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NMP and O_2 as Radical Initiator: Trifluoromethylation of Alkenes to Tertiary β-Trifluoromethyl Alcohols at Room Temperature

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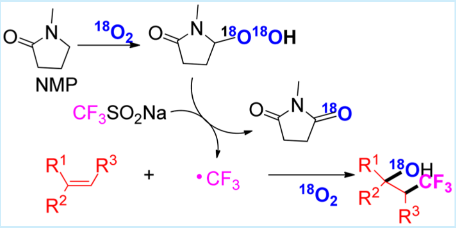
Supporting Information

ABSTRACT: A novel strategy was developed to trigger $\cdot CF_3$ by using *in situ* generated peroxide in NMP under O_2 or air as the radical initiator. Radical trifluoromethylation of alkenes was achieved toward tertiary β-trifluoromethyl alcohols. Various tertiary β-trifluoromethyl alcohols can be synthesized in good yields without extra oxidants or transition metal catalysts. Preliminary mechanistic investigation revealed that O_2 diffusion can influence the reaction rate.

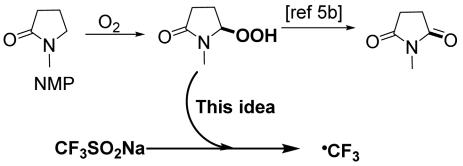


Free radicals have attracted extensive attention in organic synthesis, due to the presence of an unpaired electron that makes them highly reactive.[1] As an important research point of radical chemistry, the generation of radical species has been studied continuously. To date, transition metal catalysts, stoichiometric amount of oxidants, and organometallic reagents have been the most widely applied methodologies to initiate radicals.[2] Solely using molecular oxygen to initiate some highly active precursors to radicals has also been developed in recent years.[3] However, it is always valuable to seek general and environmentally friendly methods to update these existing achievements.

Peroxides have been demonstrated as one of the most effective radical initiators.[4] Nevertheless, the preparation of peroxides is an energy consuming process, and handling of concentrated peroxides is dangerous. Undoubtedly, if peroxides could be produced in situ, more environmentally friendly synthesis will be realized. It is well-known that peroxides widely exist in solvents such as terahydrofuran (THF), *N*-methyl-2-pyrrolidone (NMP), etc., under an O_2 or air atmosphere.[5] However, on one hand, these peroxides sometimes induce side reactions; on the other hand, the extremely slow generation process and low concentration make them hard to put into use. They are usually regarded as useless, harmful, and hazardous. Based on these conditions, in situ generated peroxides in solvents have been seldom utilized. Thus, new strategies making use of those undesirable and "harmful" peroxides would be meaningful, which would also deepen our understanding of radical initiators for both academic and industrial research.

To make the low-concentration in situ generated peroxides in solvents valuable, a suitable radical acceptor which can efficiently react with them might be the critical factor. We envisioned CF_3SO_2Na (Langlois reagent) would be a good choice. As an inexpensive, stable, easily handled, and stored trifluoromethylation reagent, CF_3SO_2Na has been extensively studied since the pioneering work by Langlois and co-workers in 1991.[6] In many previous reports, CF_3SO_2Na can be oxidized to $CF_3SO_2\cdot$ by many different oxidants, such as *tert*-butyl hydroperoxide (TBHP), $PhI(OAc)_2$, etc.,[7] and then $CF_3SO_2\cdot$ can easily decompose to $\cdot CF_3$[8] with the release of SO_2. Those results inspired us to make use of the low-concentration peroxides in solvents by using CF_3SO_2Na as the radical acceptor. In this regard, we proposed a new strategy for the generation of $\cdot CF_3$ by utilizing NMP and O_2 together as the radical initiator (Scheme 1).

Scheme 1. New Strategy to Generate $\cdot CF_3$ by Utilizing NMP and O_2 as Radical Initiator



To evaluate the practicality of our design, we attempted to use operando IR to monitor the conversions of CF_3SO_2Na in NMP and other solvents under an O_2 atmosphere. Indeed, in NMP, CF_3SO_2Na was gradually consumed along with the generation of CF_3SO_3Na, which was the oxidized product of CF_3SO_2Na initiated by $CF_3SO_2\cdot$ under O_2 or air.[9] The reason that the conversion of CF_3SO_2Na (51%) in NMP is bigger than the generation of CF_3SO_3Na (18%) is possibly due to the

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simultaneous desulfurization of $CF_3SO_2\cdot$ to $\cdot CF_3$ (blue line in Figure 1). While use of other solvents, such as dimethylformamide (DMF) or ethyl acetate (EtOAc), resulted in no obvious consumption of CF_3SO_2Na and no obvious generation of CF_3SO_3Na (Figure 1). Additionally, no reaction occurred when conducting this experiment under a N_2 atmosphere in NMP (see Supporting Information (SI) for more details). These results indicated that the combination of NMP and O_2 are essential for facilitating the consumption of CF_3SO_2Na, which is consistent with our design in Scheme 1.

