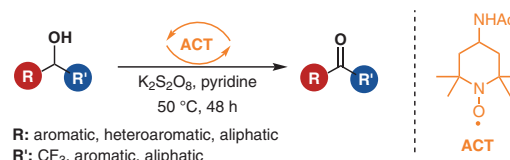


Oxidation of α -Trifluoromethyl and Nonfluorinated Secondary Alcohols to Ketones Using a Nitroxide Catalyst

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- employed to prepare trifluoromethyl ketones and non-fluorinated ketones
- broad substrate scope
- 27 examples; 44–95% yields

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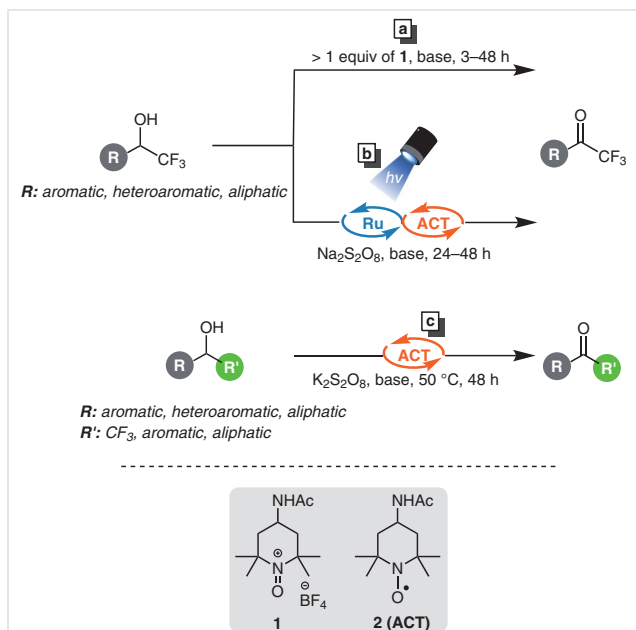
Abstract A methodology for the oxidation of α -trifluoromethyl alcohols to the corresponding trifluoromethyl ketones is presented. A catalytic quantity of a nitroxide is used, and potassium persulfate serves as the terminal oxidant. The methodology proves effective for aromatic, heteroaromatic, and conjugated alcohol substrates. It can be extended to nonfluorinated secondary alcohols and, in this case, can be applied to a range of aromatic, heteroaromatic, and aliphatic alcohols.

Key words oxidation, trifluoromethyl ketones, nitroxide, persulfate, ketones, alcohols

Trifluoromethyl ketones (TFMKs) have proved to be useful starting materials for a number of synthetic transformations.^{1,2} They can also be used as synthons for rapid ¹⁹F-labelling of compounds.³ TFMKs are also interesting in their own right. For example, the motif is the subject of significant medicinal chemistry and chemical biology research.⁴ Given their applicability, the expedient synthesis of TFMKs is an important area of current research. They are challenging to prepare; access to the motif often being approached through the functionalization of carboxylic acids⁵ and acid chlorides.⁶ However, this route tends to rely on the use of an excess of fluorinating agent and conditions that limit functional group compatibility. Other approaches include the nucleophilic trifluoromethylation of esters,⁷ the cleavage of carbon–carbon multiple bonds with fluorinating agents,^{8,9} or two-step routes.¹⁰ Perhaps the simplest route to TFMKs is by means of the oxidation of α -trifluoromethyl alcohols, but classical methods for alcohol oxidation are typically insufficient. The inductive effect of the trifluoromethyl group raises the activation barrier for oxidation. This can likely be explained by either the diminished nucleophilicity of the OH group or through an increase in the bond enthalpy of

the α -C–H bond. Since the majority of traditional oxidation protocols rely on attack of the oxygen on an activated complex, many well-known oxidants fail to oxidize trifluoromethyl carbinols. As a result, less favorable oxidants such as Dess–Martin periodinane (DMP),¹¹ or hexavalent chromium reagents are traditionally used.¹² More recently, there has been a push to develop oxidants that are milder and more sustainable. In this vein, *o*-iodoxybenzoic acid (IBX), a precursor to DMP, has been used, although this compound is shock-sensitive and does not serve as an atom-efficient oxidant.¹³ Another example is 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**1**, ACT⁺BF₄⁻), which is a mild, recyclable, and environmentally friendly oxidant capable of accessing TFMKs (Scheme 1a).¹⁴ Both IBX and **1** have to be used in superstoichiometric loadings to drive the reaction to completion.

Achieving the goal of developing an oxidation approach using a catalytic loading of active oxidant, our group has recently reported a merger of photoredox catalysis¹⁵ with the oxidant 4-acetamido-(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (**2**, ACT) to prepare both nonfluorinated and fluorinated ketones from the corresponding alcohols (Scheme 1b).¹⁶ The methodology involves the use of a persulfate salt as the primary oxidant and Ru(bpy)₃(PF₆)₂ as the photocatalyst. The latter regenerates the oxoammonium cation, which itself catalyzes the oxidative process. We have used a similar approach to perform a variety of oxidative functionalization reactions, including the conversion of aldehydes into amides¹⁷ and nitriles,¹⁸ and conversion of primary alcohols into carboxylic acids.¹⁹ We subsequently found that by some modification of the reaction conditions, aldehydes can be transformed into esters,²⁰ amides,²¹ and nitriles²² using a catalytic quantity of **2**, without the need for tandem photocatalysis. Key to the success of this approach is the use of sodium persulfate as a terminal oxidant, pyridine as a base, and mild heating. A key operational advantage to

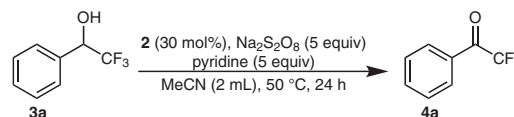


this is that it obviates the need for equipment required for photochemistry as well as a metal-containing complex as the photocatalyst, the latter of which then needs to be removed at the end of the reaction. Encouraged by these results, we posited that this route may allow us access to TFMKs from α -trifluoromethyl alcohols and to nonfluorinated ketones from their alcohol congeners (Scheme 1c). We report the results of this endeavor here.

