicted in Scheme 3 [22,24–31]. Initially, $CF_3SO_2^-$ reacts with ^{t}BuOOH to form •CF_3 (**A**). Alternatively, **A** could also be derived from $CF_3SO_2^-$ and ^{t}BuO• (**B**). Subsequently, in situ-generated •CF_3 species **A** adds to indole **1**, affording radical intermediate **C**. Thereafter, intermediate **D** is formed by the oxidation of the Cu(II) catalyst, which regenerates the Cu(I) catalyst. Following deprotonation, **D** reacts with base to give the expected products **3** and **4**. In addition, the Cu(I) catalyst is oxidized to Cu(II) by ^{t}BuOOH to complete the catalytic cycle.



Scheme 3. Proposed mechanism study.

3. Materials and Methods

^{1}H NMR spectra were recorded on Bruker 500 MHz spectrometer and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained at Bruker 125 MHz and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$). The NMR yield was determined by ^{1}H NMR using CH_2Br_2 as an internal standard. APEX II (Bruker Inc.) was used for ESI-HRMS. ^{19}F NMR spectra were recorded on Bruker 470 MHz spectrometer (see Supplementary Materials). IR spectra were recorded by a Nicolet 5MX-S infrared spectrometer. Flash column chromatography was performed over silica gel 200–300. All reagents were weighed and handled in air at room temperature. All chemical reagents were purchased from Alfa, Acros, Aldrich, and TCI, J&K and used without further purification.

A dry Schlenk tube was charged with **1** (0.5 mmol), **2** (1.5 mmol), $CuSO_4$ (12.5 mg, 10 mol%) and KF (14.7 mg, 50 mol%). DMA (dimethylacetamide, 3.0 mL) was added under argon, and the mixture was stirred at room temperature. *tert*-Butyl hydroperoxide (^{t}BuOOH, 70% solution in H_2O, 2.5 mmol) was dropped into the mixture under argon at room temperature. The resulting mixture was stirred at 85 °C for 1 h. Once the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether) to give product **3** or **4**.

3-Methyl-2-(trifluoromethyl)-1*H*-indole (3a) (86 mg, 86%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 3391, 2921, 2803, 1452, 1257, 1077, 1030, 754, 715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.20 (t, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 128.0, 124.7, 124.3 (q, J_{C-F} = 262.5 Hz), 121.6 (q, J^2 = 37.5 Hz), 120.4, 120.1, 114.0 (q, J^3 = 3.0 Hz) 111.5, 8.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.6 (d, *J* = 1.1 Hz); HRMS (ESI) calcd. for $C_{10}H_7NF_3$ $[M - H]^-$, 198.0536; found: 198.0538.

Dimethyl 2-(2-(2-(trifluoromethyl)-1*H*-indol-3-yl)ethyl)malonate (3b). (117 mg, 68%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:40, R_f = 0.3); IR (neat): ν_{max} 3394, 2923, 2843, 1724, 1260, 1111, 1078, 908, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.30 (t, *J* = 7.60 Hz, 1H), 7.20 (t, 1H), 3.75 (s, 6H), 3.45 (t, *J* = 7.3 Hz, 1H), 2.30–2.95 (m, 2H), 2.35–2.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 135.3, 127.1, 124.8, 122.0 (q, J_{C-F} = 267.3 Hz), 121.7 (q, J^2 = 36.8 Hz), 120.6, 120.1, 116.7 (q, J^3 = 3.0 Hz), 111.8, 52.5, 51.1, 29.6, 21.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.3 (s); HRMS (ESI) calcd. for $C_{16}H_{15}O_4NF_3$ $[M - H]^-$, 342.0959; found: 342.0956; HRMS (ESI) calcd. for $C_{16}H_{15}O_4NF_3$ $[M - H]^-$, 342.0959; found: 342.0956.

Diethyl 2-(2-(2-(trifluoromethyl)-1*H*-indol-3-yl)ethyl)malonate (3c). (97 mg, 52%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:40, R_f = 0.3); IR (neat): ν_{max} 3371, 2993, 2863, 1721, 1260, 1161, 1118, 908, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.20 (t, 1H), 4.30–4.15 (m, 4H), 3.45 (t, *J* = 7.3 Hz, 1H), 3.00–2.90 (m, 2H), 2.35–2.20 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.28, 135.27, 127.16, 124.78, 121.9 (q, J_{C-F} = 267.4 Hz), 121.6 (q, J^2 = 36.8 Hz), 120.57, 120.17, 116.9 (q, J^3 = 2.6 Hz), 111.73, 61.47, 51.57, 29.60, 21.57, 13.98; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.3 (s); HRMS (ESI) calcd. for $C_{18}H_{19}O_4NF_3$ $[M - H]^-$, 370.1272; found: 370.1280.