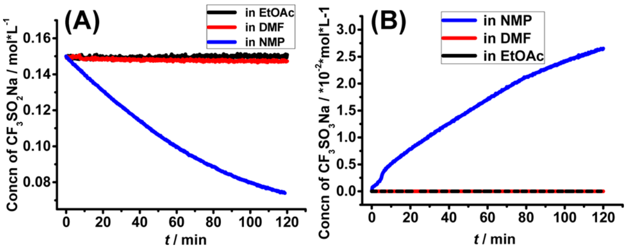
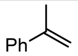
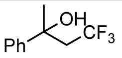
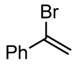
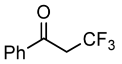
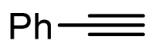
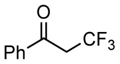
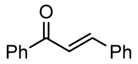


Figure 1. Kinetic profile of the reaction of CF_3SO_2Na (0.6 mmol) at 25 °C for 2 h in different solvents (4.0 mL) under 1 atm of O_2 (balloon). (A) The concentration of CF_3SO_2Na in different solvents. (B) The concentration of generated CF_3SO_3Na in different solvents.

Based on the above IR experiment, we speculated that $\cdot CF_3$ might be generated upon mixing CF_3SO_2Na, NMP, and O_2 together. To verify our speculation, alkenes and alkynes were employed as radical acceptors to capture the $\cdot CF_3$. As shown in Table 1, the trifluoromethylation product was obtained in 53% yield when α-methylstyrene was used. In contrast, α-bromostyrene could only provide 8% trifluoromethylation product, and trace or no corresponding product could be observed when phenylacetylene or chalcone was employed. These results not only elucidated the generation of $\cdot CF_3$ but also suggested that the electrophilic $\cdot CF_3$ was more apt to add to electron-rich unsaturated compounds.

Table 1. Tested Acceptors for the Capture of $\cdot CF_3$[a]

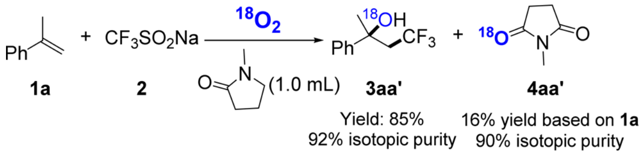
substrate	product	yield (%)
		53
		8
		trace
	-	N.D.

[a] All reactions were carried out using alkene or alkyne (0.2 mmol), CF_3SO_2Na (0.6 mmol), and NMP (2.0 mL) under an O_2 atmosphere at 25 °C for 2 h. Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard. N.D. = not detected.

The above kinetic investigations and $\cdot CF_3$ capture experiments concluded that the combination of NMP and O_2 could be a novel initiation strategy for radicals. However, as described in Table 1, when this new radical initiation strategy was utilized in the synthesis of 4,4,4-trifluoro-2-phenyl-2-butanol (**3aa**) from α-methylstyrene (**1a**) and CF_3SO_2Na (**2**), only a moderate yield was obtained. To make this new strategy more effective, several experiments were performed (for more details, see SI). Initially, different reaction temperatures were tested, and the results showed that room temperature gave the best yield. Reaction at 45 °C gave a similar result as that at room temperature, and higher temperatures did not work well. Solvent screening revealed NMP was the best choice since other solvents, such as toluene, resulted in no desired product. Finally, an excellent yield of 82% was obtained when the volume of NMP decreased from 2 to 1 mL. Further reducing the volume of NMP did not give a better result. Notably, no desired product could be detected when the reaction was carried out under a N_2 atmosphere, indicating that O_2 plays a vital role in this transformation.

Mechanistic investigations were performed to understand this highly selective transformation. As proposed in Scheme 1, the *in situ* generated hydroperoxide from the reaction of NMP and O_2 might be the key intermediate for initiating the $\cdot CF_3$, itself decomposing to *N*-methylsuccinimide (**4aa**) eventually. To verify our hypothesis, an $^{18}O_2$ labeling experiment of model reaction was conducted. Since the hydroperoxide was formed with the participation of O_2, ^{18}O-labeled hydroperoxide or **4aa** should be detected. As expected, ^{18}O-labeled **4aa′** was obtained in 16% yield and in 90% isotopic purity (Scheme 2; see SI for more details). Hence, hydroperoxide might be produced and work as the vital intermediate for initiating $\cdot CF_3$.