To optimize reaction conditions for the oxidation of α -trifluoromethyl alcohols to TFMKs, we decided to use 2,2,2-trifluoro-1-phenylethanol (**3a**) as a model substrate. As a launching point, we chose reaction conditions similar to those employed in our other oxidative transformations;^{20–22} namely, alcohol substrate (1 mmol), sodium persulfate (5 equiv), ACT (**2**; 0.3 equiv), and pyridine (5 equiv), in acetonitrile (2 mL). We heated the reaction mixture at 50 °C for 24 h and observed a 62% conversion into the desired TFMK product, **4a** (Table 1, entry 1). We next performed a series of trials to probe the importance of each component in the reaction mixture. Negligible product was obtained in the absence of base (entry 2), of sodium persulfate (entry 3), or of ACT (entry 4). The same was true when the reaction was performed at below 50 °C (entries 5–7). Heating the reaction mixture to temperatures above 50 °C also proved deleterious (entry 8). Moving next to a solvent screen, changing from acetonitrile to dichloromethane did not lead to a significant change in product conversion (entry 9), but use of either ethyl acetate or water proved ineffective (entries 10 and 11). In the latter case, the geminal diol form of the

TFMK was obtained; this was not surprising since TFMKs are very prone to hydration.²³ Since chlorinated solvents are not preferable,²⁴ acetonitrile remained our solvent of choice. Replacing ACT with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) resulted in a lower product conversion (entry 12), showing that the former is the better catalyst. Varying the loading of ACT showed that while decreasing the quantity used led to lower product conversion (entries 13 and 14), increasing the amount from 30 to 40 mol% did not furnish any operational advantage (entry 15). In some of our previous work, and in other reports, the use of lutidine in place of pyridine as a base proved advantageous,^{25–27} but in this case employing 3,5-, or 2,6-lutidine did not improve the outcome of the reaction (entries 16 and 17). Returning

Table 1 Optimization of Reaction Conditions^a



Entry	Deviation from above	4a (%) ^b
1	none	63
2	no base added	1
3	no sodium persulfate added	<1
4	no ACT (2) added	2
5	no heating	1
6	heating at 30 °C	3
7	heating at 40 °C	3
8	heating at 60 °C	43
9	dichloromethane as the solvent	61
10	ethyl acetate as the solvent	5
11	water as the solvent	– ^c
12	TEMPO instead of ACT (2)	25
13	10 mol% ACT (2)	4
14	20 mol% ACT (2)	21
15	40 mol% ACT (2)	60
16	3,5-lutidine used as a base	32
17	2,6-lutidine used as a base	24
18	6 equiv pyridine used	56
19	4 equiv pyridine used	62
20	3 equiv pyridine used	72
21	K ₂ S ₂ O ₈ instead of Na ₂ S ₂ O ₈	82
22	3 equiv of K ₂ S ₂ O ₈	81
23	3 equiv of K ₂ S ₂ O ₈ and 3 equiv of pyridine	90
24	3 equiv of K ₂ S ₂ O ₈ and 3 equiv pyridine for 48 h	99

^a Reaction performed in a sealed vial using **3a** (1 mmol, 1 equiv).

^b Product conversion determined by ¹⁹F NMR analysis.

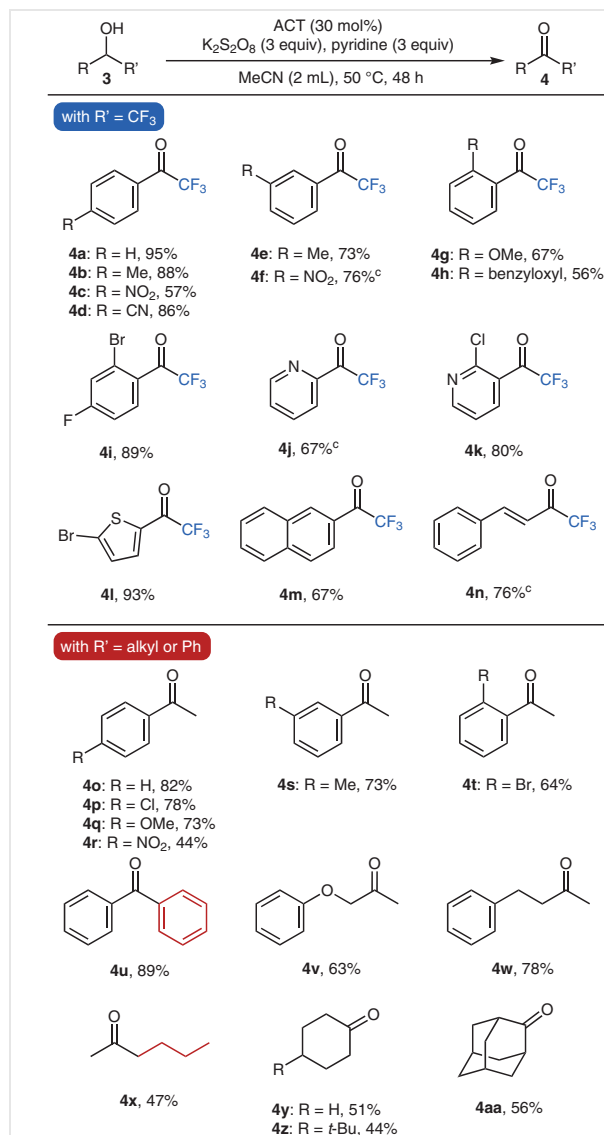
^c Hydrate formation.

to pyridine, decreasing the loading from 5 to 3 equivalents had a positive effect on product conversion (entries 18–20), which was attributed to diminution of off-target reactions. Going back to 5 equivalents of pyridine but replacing sodium persulfate with its potassium analogue increased the product conversion, even when a lower loading of 3 equivalents instead of 5 equivalents was used (entries 21 and 22). Bringing together this modification and the lower pyridine loading further improved the outcome (entry 23). Finally, performing the reaction for 48 h instead of 24 h resulted in essentially quantitative conversion of the alcohol into the desired TFMK (entry 24). Thus, our optimized conditions were ACT (30 mol%), $K_2S_2O_8$ (3 equiv), pyridine (3 equiv), in acetonitrile at 50 °C for 48 h.