Methyl 3-(2-(trifluoromethyl)-1*H*-indol-3-yl)propanoate (3d). (61 mg, 47%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 3386, 2943, 2822, 1324, 1261, 1106, 1076, 747, 725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.35–7.25 (m, 2H), 7.25–7.20 (m, 1H), 3.95 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 135.1, 127.2, 124.9, 123.8 (q, J_{C-F} = 267.4 Hz), 122.8 (q, J^2 = 36.9 Hz), 121.0, 120.0, 111.8, 110.2 (q, J^3 = 2.8 Hz), 52.2, 29.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.6 (s); HRMS (ESI) calcd. for $C_{12}H_9O_2NF_3$ $[M - H]^-$, 256.0591; found: 256.0588.

Ethyl 3-(2-(trifluoromethyl)-1*H*-indol-3-yl)propanoate (3e). (93 mg, 72%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:40, R_f = 0.3); IR (neat): ν_{max} 3321, 2823, 1323, 1146, 1097, 1052, 741, 726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.20 (t, 1H), 3.70 (t, *J* = 7.7 Hz, 2H), 3.55 (q, *J* = 7.0 Hz, 2H), 3.25–3.15 (m, 2H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 127.6, 124.7, 122.1 (q, J^2 = 36.5 Hz), 122.0 (q, J_{C-F} = 267.4 Hz), 120.5, 120.3, 114.9 (q, J^3 = 3.0 Hz), 111.7, 70.6, 66.2, 24.6, 15.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.3 (s); HRMS (ESI) calcd. for $C_{12}H_9O_2NF_3$ $[M - H]^-$, 256.0955; found: 256.0954.

3-Cyclohexyl-2-(trifluoromethyl)-1*H*-indole (3f). (72 mg, 54%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:40, R_f = 0.3); IR (neat): ν_{max} 3387, 2922, 2823, 1318, 1249, 1115, 1082, 740, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 3.00 (t, *J* = 12.1 Hz, 1H), 2.00–1.80 (m, 8H), 1.50–1.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 126.3, 124.3, 123.9 (q, J^3 = 3.0 Hz), 122.2, 122.1 (q, J_{C-F} = 267.3 Hz), 120.5 (q, J^2 = 36.0 Hz), 120.0, 111.9, 36.2, 32.8, 27.0, 26.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −57.5 (s); HRMS (ESI) calcd. for $C_{15}H_{15}NF_3$ $[M - H]^-$, 266.1162; found: 266.1163.

2-(2-(Trifluoromethyl)-1*H*-indol-3-yl)ethyl acetate (3g). (75 mg, 55%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:40, R_f = 0.3); IR (neat): ν_{max} 3361, 2954, 1719, 1160, 1086, 1037, 907, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.3, 0.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.20 (t, 1H), 4.30 (t, *J* = 6.9 Hz, 2H), 3.25 (t, 2H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 135.2, 127.3, 124.8, 122.4 (q, J^2 = 36.5 Hz), 121.9 (q, J_{C-F} = 267.4 Hz), 120.7, 113.8 (q, J^3 = 2.9 Hz), 111.8, 64.1, 23.4, 20.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.3 (s); HRMS (ESI) calcd. for $C_{13}H_{11}O_2NF_3$ $[M - H]^-$, 270.0747; found: 270.0745.

1-(2-(Trifluoromethyl)-1*H*-indol-3-yl)propan-2-one (3h). (105 mg, 87%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:10, R_f = 0.3); IR (neat): ν_{max} 3389, 2933, 2823, 1703, 1253, 1109, 1074, 740, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.34–7.29 (m, 1H), 7.20–7.15 (m, 1H), 3.98 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 135.3, 127.2, 126.0, 125.1, 124.0 (q, J_{C-F} = 267.5 Hz), 123.1 (q, J^3 = 3.4 Hz), 122.7 (q, J^2 = 36.8 Hz), 121.1, 120.0, 112.0, 39.3, 28.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.3 (s); HRMS (ESI) calcd. for $C_{12}H_9ONF_3$ $[M - H]^-$, 240.0642; found: 240.0639.

Tert-butyl (2-(2-(trifluoromethyl)-1*H*-indol-3-yl)ethyl)carbamate (3i). (87 mg, 53%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:5, R_f = 0.3); IR (neat): ν_{max} 3351, 2961, 2853, 1688, 1250, 1111, 1083, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 6.6 Hz, 1H), 4.65 (s, 1H), 3.45 (s, 2H), 3.10 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 135.4, 127.4, 124.7, 122.3 (q, J^2 = 36.4 Hz), 122.0 (q, J_{C-F} = 267.5 Hz), 120.5, 120.2, 115.0 (q, J^3 = 3.0 Hz), 111.8, 79.3, 41.1, 28.3, 24.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −57.9 (s); HRMS (ESI) calcd. for $C_{16}H_{18}O_2N_2F_3$ $[M - H]^-$, 327.1326; found: 327.1322.