Scheme 2. Labeling Experiment of Model Reaction[a]



[a] Reaction was carried out using **1a** (0.2 mmol), **2** (0.6 mmol), and NMP (1.0 mL) at 25 °C for 2 h under $^{18}O_2$ atmosphere. Yield of **3aa** was determined by ^{19}F NMR spectroscopy. Yield of **4aa** was determined by GC analysis.

Meanwhile, the model reaction under an $^{18}O_2$ atmosphere provides further chance to probe the vital role of O_2. As shown in Scheme 2, the ^{18}O-isotopologue **3aa′** was obtained in 85% yield and in 92% isotopic purity. This result revealed that O_2 also acted as a reaction participant and was transferred into the final product. This is the first report of highly selective synthesis toward β-trifluoromethyl alcohols through the oxygenation process.[10]

It is well-known that the reaction between NMP and O_2 toward peroxide formation is slow at room temperature. Therefore, we conjectured that the concentration of O_2 should affect the reaction rate. In this regard, the kinetic behavior of O_2 was investigated by studying the reaction between **1a** and **2**. As shown in Figure 2, the reaction rate decreased by decreasing the concentration of O_2 or by slowing down the stirring rate under O_2 in NMP. These results fit well with our hypothesis, suggesting that O_2 diffusion can influence the reaction rate.

Additionally, the model reaction between **1a** and **2** was also monitored by operando IR. Compared with the blank reaction in the absence of **1a**, the conversion of **2** in the model reaction was faster than the one in the blank reaction (Figure 3), and the final conversions were 66% versus 51%. This result showed that **1a** accelerates the consumption of **2**, presumably because the alkene shifts the reaction equilibrium to accelerate the evolution of SO_2 by trapping the generated $\cdot CF_3$.

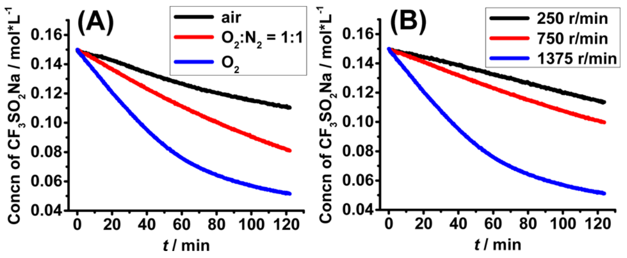


Figure 2. Kinetic profile of the reaction of **1a** (0.2 mmol), **2** (0.6 mmol) at 25 °C for 2 h in NMP (4.0 mL) under different conditions. (A) The concentration of CF_3SO_2Na at different O_2 concentrations. (B) The concentration of generated CF_3SO_2Na at different stirring rates.

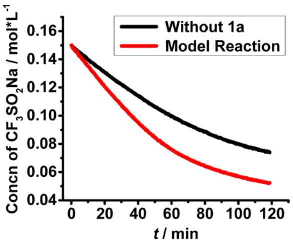
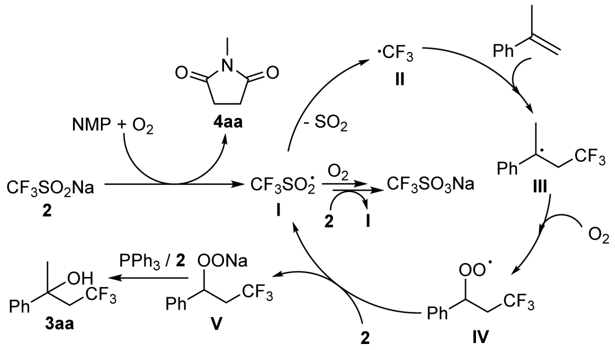


Figure 3. Concentration of CF_3SO_2Na under two different conditions. Red line: **1a** (0.2 mmol) and **2** (0.6 mmol) in NMP (4.0 mL) at 25 °C for 2 h under 1 atm of O_2 (balloon). Black line: **2** (0.6 mmol) in NMP (4.0 mL) at 25 °C for 2 h under 1 atm of O_2 (balloon).

Based on the previous reports and the above-mentioned results, a tentative mechanism was proposed in Scheme 3.