With optimized reaction conditions in hand, we proceeded to evaluate the substrate scope of our methodology (Scheme 2). Oxoammonium salt mediated oxidation reactions generally have a wide tolerance of ancillary functional groups. In our screen, a range of α -trifluoromethyl functionalized benzyl alcohols, bearing electronically different substituents, were first examined. All could be converted into the corresponding TFMK **4a–h**, with yields ranging from good to excellent. Products were isolated by means of extraction, with pentane being employed as the organic solvent. This choice was selected both because pentane allows for an effective extraction, and because it has a low boiling point so it can be removed from the product. Many TFMKs are volatile, meaning that longer-chain hydrocarbon solvents do not prove as useful. Proceeding with the substrate scope, a representative polysubstituted substrate afforded the expected ketone **4i** in 89% yield, as did three heteroaromatic examples (**4j–l**). We also evaluated two compounds with extended conjugated systems, with the TFMKs **4m** and **4n** being obtained in good yields. Unfortunately, aliphatic α -trifluoromethyl alcohols proved resistant to oxidation under our conditions.

Building on the success of our methodology for converting α -trifluoromethyl alcohols into TFMKs, we decided to test the approach for the oxidation of nonfluorinated examples. Again, benzyl alcohols bearing electron-donating or electron-withdrawing substituents were readily oxidized (**4o–u**). We also screened representative aliphatic secondary alcohols, and all could to be oxidized to the desired ketones **4v–aa** in moderate to good yields.

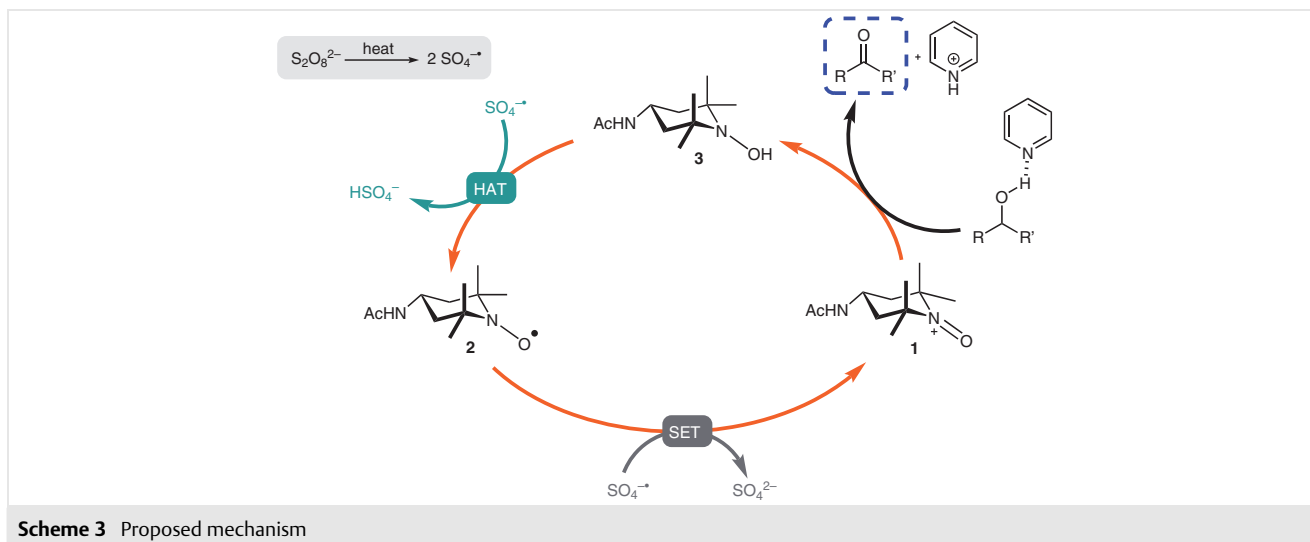
A proposed mechanism for the oxidation reaction is shown in Scheme 3. The first step is the heat-activated homolytic cleavage of sodium persulfate, generating two equivalents of the sulfate radical anion ($SO_4^{\cdot-}$).^{28–32} This radical anion oxidizes ACT (**2**) to the corresponding oxoammonium cation (**1**) by means of a single-electron transfer (SET) process. This cation then performs the oxidation of the alcohol substrate (activated by coordination with pyridine) to form the ketone product. The hydroxylamine (**5**) generated is then converted back into **2** by a sulfate radical anion me-



Scheme 2 Substrate scope for the oxidation of alcohols. Reaction performed in a sealed vial using **3** (1 mmol, 1 equiv). Isolated yield after purification, unless noted otherwise. ^c Product conversion determined by ¹⁹F NMR analysis.

diated hydrogen-atom transfer process (HAT), closing the catalytic cycle.

In summary, we have developed a methodology for the oxidation of α -trifluoromethyl alcohols to the corresponding trifluoromethyl ketones. The approach uses a catalytic quantity of a nitroxide, and potassium persulfate as the terminal oxidant. It proves effective for aromatic, heteroaromatic, and conjugated alcohol substrates. The methodology can be extended to nonfluorinated secondary alcohols and, in this case, can be applied to a range of aromatic, heteroaromatic, and aliphatic alcohols.