***N*-(2-(2-(trifluoromethyl)-1*H*-indol-3-yl)ethyl)acetamide (3j).** (78 mg, 58%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.3); IR (neat): ν_{max} 3309, 2923, 2813, 1051, 1024, 1005, 820, 757 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 11.90 (s, 1H), 8.00 (t, *J* = 5.8 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 5.75 (s, 1H), 3.30–3.25 (m, 2H), 3.00 (t, *J* = 7.1 Hz, 2H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 169.2, 135.8, 126.9, 124.4, 122.4 (q, J_{C-F} = 267.4 Hz), 121.2 (q, J^2 = 36.0 Hz), 120.0, 117.9, 114.6 (q, J^3 = 2.8 Hz), 112.4, 24.0, 22.7, 22.6; ^{19}F NMR (470 MHz, DMSO) δ −56.5 (s); HRMS (ESI) calcd. for $C_{13}H_{14}ON_2F_3$ $[M + H]^+$, 271.1053; found: 271.1057.

3-(2-Bromoethyl)-2-(trifluoromethyl)-1*H*-indole (3k). (66 mg, 45%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:50, R_f = 0.3); IR (neat): ν_{max} 3388, 2932, 2860, 1313, 1251, 1109, 1068, 741, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.25–7.20 (m, 1H), 3.60–3.55 (m, 2H), 3.50–3.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 126.9, 125.1, 122.2 (q, J^2 = 36.9 Hz), 121.7 (q, J_{C-F} = 267.5 Hz), 120.9,

119.9, 115.3 (q, J^3 = 2.8 Hz), 111.8, 31.3, 27.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.3 (s); HRMS (ESI) calcd. for $C_{11}H_8NBrF_3$ $[M - H]^-$, 289.9798; found: 289.9792.

2-(2-(Trifluoromethyl)-1*H*-indol-3-yl)acetonitrile (3l). (65 mg, 58%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:10, R_f = 0.3); IR (neat): ν_{max} 3396, 2995, 2873, 1328, 1161, 1133, 1073, 740, 618 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.30–7.25 (m, 1H), 4.00 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 125.9, 125.6, 122.8 (q, J^2 = 37.5 Hz), 121.7, 121.2 (q, J_{C-F} = 267.6 Hz),119.4, 116.8, 112.2, 105.5 (q, J^3 = 2.5 Hz), 12.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.5 (s); HRMS (ESI) calcd. for $C_{11}H_6N_2F_3$ $[M - H]^-$, 223.0489; found: 223.0489.

Tert-butyl 3-methyl-2-(trifluoromethyl)-1*H*-indole-1-carboxylate (3m). (117 mg, 78%). Isolated by flash column chromatography (petroleum ether, R_f = 0.3); IR (neat): ν_{max} 2921, 2873, 1738, 1324, 1126, 1087, 743, 731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.45–7.40 (m, 1H), 7.35–7.30 (m, 1H), 2.45 (q, *J* = 2.9 Hz, 3H), 1.65 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 136.8, 128.6, 127.2, 123.0, 122.2 (q, J^2 = 36.9 Hz), 121.9 (q, J_{C-F} = 267.9 Hz), 119.9, 115.4, 111.5 (q, J^3 = 3.0 Hz), 85.0, 29.7, 27.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −54.1 (d, *J* = 2.9 Hz); HRMS (ESI) calcd. for $C_{15}H_{16}O_2NF_3K$ $[M + K]^+$, 338.0770; found: 338.0773.

1-Benzyl-3-methyl-2-(trifluoromethyl)-1*H*-indole (3n). (78 mg, 54%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 2911, 1428, 1270, 1163, 1098, 1046, 737, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.30–7.25 (m, 3H), 7.25–7.20 (m, 3H), 7.00 (d, *J* = 7.2 Hz, 2H), 5.45 (s, 2H), 2.55–2.50 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 137.4, 128.8, 128.6, 127.3, 125.8, 125.5, 124.9, 122.7 (q, J_{C-F} = 268.3 Hz),122.7 (q, J^2 = 34.9 Hz), 120.3, 114.9 (q, J^3 = 2.9 Hz), 114.9, 110.5, 48.1, 29.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −55.1 (d, *J* = 1.6 Hz); HRMS (ESI) calcd. for $C_{17}H_{15}NF_3$ $[M + H]^+$, 290.1078; found: 290.1070.

(3-Methyl-2-(trifluoromethyl)-1*H*-indol-1-yl)(phenyl)methanone (3o). (106 mg, 70%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 2925, 2886, 1708, 1322, 1125, 1020, 711, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.85 (m, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.25–7.20 (m, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 2.55–2.50 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 136.8, 134.1, 133.9, 130.3, 129.0, 128.8, 126.2, 124.3 (q, J^2 = 37.0 Hz), 123.8 (q, J_{C-F} = 271.1 Hz), 122.9 (q, J^3 = 2.8 Hz), 122.7, 120.3, 113.7, 29.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −54.4 (d, *J* = 2.1 Hz); HRMS (ESI) calcd. for $C_{17}H_{11}ONF_3$ $[M - H]^-$, 302.0798; found: 302.0793.