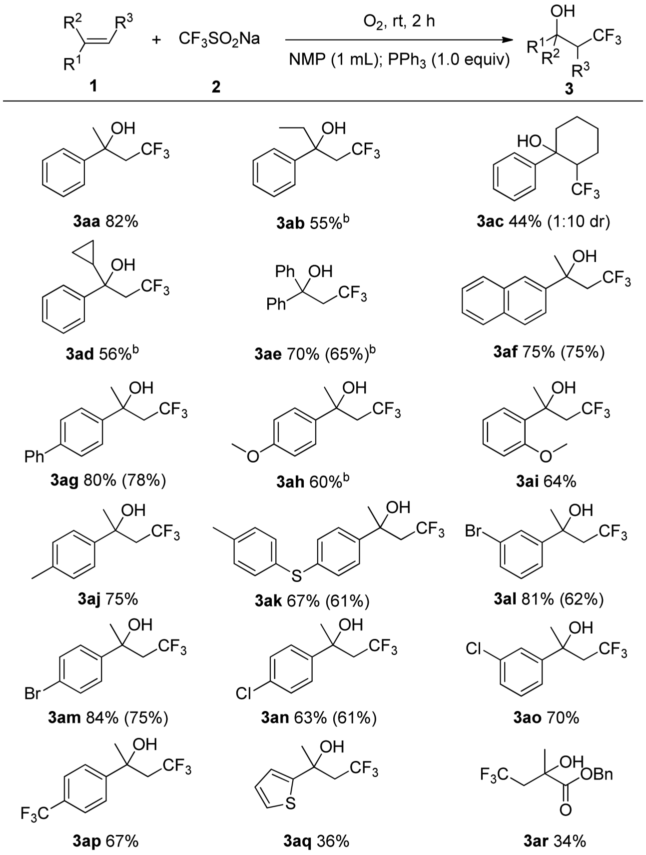
Scheme 3. Tentative Reaction Mechanism



NMP reacted with O_2 to generate the hydroperoxide intermediate, which serves as a radical initiator to oxidize CF_3SO_2Na to $CF_3SO_2\cdot$ (**I**), itself decomposing to *N*-methylsuccinimide (**4aa**) eventually. The radical **I** could react with O_2 toward the formation of CF_3SO_3Na or decompose to $\cdot CF_3$ (**II**) with the evolution of SO_2. The resulting **II** adds to **1a** to afford the carbon-centered radical intermediate **III**, which would be further captured by O_2 and transformed into peroxide radical **IV**. This newly formed O-centered radical could also serve as an electron acceptor from **2** via a single electron oxidation process to intermediate **V** with the regeneration of **I**.[11] Finally, the desired product **3aa** could be achieved after the hydrogen abstraction process and reduced either by **2** or by the extraneous reductant.

With an understanding of this NMP and O_2 initiated radical trifluoromethylation reaction, the generality of this transformation was evaluated, and the results are summarized in Scheme 4. A series of α-substituted styrenes, such as ethyl, cyclopropyl, phenyl substituted styrenes and 1-phenyl-1-cyclohexene, afforded the desired products in moderate to excellent yields (**3aa**–**3ae**). α-Methylstyrene derivatives bearing either electron-withdrawing or -donating groups on the aryl ring provided the corresponding products **3af**–**3ap** in good to excellent yields. A range of functional groups including OMe (**3ah** and **3ai**), halogens (**3al**–**3ao**), and CF_3 substituents (**3ap**) were demonstrated to be well tolerated in this transformation. Notably, a thiophenyl substituent, which is easily overoxidized in oxidative conditions, was well tolerated in this method, giving the corresponding product **3ak** in 67% yield. The heteroaryl substrate, 2-(prop-1-en-2-yl)thiophene, was also well-behaved to give the expected product **3aq** in 36% yield. Notably, nonconjugated olefin, such as benzyl methacrylate, was suitable for this protocol, giving the desired product **3ar** in 34% yield.

Scheme 4. Substrate Scope of Trifluoromethylation of Alkenes[a]



[a] Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol), **2** (0.6 mmol), and NMP (1.0 mL) under different conditions. Yields are determined by ^{19}F NMR spectroscopy, and yields of isolated products are shown in parentheses after PPh$_3$ worked. [b] 1.0 mmol of CF_3SO_2Na, 2 mL of NMP for 12 h.

In conclusion, we have developed a novel strategy combining NMP and O_2 as the radical initiator to activate CF_3SO_2Na. By using this novel strategy, an aerobic radical trifluoromethylation of alkenes to tertiary β-trifluoromethyl alcohols was achieved. This protocol exhibits a broad substrate scope for the synthesis of various valuable β-trifluoromethyl alcohols at room temperature without extra oxidants or transition metal catalysts.

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Kinetic investigations revealed O_2 diffusion can influence the reaction rate. Further studies on more mechanistic details are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03035.

The experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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