NMR spectra (^1H , ^{13}C , and ^{19}F) were recorded at 300 K with a Bruker Avance Ultra Shield 300 MHz, Bruker DRX-400 400 MHz, or Bruker Avance 500 MHz spectrometer. ^1H NMR spectra were referenced to residual chloroform (7.26 ppm) in CDCl_3 or residual dimethylsulfoxide (2.50 ppm) in $\text{DMSO}-d_6$. ^{13}C NMR spectra were referenced to CDCl_3 (77.16 ppm) or $\text{DMSO}-d_6$ (39.52 ppm). ^{19}F NMR spectra were referenced to hexafluorobenzene (-161.64 ppm).³³ Reactions were monitored with an Agilent Technologies 7820A gas chromatograph attached to a 5975 Mass Spectrometer, ^{19}F NMR analysis, and/or by TLC on silica gel plates (60 Å porosity, 250 μm thickness). TLC analysis was performed using a solution of 8:2 hexanes/ethyl acetate, and visualized with UV light.

Deuterated chloroform (CDCl_3) was purchased from Cambridge Isotope Laboratories. 4-Acetamido-TEMPO (ACT, **2**) was prepared by using a reported protocol.³⁴ Potassium persulfate was purchased from Sigma-Aldrich. Sodium persulfate was purchased from Sigma-Aldrich and Acros. All the aldehydes and nonfluorinated alcohols used were purchased from Oakwood Chemicals, Sigma-Aldrich or Alfa Aesar and distilled before use if required. Alcohol **4a** was acquired from Oakwood Chemicals; alcohols **4b–g,i,j,l,m** were prepared using a reported protocol^{14,16,25} (see the Supporting Information); alcohols **4h,k,n** were available at our laboratory from previous projects.^{14,16,35,36}

Synthesis of Fluorinated and Nonfluorinated Ketones; General Procedure

To a 14-mL capacity vial equipped with a stir bar was added pyridine (0.395 g, 3 mmol, 3 equiv), $\text{K}_2\text{S}_2\text{O}_8$ (0.811 g, 3 mmol, 3 equiv), ACT (0.064 g, 0.3 mmol, 0.3 equiv), the requisite alcohol **3** (1 mmol, 1 equiv), and acetonitrile (2 mL). The vial was closed tightly, and the contents were heated in an aluminum block at 50 °C for 48 h. The reaction vial was occasionally rotated to ensure there was no buildup of material on the sides. Upon completion of the heating step, the vial and its contents were allowed to cool to room temperature and then the product mixture was transferred to a 250-mL separatory funnel, rinsing the vial with pentane (3 \times 15 mL) and then with deionized water (3 \times 15 mL). The layers were then separated and the aqueous layer was back extracted with pentane (2 \times 20 mL). The organic layers

were combined and washed with 0.5 M HCl (25 mL) and then dried over sodium sulfate and the solvent removed *in vacuo* to afford the product **4**.

1-Phenyl-2,2,2-trifluoroethanone (**4a**)

Obtained according to the General Procedure as a clear liquid (0.165 g, 95%).

^1H NMR (400 MHz, CDCl_3): δ = 8.08 (dt, J = 8.3, 1.2 Hz, 2 H), 7.76–7.67 (m, 1 H), 7.56 (t, J = 7.9 Hz, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 180.70 (q, J = 35.0 Hz), 116.83 (q, J = 291.3 Hz).

^{19}F NMR (376 MHz, CDCl_3): δ = -104.57 to -104.66 (m).

Spectral data for this compound are consistent with those previously reported.³⁶

2,2,2-Trifluoro-1-(*p*-tolyl)ethanone (**4b**)

Obtained according to the General Procedure as a clear liquid (0.165 g, 88%).

^1H NMR (400 MHz, CDCl_3): δ = 8.01–7.94 (m, 2 H), 7.34 (d, J = 8.1 Hz, 2 H), 2.46 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 180.29 (q, J = 34.7 Hz), 147.18, 130.42, 130.39, 129.97, 127.63, 116.93 (q, J = 291.4 Hz), 22.05.

^{19}F NMR (377 MHz, CDCl_3): δ = -71.18 .

Spectral data for this compound are consistent with those previously reported.³⁶

2,2,2-Trifluoro-1-(4-nitrophenyl)ethanone (**4c**)

Obtained according to the General Procedure as a light-yellow solid (0.125 g, 57%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$, hydrate): δ = 8.27 (d, J = 8.4 Hz, 1 H), 7.94 (s, 1 H), 7.87 (d, J = 8.4 Hz, 1 H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$, hydrate): δ = 148.09, 145.45, 128.99, 123.15 (q, J = 290.0 Hz), 122.97, 92.28 (q, J = 31.7 Hz).

^{19}F NMR (376 MHz, $\text{DMSO}-d_6$): δ = -81.73 .

Spectral data for this compound are consistent with those previously reported.³⁶

4-(2,2,2-Trifluoroacetyl)benzotrile (4d)

Obtained according to the General Procedure as a white solid (0.172 g, 86%).

^1H NMR (400 MHz, DMSO- d_6 , hydrate): δ = 7.93–7.87 (m, 2 H), 7.86 (s, 2 H), 7.78 (d, J = 8.3 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO- d_6 , hydrate): δ = 143.68, 131.87, 128.44, 123.19 (q, J = 289.1 Hz), 118.54, 112.02, 92.24 (q, J = 31.3 Hz).

^{19}F NMR (376 MHz, DMSO- d_6): δ = –81.78.

Spectral data for this compound are consistent with those previously reported.³⁶

2,2,2-Trifluoro-1-(*m*-tolyl)ethan-1-one (4e)

Obtained according to the General Procedure as a clear liquid (0.146 g, 78%).

^1H NMR (300 MHz, CDCl_3): δ = 7.91–7.85 (m, 2 H), 7.56–7.49 (m, 1 H), 7.48–7.39 (m, 1 H), 2.45 (s, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 180.83 (q, J = 34.8 Hz), 139.27, 136.51, 130.62, 130.11, 129.09, 127.53, 116.86 (q, J = 291.4 Hz), 21.42.

^{19}F NMR (376 MHz, DMSO- d_6): δ = –71.15.

Spectral data for this compound are consistent with those previously reported.³⁷

2,2,2-Trifluoro-1-(2-methoxyphenyl)ethanone (4g)

Obtained according to the General Procedure as a yellow oil (0.140 g, 67%).