4-Fluoro-3-methyl-2-(trifluoromethyl)-1*H*-indole (4a). (79 mg, 73%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:50, R_f = 0.3); IR (neat): ν_{max} 2204, 1165, 1118, 1054, 1027, 909, 731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.20–7.15 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.80 (dd, *J* = 11.0, 7.9 Hz, 1H), 2.55 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 157.2, 137.5 (d, *J* = 10.9 Hz), 125.3 (d, *J* = 8.0 Hz), 121.7 (q, J_{C-F} = 267.3 Hz), 121.6 (q, J^2 = 36.5 Hz), 113.0 (q, J^3 = 3.0 Hz), 107.6 (d, *J* = 4.0 Hz), 105.5 (d, *J* = 19.1 Hz), 9.9 (d, *J* = 2.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.8 (d, *J* = 1.3 Hz), -123.3 (dd, *J* = 11.1, 4.7 Hz); HRMS (ESI) calcd. for $C_{10}H_6NF_4$ $[M - H]^-$, 216.0442; found: 216.0443.

***N*-benzyl-*N*-methyl-3-phenylprop-2-yn-1-amine (4b).** (81 mg, 58%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:50, R_f = 0.3); IR (neat): ν_{max} 1253, 1181, 1162, 1120, 1027, 908, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.35–7.30 (m, 2H), 7.10 (t, *J* = 7.9 Hz, 1H), 2.70 (dd, *J* = 3.3, 1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 125.9, 125.3, 125.1, 122.9 (q, J^2 = 36.1 Hz), 121.8 (q, J_{C-F} = 267.5 Hz),115.9, 115.2 (q, J^3 = 2.9 Hz), 111.0, 10.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.6 (d, *J* = 0.9 Hz); HRMS (ESI) calcd. for $C_{10}H_6NBrF_3$ $[M - H]^-$, 275.9641; found: 275.9644.

4-Methoxy-3-methyl-2-(trifluoromethyl)-1*H*-indole (4c). (62 mg, 54%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 3402, 2927, 2813,

1311, 1251, 1165, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 3.90 (s, 3H), 2.60 (dd, *J* = 3.6, 1.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 136.7, 125.5, 121.1 (q, J_{C-F} = 266.8 Hz), 120.1 (q, J^2 = 36.4 Hz), 118.1, 114.9 (q, J^3 = 3.1 Hz), 104.5, 100.1, 55.1, 10.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.4 (d, *J* = 1.3 Hz); HRMS (ESI) calcd. for $C_{11}H_9ONF_3$ $[M - H]^-$, 228.0642; found: 228.0641.

5-Chloro-3-methyl-2-(trifluoromethyl)-1*H*-indole (4d). (78 mg, 67%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:50, R_f = 0.3); IR (neat): ν_{max} 3396, 2995, 2874, 1445, 1251, 1094, 1025, 797, 720, 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.30–7.25 (m, 2H), 2.40 (dd, *J* = 3.4, 1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.43, 129.06, 126.12, 125.17, 122.8 (q, J^2 = 36.9 Hz), 121.7 (q, J_{C-F} = 267.4 Hz), 119.57, 113.6 (q, J^3 = 2.9 Hz), 112.69, 8.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.9 (d, *J* = 1.3 Hz); HRMS (ESI) calcd. for $C_{10}H_6NClF_3$ $[M - H]^-$, 232.0146; found: 232.0148.

5-Bromo-3-methyl-2-(trifluoromethyl)-1*H*-indole (4e). (113 mg, 81%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 3520, 2988, 2873, 1317, 1105, 1047, 1023, 793, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.75 (s, 1H), 7.40 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 2.40 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 129.7, 127.7, 122.8, 122.3 (q, J^2 = 36.8 Hz), 121.7 (q, J_{C-F} = 272.9 Hz), 113.6, 113.5 (q, J^3 = 3.1 Hz), 113.1, 8.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.9 (d, *J* = 1.3 Hz); HRMS (ESI) calcd. for $C_{10}H_6NBrF_3$ $[M - H]^-$, 275.9641; found: 275.9645.

5-Methoxy-3-methyl-2-(trifluoromethyl)-1*H*-indole (4f). (66 mg, 58%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:50, R_f = 0.3); IR (neat): ν_{max} 3367, 2911, 2823, 1469, 1165, 1067, 1018, 840, 798, 725, 701, 624 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.30–7.25 (m, 1H), 7.00 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 3.90 (d, *J* = 0.9 Hz, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 130.3, 128.4, 122.1 (q, J^2 = 36.8 Hz), 122.0 (q, J_{C-F} = 267.1 Hz), 115.6, 113.5 (q, J^3 = 3.1 Hz), 112.5, 100.9, 55.8, 8.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.7 (d, *J* = 1.3 Hz); HRMS (ESI) calcd. for $C_{11}H_9ONF_3$ $[M - H]^-$, 228.0642; found: 228.0640.