^1H NMR (400 MHz, CDCl_3): δ = 7.67 (dd, J = 7.7, 1.7 Hz, 1 H), 7.59 (ddd, J = 8.9, 7.5, 1.8 Hz, 1 H), 7.09–6.99 (m, 2 H), 3.91 (s, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 183.11 (q, J = 36.5 Hz), 159.99, 135.97, 131.48, 121.88, 120.83, 116.33 (q, J = 291.0 Hz), 112.24, 56.02.

^{19}F NMR (376 MHz, CDCl_3): δ = –74.00.

Spectral data for this compound are consistent with those previously reported.³⁶

1-(2-(Benzyloxy)phenyl)-2,2,2-trifluoroethanone (4h)

Obtained according to the General Procedure as a clear liquid (0.156 g, 56%).

^1H NMR (400 MHz,): δ = 7.72–7.66 (m, 1 H), 7.55 (ddd, J = 8.8, 7.4, 1.7 Hz, 1 H), 7.46–7.33 (m, 5 H), 7.11–7.02 (m, 2 H), 5.20 (s, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 183.12 (q, J = 39.2 Hz), 158.98, 135.87, 135.79, 131.52, 128.79, 128.34, 127.41, 122.24, 121.04, 116.32 (q, J = 291.0 Hz), 113.50, 71.00.

^{19}F NMR (377 MHz, CDCl_3): δ = –73.68.

Spectral data for this compound are consistent with those previously reported.³⁵

1-(2-Bromo-4-fluorophenyl)-2,2,2-trifluoroethanone (4i)

Obtained according to the General Procedure as a yellow oil (0.241 g, 89%).

^1H NMR (400 MHz, CDCl_3): δ = 7.78 (ddd, J = 8.7, 5.6, 1.4 Hz, 1 H), 7.51 (dd, J = 8.1, 2.5 Hz, 1 H), 7.19 (ddd, J = 8.8, 7.5, 2.5 Hz, 1 H)

^{13}C NMR (101 MHz, CDCl_3): δ = 180.67 (q, J = 40.3, 37.2 Hz), 164.78 (d, J = 261.1 Hz), 132.52 (dq, J = 9.9, 3.3 Hz), 128.20 (d, J = 3.6 Hz), 124.17 (d, J = 9.5 Hz), 123.23 (dd, J = 24.8, 6.5 Hz), 115.82 (q, J = 291.8 Hz), 115.06 (dd, J = 21.8, 2.7 Hz)

^{19}F NMR (377 MHz, CDCl_3): δ = –72.37, –101.28 to –101.37 (m).

Spectral data for this compound are consistent with those previously reported.³⁶

1-(2-Chloropyridin-3-yl)-2,2,2-trifluoroethanone (4k)

Obtained according to the General Procedure as a white solid (0.167 g, 80%).

^1H NMR (500 MHz, DMSO- d_6 , hydrate): δ = 8.44 (dd, J = 4.6, 1.9 Hz, 1 H), 8.20 (dd, J = 7.8, 1.9 Hz, 1 H), 7.91 (s, 2 H), 7.49 (dd, J = 7.8, 4.6 Hz, 1 H).

^{13}C NMR (126 MHz, DMSO- d_6 , hydrate): δ = 150.12, 149.15, 140.65, 132.21, 123.32 (q, J = 289.8 Hz), 122.56, 92.14 (q, J = 32.6 Hz).

^{19}F NMR (377 MHz, DMSO- d_6): δ = –80.71.

Spectral data for this compound are consistent with those previously reported.³⁶

1-(5-Bromothiophen-2-yl)-2,2,2-trifluoroethanone (4l)

Obtained according to the General Procedure as an orange oil (0.242 g, 93%).

^1H NMR (300 MHz, CDCl_3): δ = 7.71 (dq, J = 4.5, 1.6 Hz, 1 H), 7.22 (d, J = 4.2 Hz, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 172.73 (q, J = 37.3 Hz), 137.93, 136.98 (q, J = 3.1 Hz), 132.55, 128.10, 116.34 (q, J = 290.3 Hz).

^{19}F NMR (377 MHz, CDCl_3): δ = –72.16.

Spectral data for this compound are consistent with those previously reported.³⁶

2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanone (4m)

Obtained according to the General Procedure as an orange oil (0.150 g, 67%).

^1H NMR (300 MHz, CDCl_3): δ = 8.89–8.79 (m, 1 H); δ = 8.21 (dt, J = 7.4, 1.6 Hz, 1 H), 8.17 (dt, J = 8.3, 1.2 Hz, 1 H), 7.94 (dd, J = 8.1, 1.5 Hz, 1 H), 7.71 (ddd, J = 8.7, 6.9, 1.5 Hz, 1 H), 7.66–7.53 (m, 2 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 182.50 (q, J = 34.0 Hz), 136.35, 134.14, 131.83 (q, J = 3.5 Hz), 131.36, 129.68, 129.16, 127.32, 126.54, 125.38, 124.33, 116.79 (q, J = 293.0 Hz).

^{19}F NMR (377 MHz, CDCl_3): δ = –70.08.

Spectral data for this compound are consistent with those previously reported.³⁶

Acetophenone (4o)

Obtained according to the General Procedure as a clear liquid (0.099 g, 82%).

^1H NMR (400 MHz, CDCl_3): δ = 7.99–7.92 (m, 2 H), 7.60–7.52 (m, 1 H), 7.50–7.41 (m, 2 H), 2.60 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 198.44, 137.23, 133.25, 128.69, 128.43, 26.68.

Spectral data for this compound are consistent with those previously reported.³⁶

1-(4-Chlorophenyl)ethanone (4p)

Obtained according to the General Procedure as a white solid (0.122 g, 78%).

^1H NMR (400 MHz, CDCl_3): δ = 7.89 (d, J = 8.6 Hz, 2 H), 7.43 (d, J = 8.3 Hz, 2 H), 2.58 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 196.97, 139.71, 135.59, 129.86, 129.03, 26.66.

Spectral data for this compound are consistent with those previously reported.³⁸

1-(4-Methoxyphenyl)ethanone (4q)

Obtained according to the General Procedure as a clear liquid (0.11 g, 73%).

¹H NMR (400 MHz, CDCl₃): δ = 7.98–7.90 (m, 2 H), 6.98–6.89 (m, 2 H), 3.87 (s, 3 H), 2.56 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 197.09, 163.69, 130.77, 130.49, 113.85, 55.61, 26.46.

Spectral data for this compound are consistent with those previously reported.³⁹

1-(4-Nitrophenyl)ethanone (4r)

Obtained according to the General Procedure as a white solid (0.072 g, 44%).

¹H NMR (400 MHz, CDCl₃): δ = 8.40–8.30 (m, 2 H), 8.24–8.13 (m, 2 H), 2.67 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 197.20, 141.33, 129.59, 123.83, 27.21.

Spectral data for this compound are consistent with those previously reported.⁴⁰

1-(*m*-Tolyl)ethanone (4s)

Obtained according to the General Procedure as a pale-yellow oil (0.103 g, 77%).

¹H NMR (400 MHz, CDCl₃): δ = 7.80–7.72 (m, 2 H), 7.42–7.30 (m, 2 H), 2.59 (s, 3 H), 2.41 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 198.57, 138.50, 137.33, 134.00, 128.94, 128.58, 125.73, 26.79, 21.46.

Spectral data for this compound are consistent with those previously reported.⁴¹

1-(2-bromophenyl)ethanone (4t)

Obtained according to the General Procedure as a clear liquid (0.128 g, 64%).

¹H NMR (400 MHz, CDCl₃): δ = 7.61 (dd, *J* = 7.9, 1.2 Hz, 1 H), 7.46 (dd, *J* = 7.5, 1.8 Hz, 1 H), 7.37 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.29 (td, *J* = 7.7, 1.8 Hz, 1 H), 2.63 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 201.53, 141.66, 134.00, 131.93, 129.06, 127.59, 119.07, 30.46.

Spectral data for this compound are consistent with those previously reported.³⁸

Benzophenone (4u)

Obtained according to the General Procedure as a white solid (0.164 g, 90%).

¹H NMR (400 MHz, CDCl₃): δ = 7.84–7.77 (m, 4 H), 7.64–7.55 (m, 2 H), 7.49 (t, *J* = 7.6 Hz, 4 H).

¹³C NMR (101 MHz, CDCl₃): δ = 196.94, 137.73, 132.54, 130.18, 128.40.

Spectral data for this compound are consistent with those previously reported.³⁶

1-Phenoxypropan-2-one (4v)

Obtained according to the General Procedure as a clear liquid (0.094 g, 63%).

¹H NMR (400 MHz, CDCl₃): δ = 7.35–7.26 (m, 2 H), 7.05–6.96 (m, 1 H), 6.93–6.85 (m, 2 H), 4.53 (s, 2 H), 2.28 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 205.98, 157.85, 129.80, 121.84, 114.62, 73.12, 26.68.

Spectral data for this compound are consistent with those previously reported.³⁶

4-Phenylbutan-2-one (4w)

Obtained according to the General Procedure as a clear liquid (0.116 g, 78%).

¹H NMR (400 MHz, CDCl₃): δ = 7.33–7.24 (m, 2 H), 7.23–7.15 (m, 3 H), 2.90 (t, *J* = 7.6 Hz, 2 H), 2.76 (dd, *J* = 8.3, 6.7 Hz, 2 H), 2.14 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 207.21, 141.65, 128.66, 128.45, 126.28, 45.34, 30.23, 29.91.

Spectral data for this compound are consistent with those previously reported.³⁹

Hexan-2-one (4x)

Obtained according to the General Procedure as a clear liquid (0.047 g, 47%).

¹H NMR (400 MHz, CDCl₃): δ = 2.42 (t, *J* = 7.4 Hz, 2 H), 2.13 (s, 3 H), 1.55 (p, *J* = 7.5 Hz, 2 H), 1.31 (dq, *J* = 14.6, 7.3 Hz, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 210.03, 43.68, 29.95, 26.11, 22.42, 13.94.

Spectral data for this compound are consistent with those previously reported.⁴²

Cyclohexanone (4y)

Obtained according to the General Procedure as a clear liquid (0.005 g, 51%).

¹H NMR (400 MHz, CDCl₃): δ = 2.34 (t, *J* = 6.7 Hz, 4 H), 1.86 (p, *J* = 6.1 Hz, 4 H), 1.72 (tq, *J* = 8.4, 4.9, 4.1 Hz, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ = 212.38, 42.11, 27.15, 25.13.

Spectral data for this compound are consistent with those previously reported.³⁶

4-(*tert*-Butyl)cyclohexanone (4z)

Obtained according to the General Procedure as a clear liquid (0.068 g, 44%).

¹H NMR (400 MHz, CDCl₃): δ = 2.41–2.27 (m, 4 H), 2.14–2.01 (m, 2 H), 1.53–1.36 (m, 3 H), 0.90 (s, 9 H).

¹³C NMR (101 MHz, CDCl₃): δ = 213.31, 46.80, 41.39, 32.57, 27.70.

Spectral data for this compound are consistent with those previously reported.³⁶

2-Adamantanone (4aa)

Obtained according to the General Procedure as a white solid (0.084 g, 56%).

¹H NMR (400 MHz, CDCl₃): δ = 2.55 (s, 2 H), 2.10–1.92 (m, 13 H).

¹³C NMR (101 MHz, CDCl₃): δ = 47.14, 39.42, 36.47, 27.61.