6-Fluoro-3-methyl-2-(trifluoromethyl)-1*H*-indole (4g). (68 mg, 63%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 1318, 1258, 1118, 1027, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.55 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.05 (dd, *J* = 9.3, 2.1 Hz, 1H), 7.00–6.90 (m, 1H), 2.40 (dd, *J* = 3.6, 1.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4 (d, *J* = 239.8 Hz), 135.2 (d, *J* = 13.3 Hz), 124.7, 121.9 (q, J_{C-F} = 266.9 Hz), 121.8 (q, J^2 = 36.6 Hz), 121.2 (d, *J* = 10.4 Hz), 114.3 (q, J^3 = 2.8 Hz), 109.6 (d, *J* = 24.9 Hz), 97.7 (d, *J* = 26.4 Hz), 8.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.8 (d, J = 1.0 Hz), -117.1 (td, *J* = 9.4, 5.3 Hz); HRMS (ESI) calcd. for $C_{10}H_6NF_4$ $[M - H]^-$, 216.0442; found: 216.0441.

6-Chloro-3-methyl-2-(trifluoromethyl)-1H-indole (4h). (89 mg, 76%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 2223, 1052, 1025, 1007, 751, 726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 1.5 Hz, 1H), 7.15 (dd, *J* = 8.5, 1.8 Hz, 1H), 2.40 (dd, *J* = 3.6, 1.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 130.7, 126.6, 121.8 (q, J_{C-F} = 267.1 Hz), 122.1 (q, J^2 = 36.8 Hz), 121.3, 121.1, 114.2 (q, J^3 = 3.0 Hz), 111.4, 8.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.9 (d, *J* = 1.3 Hz); HRMS (ESI) calcd. for $C_{10}H_6NClF_3$ $[M - H]^-$, 232.0146; found: 232.0146.

6-Methoxy-3-methyl-2-(trifluoromethyl)-1*H*-indole (4i). (74 mg, 65%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:50, R_f = 0.3); IR (neat): ν_{max} 2343, 1053, 1025, 1006, 819, 757, 727 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 11.60 (s, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 6.85 (s, 1H), 6.75 (dd, *J* = 8.8, 1.9 Hz, 1H), 3.80 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 157.7, 136.7, 122.7 (q, J_{C-F} = 266.5 Hz), 121.6, 120.8, 119.2 (q, J^2 = 35.8 Hz), 112.7 (q, J^3 = 3.1 Hz), 110.9, 94.1, 55.3, 8.3; ^{19}F NMR (470 MHz, DMSO) δ −56.4 (d, *J* = 1.5 Hz); HRMS (ESI) calcd. for $C_{11}H_9ONF_3$ $[M - H]^-$, 228.0642; found: 228.0641.

7-Fluoro-3-methyl-2-(trifluoromethyl)-1*H*-indole (4j). (74 mg, 68%). Isolated by flash column chromatography (petroleum ether, R_f = 0.3); IR (neat): ν_{max} 2287, 1052, 1026, 1007, 908, 723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.15–7.05 (m, 1H), 7.05 (dd, *J* = 10.8, 7.8 Hz, 1H), 2.45 (dd, *J* = 3.5, 1.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5 (d, *J* = 244.4 Hz), 131.6 (d, *J* = 4.9 Hz), 123.9 (q, J_{C-F} = 267.5 Hz), 122.4 (q, J^2 = 36.6 Hz), 120.7 (d, *J* = 5.9 Hz), 115.8 (d, *J* = 3.6 Hz), 114.7 (q, J^3 = 2.8 Hz), 109.3 (d, *J* = 15.6 Hz), 107.8 (d, *J* = 16.3 Hz), 8.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −59.0 (d, *J* = 1.0 Hz), -134.7 (dd, *J* = 11.0, 4.7 Hz); HRMS (ESI) calcd. for $C_{10}H_6NF_4$ $[M - H]^-$, 216.0442; found: 216.0442.

7-Chloro-3-methyl-2-(trifluoromethyl)-1*H*-indole (4k). (76 mg, 65%). Isolated by flash column chromatography (petroleum ether, R_f = 0.3); IR (neat): ν_{max} 1313, 1164, 1119, 1027, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.6, 129.3, 124.0, 122.3 (q, J^2 = 37.0 Hz), 121.7 (q, J_{C-F} = 267.4 Hz), 121.2, 118.7, 117.0, 115.1 (q, J^3 = 2.9 Hz), 8.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.9 (d, *J* = 1.2 Hz); HRMS (ESI) calcd. for $C_{10}H_6NClF_3$ $[M - H]^-$, 232.0146; found: 232.0146.

7-Bromo-3-methyl-2-(trifluoromethyl)-1*H*-indole (4l). (99 mg, 71%). Isolated by flash column chromatography (petroleum ether, R_f = 0.3); IR (neat): ν_{max} 3471, 2931, 2813, 1580, 1328, 1115, 908, 779, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 2.45 (dd, *J* = 3.4, 1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.0, 129.0, 127.0, 122.2 (q, J^2 = 36.8 Hz), 121.7 (q, J_{C-F} = 267.3 Hz), 121.5, 119.3, 115.2 (q, J^3 = 3.0 Hz), 105.0, 8.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.8 (d, *J* = 1.1 Hz); HRMS (ESI) calcd. for $C_{10}H_6NBrF_3$ $[M - H]^-$, 275.9641; found: 275.9643.