Spectral data for this compound are consistent with those previously reported.³⁶

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References

- (1) For reviews, see: (a) Chaudhary, B.; Kulkarni, N.; Saiyed, N.; Chaurasia, M.; Desai, S.; Potkule, S.; Sharma, S. *Adv. Synth. Catal.* **2020**, *362*, 4794. (b) Wu, W.; Weng, Z. *Synlett* **2018**, *50*, 1958. (c) Kelly, C. B.; Mercadante, M. A.; Leadbeater, N. E. *Chem. Commun.* **2013**, *49*, 11133.
- (2) For recent examples, see: (a) Shan, Q.-C.; Liu, S.; Shen, Y.; Ma, M.; Duan, X.-H.; Gao, P.; Guo, L.-N. *Org. Lett.* **2022**, *24*, 6653. (b) Zhang, X.; Ning, Y.; Liu, Z.; Li, S.; Zanoni, G.; Bi, X. *ACS Catal.* **2022**, *12*, 8802. (c) Zhang, X.; Li, L.; Zanoni, G.; Han, X.; Bi, X. *Chem. Eur. J.* **2022**, *28*, e202200280. (d) Carceller-Ferrer, L.; González del Campo, A.; Vila, C.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *J. Org. Chem.* **2022**, *87*, 4538. (e) Alberca, S.; Matador, E.; Iglesias-Sigüenza, J.; de Gracia Retamosa, M.; Fernández, R.; Lassaletta, J. M.; Monge, D. *Chem. Commun.* **2021**, *57*, 11835. (f) Park, D.; Jette, C. I.; Kim, J.; Jung, W.-O.; Lee, Y.; Park, J.; Kang, S.; Han, M. S.; Stoltz, B. M.; Hong, S. *Angew. Chem. Int. Ed.* **2020**, *59*, 775. (g) Liu, Z.; Zhang, Z.; Zhu, G.; Zhou, Y.; Yang, L.; Gao, W.; Tong, L.; Tang, B. *Org. Lett.* **2019**, *21*, 7324. (h) Balaraman, K.; Moskowitz, M.; Wolf, C. *Adv. Synth. Catal.* **2018**, *360*, 4705.
- (3) (a) Francis, F.; Wuest, F. *Molecules* **2021**, *26*, 6478. (b) Meyer, D. N.; Cortés González, M. A.; Jiang, X.; Johansson-Holm, L.; Pourghasemi Lati, M.; Elgland, M.; Nordeman, P.; Antoni, G.; Szabó, K. J. *Chem. Commun.* **2021**, *57*, 8476.
- (4) For recent examples, see: (a) Nguyen, T. H.; Tran, P.-T.; Pham, N. Q. A.; Hoang, V.-H.; Hiep, D. M.; Ngo, S. T. *ACS Omega* **2022**, *7*, 20673. (b) Hassan, J. J.; Lieske, A.; Dörpmund, N.; Klatt, D.; Hoffmann, D.; Kleppa, M.-J.; Kustikova, O. S.; Stahlhut, M.; Schwarzer, A.; Schambach, A.; Maetzg, T. *Int. J. Mol. Sci.* **2021**, *22*, 9411. (c) Makhaeva, G. F.; Lushchekina, S. V.; Boltneva, N. P.; Serebryakova, O. G.; Kovaleva, N. V.; Rudakova, E. V.; Elkina, N. A.; Shchegolkov, E. V.; Burgart, Y. V.; Stupina, T. S.; Terentiev, A. A.; Radchenko, E. V.; Palyulin, V. A.; Saloutin, V. I.; Bachurin, S. O.; Richardson, R. J. *Eur. J. Med. Chem.* **2021**, *218*, 113385. (d) Zafrani, Y.; Parvari, G.; Amir, D.; Ghindes-Azaria, L.; Elias, S.; Pevzner, A.; Fridkin, G.; Berliner, A.; Gershonov, E.; Eichen, Y.; Saphier, S.; Katalan, S. *J. Med. Chem.* **2021**, *64*, 4516. (e) Zhang, Z.; Wang, Y.; Chen, X.; Song, X.; Tu, Z.; Chen, Y.; Zhang, Z.; Ding, K. *Bioorg. Med. Chem.* **2021**, *50*, 116457. (f) Cheng, A.; Zhang, L.; Zhou, Q.; Liu, T.; Cao, J.; Zhao, G.; Zhang, K.; Song, G.; Zhao, B. *Angew. Chem. Int. Ed.* **2021**, *60*, 20166. (g) Citarella, A.; Micalé, N. *Molecules* **2020**, *25*, 4031. (h) Agback, P.; Woestenenk, E.; Agback, T. *BMC Mol. Cell Biol.* **2020**, *21*, 38. (i) da Silva-Júnior, E. F.; de Araújo-Júnior, J. X. *Bioorg. Med. Chem.* **2019**, *27*, 3963.
- (5) See, for example: (a) Wu, J.; Wu, H.; Liu, X.; Zhang, Y.; Huang, G.; Zhang, C. *Org. Lett.* **2022**, *24*, 4322. (b) Reeve, J. T.; Song, J. J.; Tan, Z.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2008**, *73*, 9476.
- (6) See, for example: (a) Wu, J.; Wu, H.; Liu, X.; Zhang, Y.; Huang, G.; Zhang, C. *Org. Lett.* **2022**, *24*, 4322. (b) Boivin, J.; El Kaim, L.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2573.
- (7) Fujihira, Y.; Liang, Y.; Ono, M.; Hirano, K.; Kagawa, T.; Shibata, N. *Beilstein J. Org. Chem.* **2021**, *17*, 431.
- (8) For a review, see: Yue, N.; Sheykahmad, F. R. *J. Fluor. Chem.* **2020**, *238*, 109629.
- (9) For a recent example, see: Gan, L.; Yu, Q.; Liu, Y.; Wan, J.-P. *J. Org. Chem.* **2021**, *86*, 1231.
- (10) See, for example: (a) Colas, K.; dos Santos, A. C. V. D.; Kohlhepp, S. V.; Mendoza, A. *Chem. Eur. J.* **2022**, *28*, e202104053. (b) Johansen, M. B.; Gedde, O. R.; Mayer, T. S.; Skrydstrup, T. *Org. Lett.* **2020**, *22*, 4068.
- (11) Linderman, R. J.; Graves, D. M. *J. Org. Chem.* **1989**, *54*, 661.
- (12) Stewart, R.; Lee, D. G. *Can. J. Chem.* **1964**, *42*, 439.
- (13) Cheng, H.; Pei, Y.; Leng, F.; Li, J.; Liang, A.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron Lett.* **2013**, *54*, 4483.
- (14) Kelly, C. B.; Mercadante, M. A.; Hamlin, T. A.; Fletcher, M. H.; Leadbeater, N. E. *J. Org. Chem.* **2012**, *77*, 8131.
- (15) For reviews on the use of photocatalysis in tandem with other catalytic methods, see: (a) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. *Chem. Rev.* **2022**, *122*, 1485. (b) Xu, G.-Q.; Xu, P.-F. *Chem. Commun.* **2021**, *57*, 12914. (c) Prier, C. K.; MacMillan, D. W. C. In *Visible Light Photocatalysis in Organic Chemistry*; John Wiley & Sons, Ltd: Weinheim, **2018**, 299. (d) Connell, T. U. *Dalton Trans.* **2022**, *51*, 13176. (e) McAtee, R. C.; McClain, E. J.; Stephenson, C. R. J. *Trends Chem.* **2019**, *1*, 111.
- (16) Pistritto, V. A.; Paolillo, J. M.; Bisset, K. A.; Leadbeater, N. E. *Org. Biomol. Chem.* **2018**, *16*, 4715.
- (17) (a) Ovian, J. M.; Kelly, C. B.; Pistritto, V. A.; Leadbeater, N. E. *Org. Lett.* **2017**, *19*, 1286. (b) Nandi, J.; Ovian, J. M.; Kelly, C. B.; Leadbeater, N. E. *Org. Biomol. Chem.* **2017**, *15*, 8295.
- (18) (a) Nandi, J.; Leadbeater, N. E. *Org. Biomol. Chem.* **2019**, *17*, 9182. (b) Nandi, J.; Witko, M. L.; Leadbeater, N. E. *Synlett* **2018**, *29*, 2185.
- (19) Nandi, J.; Hutcheson, E. L.; Leadbeater, N. E. *Tetrahedron Lett.* **2021**, *63*, 152632.
- (20) Sandoval, A. L.; Politano, F.; Witko, M. L.; Leadbeater, N. E. *Org. Biomol. Chem.* **2021**, *19*, 2986.
- (21) Politano, F.; Sandoval, A. L.; Witko, M. L.; Doherty, K. E.; Schroeder, C. M.; Leadbeater, N. E. *Eur. J. Org. Chem.* **2022**, e202101239.
- (22) Sandoval, A. L.; Politano, F.; Witko, M. L.; Leadbeater, N. E. *Org. Biomol. Chem.* **2022**, *20*, 667.
- (23) Reddy, V. P. In *Organofluorine Compounds in Biology and Medicine*; Elsevier: Amsterdam, **2015**, 1.
- (24) Schlosser, P. M.; Bale, A. S.; Gibbons, C. F.; Wilkins, A.; Cooper, G. S. *Environ. Health Perspect.* **2015**, *123*, 114.
- (25) Kelly, C. B.; Mercadante, M. A.; Wiles, R. J.; Leadbeater, N. E. *Org. Lett.* **2013**, *15*, 2222.

- (26) Bartelson, A. L. *Graduate Thesis*; University of Connecticut: USA, **2011**.
- (27) Politano, F.; Brydon, W. P.; Nandi, J.; Leadbeater, N. E. *Molbank* **2021**, M1180.
- (28) De Souza, G. F. P.; Salles, A. G. *Green Chem.* **2019**, *21*, 5507.
- (29) Zhao, S. C.; Ji, K. G.; Lu, L.; He, T.; Zhou, A. X.; Yan, R. L.; Ali, S.; Liu, X. Y.; Liang, Y. M. *J. Org. Chem.* **2012**, *77*, 2763.
- (30) Liang, C.; Su, H. W. *Ind. Eng. Chem. Res.* **2009**, *48*, 5558.
- (31) Borja-Miranda, A.; Valencia-Villegas, F.; Lujan-Montelongo, J. A.; Polindara-García, L. A. *J. Org. Chem.* **2021**, *86*, 929.
- (32) Lee, J.; Von Gunten, U.; Kim, J. H. *Environ. Sci. Technol.* **2020**, *54*, 3064.
- (33) Rosenau, C. P.; Jelier, B. J.; Gossert, A. D.; Togni, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 9528.
- (34) Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E. *Nat. Protoc.* **2013**, *8*, 666.
- (35) Hamlin, T.; Kelly, C.; Cywar, R.; Leadbeater, N. E. *J. Org. Chem.* **2014**, *79*, 1145.
- (36) Miller, S. A.; Bisset, K. A.; Leadbeater, N. E.; Eddy, N. A. *Eur. J. Org. Chem.* **2019**, 1413.
- (37) Kani, R.; Inuzuka, T.; Kubota, Y.; Funabiki, K. *Eur. J. Org. Chem.* **2020**, 4487.
- (38) Hu, D.; Jiang, X. *Green Chem.* **2022**, *24*, 124.
- (39) Ma, J.; Hong, C.; Wan, Y.; Li, M.; Hu, X.; Mo, W.; Hu, B.; Sun, N.; Jin, L.; Shen, Z. *Tetrahedron Lett.* **2017**, *58*, 652.
- (40) Ju, Z.-Y.; Song, L.-N.; Chong, M.-B.; Cheng, D.-G.; Hou, Y.; Zhang, X.-M.; Zhang, Q.-H.; Ren, L.-H. *J. Org. Chem.* **2022**, *87*, 3978.
- (41) Porcheddu, A.; Colacino, E.; Cravotto, G.; Delogu, F.; De Luca, L. *Beilstein J. Org. Chem.* **2017**, *13*, 2049.
- (42) Gao, J.; Ma, R.; Feng, L.; Liu, Y.; Jackstell, R.; Jagadeesh, R. V.; Beller, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 18591.