7-Methoxy-3-methyl-2-(trifluoromethyl)-1*H*-indole (4m). (61 mg, 53%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 3411, 2918, 2806, 1265, 1161, 1109, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 3.95 (s, 3H), 2.45–2.40 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 129.3, 126.1, 122.1 (q, J_{C-F} = 267.0 Hz), 121.3 (q, J^2 = 36.8 Hz), 120.8, 114.3 (q, J^3 = 2.9 Hz), 112.4, 103.9, 55.4, 8.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.7 (s); HRMS (ESI) calcd. for $C_{11}H_9ONF_3$ $[M - H]^-$, 228.0642; found: 228.0646.

5-Fluoro-3-methyl-2-(trifluoromethyl)-1*H*-indole (4n). (90 mg, 83%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:50, R_f = 0.3); IR (neat): ν_{max} 3393, 2921, 2863, 1325, 1169, 1109, 1026, 852, 796, 728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.31 (dd, *J* = 8.9, 4.2 Hz, 1H), 7.27 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.08 (td, *J* = 9.0, 2.4 Hz, 1H), 2.41–2.38 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 157.1, 131.6, 128.5, 128.4, 123.2 (q, J^2 = 36.8 Hz), 121.8 (q, J_{C-F} = 267.4 Hz), 114.0 (q, J^3 = 3.0 Hz), 113.7, 113.5, 112.6, 112.5, 104.9, 104.7, 8.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.96 (d, *J* = 1.4 Hz), -123.0 (td, *J* = 9.1, 4.2 Hz); HRMS (ESI) calcd. for $C_{10}H_6NF_4$ $[M - H]^-$, 216.0442; found: 216.0442.

6-Bromo-3-methyl-2-(trifluoromethyl)-1*H*-indole (4o). (39 mg, 28%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:100, R_f = 0.3); IR (neat): ν_{max} 3390, 2901, 2862, 1325, 1172, 1109, 1022, 842, 728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) ^1H NMR (500 MHz, cdcl$_3$) δ 8.18 (s, 1H), 7.53 (d, J = 1.4 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.29 (dd, J = 8.5, 1.6 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, cdcl$_3$) δ 135.77, 126.94, 123.89, 122.0 (q, J^2 = 36.9 Hz), 121.8 (q, J_{C-F} = 267.3 Hz) 121.39, 118.39, 114.45, 114.2 (q, J^3 = 2.9 Hz), 8.24; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.96 (d, *J* = 1.4 Hz), -123.0 (td, *J* = 9.1, 4.2 Hz); HRMS (ESI) calcd. for $C_{10}H_6NF_4$ $[M - H]^-$, 275.9641; found: 275.964.

2-(7-Ethyl-2-(trifluoromethyl)-1*H*-indol-3-yl)ethyl acetate (4q). (105 mg, 70%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:50, R_f = 0.3); IR (neat): ν_{max} 3397, 2998, 2883, 1723, 1253, 1163, 1117, 908, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.60–7.55 (m, 1H), 7.20–7.15 (m, 2H), 4.30 (dd, *J* = 9.1, 4.8 Hz, 2H), 3.25 (td, *J* = 6.9, 1.1 Hz, 2H), 2.90 (q, *J* = 7.6 Hz, 2H), 2.00 (s, 3H), 1.40 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 134.3, 129.8, 127.2, 123.2, 122.1 (q, J^2 = 36.6 Hz), 122.0 (q, J_{C-F} = 267.3 Hz), 121.1, 117.7, 114.4 (q, J^3 = 2.8 Hz), 65.6, 64.1, 23.6, 20.9, 13.6;

^{19}F NMR (470 MHz, $CDCl_3$) δ −58.1 (s); HRMS (ESI) calcd. for $C_{15}H_{15}O_2NF_3$ $[M - H]^-$, 298.1060; found: 298.1055.

2-(5-Methoxy-2-(trifluoromethyl)-1*H*-indol-3-yl)acetonitrile (4r). (54 mg, 42%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:10, R_f = 0.3); IR (neat): ν_{max} 3389, 1052, 1024, 1005, 820, 757, 624, 558 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 12.30 (s, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.9 Hz, 1H), 4.25 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 154.6, 130.7, 126.2, 122.2 (q, J^2 = 36.8 Hz), 121.8 (q, J_{C-F} = 267.5 Hz), 118.5, 116.3, 113.7, 105.4 (q, J^3 = 2.3 Hz), 100.4, 55.6, 12.0; ^{19}F NMR (470 MHz, DMSO) δ −56.9 (s); HRMS (ESI) calcd. for $C_{12}H_8ON_2F_3$ $[M - H]^-$, 253.0594; found: 253.0591.

***N*-(2-(5-methoxy-2-(trifluoromethyl)-1*H*-indol-3-yl)ethyl)acetamide (4s) [24].** (102 mg, 68%). Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:10, R_f = 0.3); ^{1}H NMR (500 MHz, DMSO) δ 12.30 (s, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.9 Hz, 1H), 4.25 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 154.7, 130.6, 127.7, 122.7 (q, J^2 = 36.4 Hz), 121.9 (q, J_{C-F} = 267.3 Hz), 116.0, 114.3 (q, J^3 = 2.8 Hz), 112.9, 100.5, 55.7, 40.0, 23.9, 23.2; ^{19}F NMR (470 MHz, DMSO) δ −57.9 (s); HRMS (ESI) calcd. for $C_{14}H_{14}O_2N_2F_3$ $[M - H]^-$, 299.1013; found: 299.1009.

4. Conclusions

In conclusion, we have demonstrated a new application of KF as a base to promote the trifluoromethylation of electron-deficient and electron-rich indoles via C-H activation. Compared with previous works, this method features broad functional group tolerance, shorter reaction times, and a less expensive trifluoromethylating agent. This methodology allows the construction of a variety of bioactive molecules containing C2-trifluoromethylated indole moieties. The value of this strategy has been highlighted via the trifluoromethylation of melatonin in 68% yield. Preliminary mechanistic studies indicate that the reaction pathway may proceed through a radical process involving a Cu(II)/Cu(I) redox process.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/3/278/s1.

Author Contributions: X.S., X.L. and D.S. designed the project. X.S. performed the experiments. X.S., X.L. and L.M. analyzed the data. X.S. wrote the manuscript.

Funding: This work was supported by the Funded by National Natural Science Foundation of China (No. 81773586, 81703354), Key research and development project of Shandong province (2016GSF201193, 2016ZDJS07A13, 2016GSF115002, 2016GSF115009), Key Research Program of Frontier Sciences, CAS (QYZDB-SSW-DQC014), the Project of Discovery, Evaluation and Transformation of Active Natural Compounds, Strategic Biological Resources Service Network Program of Chinese Academy of Sciences (ZSTH-026), Shandong Provincial Natural Science Foundation for Distinguished Young Scholars (JQ201722), National Program for Support of Top-notch Young Professionals, and Taishan scholar Youth Project of Shandong province.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Meanwell, N.A. Synopsis of some recent tactical application of bioisosteres in drug design. *J. Med. Chem.* **2011**, *54*, 2529–2591. [CrossRef] [PubMed]
2. Wang, J.; Sanchez-Rosello, M.; Acena, J.L.; Pozo, C.; Sorochinsky, A.E.; Fustero, S.; Soloshonok, V.A.; Liu, H. Fluorine in pharmaceutical industry: Fluorine-containing drugs introduced to the market in the last decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432–2506. [CrossRef] [PubMed]
3. Jeschke, P. The unique role of fluorine in the design of active ingredients for modern crop protection. *ChemBioChem* **2004**, *5*, 570–589. [CrossRef] [PubMed]
4. Hagmann, W.K. The many roles for fluorine in medicinal chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369. [CrossRef] [PubMed]
5. Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330. [CrossRef] [PubMed]

6. Merino, E.; Nevado, C. Addition of CF_3 across unsaturated moieties: A powerful functionalization tool. *Chem. Soc. Rev.* **2014**, *43*, 6598–6608. [CrossRef] [PubMed]
7. Alonson, C.; Marigorta, E.M.; Rubiales, G.; Palacios, F. Carbon trifluoromethylation reactions of hydrocarbon derivatives and heteroarenes. *Chem. Rev.* **2015**, *115*, 1847–1935. [CrossRef]
8. Furuya, T.; Kamlet, A.S.; Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature* **2011**, *473*, 470–477. [CrossRef]
9. Xu, C.; Liu, J.; Ming, W.; Liu, Y.; Liu, J.; Wang, M.; Liu, Q. In situ generation of PHI^+CF_3 and transition-metal-free oxidative sp^2 C-H trifluoromethylation. *Chem. Eur. J.* **2013**, *19*, 9104–9109. [CrossRef]
10. Miller, S.A.; Beek, B.; Hamlin, T.A.; Bickelhaupt, F.M.; Leadbeater, N.E. A methodology for the photocatalyzed radical trifluoromethylation of indoles: A combined experimental and computational study. *J. Fluorine Chem.* **2018**, *214*, 94–100. [CrossRef]
11. Studer, A. A "renaissance" in radical trifluoromethylation. *Angew. Chem. Int. Ed.* **2012**, *51*, 8950–8958. [CrossRef]
12. Lundgren, R.J.; Stradiotto, M. Transition-metal-catalyzed trifluoromethylation of aryl halides. *Angew. Chem. Int. Ed.* **2010**, *49*, 9322–9324. [CrossRef]
13. Zheng, Y.; Ma, J.-A. Combination catalysis in enantioselective trifluoromethylation. *Adv. Synth. Catal.* **2010**, *352*, 2745–2750. [CrossRef]
14. Shimizu, R.; Egami, H.; Nagi, T.; Chae, J.; Hamashima, Y.; Sodeoka, M. Direct C2-trifluoromethylation of indole derivatives catalyzed by copper acetate. *Tetrahedron Lett.* **2010**, *51*, 5947–5949. [CrossRef]
15. Zhao, S.; Guo, Y.; Han, E.J.; Luo, J.; Liu, H.M.; Liu, C.; Xie, W.; Zhang, W.; Wang, M. Copper(II)-catalyzed trifluoromethylation of iodoarenes using Chen's reagent. *Org. Chem. Front.* **2018**, *5*, 1143–1147. [CrossRef]
16. Shen, K.; Wang, Q. Copper-catalyzed aminotrifluoromethylation of alkenes: A facile synthesis of CF3-containing lactams. *Org. Chem. Front.* **2016**, *3*, 222–226. [CrossRef]
17. Wang, Q.; Tsui, G.C. Copper-mediated domino cyclization/trifluoromethylation of propargylic n-hydroxylamines: Synthesis of 4-trifluoromethyl-4isoxazolines. *J. Org. Chem.* **2018**, *83*, 2971–2979. [CrossRef]
18. Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D. Oxidative trifluoromethylation of unactivated olefins: An efficient and practical synthesis of a-trifluoromethyl-substituted ketones. *Angew. Chem.* **2013**, *125*, 9929–9932. [CrossRef]
19. Natte, K.; Jagadeesh, R.V.; He, L.; Rabeah, J.; Chen, J.; Taeschler, C.; Ellinger, S.; Zaragoza, F.; Neumann, H.; Bruckner, A.; et al. Palladium-catalyzed trifluoromethylation of (hetero)arenes with CF_3Br. *Angew. Chem. Int. Ed.* **2016**, *55*, 2782–2786. [CrossRef]
20. Mestre, J.; Lishchynskyi, A.; Castillon, S.; Boutureira, O. Trifluoromethylation of electron-rich alkenyl iodides with fluoroform-derived "ligandless" $CuCF_3$. *J. Org. Chem.* **2018**, *83*, 8150–8160. [CrossRef]
21. Liu, X.; Xu, C.; Wang, M.; Liu, Q. Trifluoromethyltrimethylsilane: Nucleophilic trifluoromethylation and beyond. *Chem. Rev.* **2015**, *115*, 683–730. [CrossRef] [PubMed]
22. Langlois, B.R.; Laurent, E.; Roidot, N. Trifluoromethylation of aromatic compounds with sodium trifluoromethanesulfinate under oxidative conditions. *Tetrahedron Lett.* **1991**, *32*, 7525–7528. [CrossRef]
23. Li, L.; Mu, X.; Liu, W.; Wang, Y.; Mi, Z.; Li, C.-J. Simple and clean photoinduced aromatic trifluoromethylation reaction. *J. Am. Chem. Soc.* **2016**, *138*, 5809–5812. [CrossRef] [PubMed]
24. Ji, Y.; Brueckl, T.; Baxter, R.D.; Fujiwara, Y.; Seiple, I.B.; Su, S.; Blackmond, D.G.; Baran, P.S. Innate C-H trifluoromethylation of heterocycles. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411–14415. [CrossRef] [PubMed]
25. Zhang, H.-Y.; Ge, C.; Zhao, J.; Zhang, Y. Cobalt-catalyzed trifluoromethylation−peroxidation of unactivated alkenes with sodium trifluoromethanesulfinate and hydroperoxide. *Org. Lett.* **2017**, *19*, 5260–5263. [CrossRef]
26. Zhang, P.-Z.; Li, C.-K.; Zhang, G.-Y.; Zhang, L.; Jiang, Y.-J.; Zou, J.-P. Direct regioselective Csp2-H trifluoromethylation of pyrimidinones and pyridinones. *Tetrahedron* **2016**, *72*, 3250–3255. [CrossRef]
27. Zhang, X.; Huang, P.; Li, Y.; Duan, C. A mild and fast continuous-flow trifluoromethylation of coumarins with the CF_3 radical derived from CF_3SO_2Na and TBHP. *Org. Biomol. Chem.* **2015**, *13*, 10917–10922. [CrossRef] [PubMed]
28. Xu, J.; Qiao, L.; Shen, J.; Chai, K.; Shen, C.; Zhang, P. Nickel(II)-catalyzed site-selective C-H bond trifluoromethylation of arylamine in water through a coordinating activation strategy. *Org. Lett.* **2017**, *19*, 5661–5664. [CrossRef]

29. Zhao, L.; Li, P.; Xie, X.; Wang, L. Selective remote C–H trifluoromethylation of aminoquinolines with CF_3SO_2Na under visible light irradiation in the absence of external photocatalyst. *Org. Chem. Front.* **2018**, *5*, 1689–1697. [CrossRef]
30. Corsico, S.; Fagnoni, M.; Ravelli, D. Sunlight decatungstate photoinduced trifluoromethylations of (hetero)aromatics and electron-poor olefins. *Photochem. Photobiol. Sci.* **2017**, *16*, 1375–1380. [CrossRef]
31. Zhang, Y.; Han, X.; Zhao, J.; Qian, Z.; Li, T.; Tang, Y.; Zhang, H.Y. Synthesis of β-trifluoromethylated alkyl azides via a manganese-catalyzed trifluoromethylazidation of alkenes with CF_3SO_2Na and $TMSN_3$. *Adv. Synth. Catal.* **2018**, *360*, 1–10. [CrossRef]

© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).