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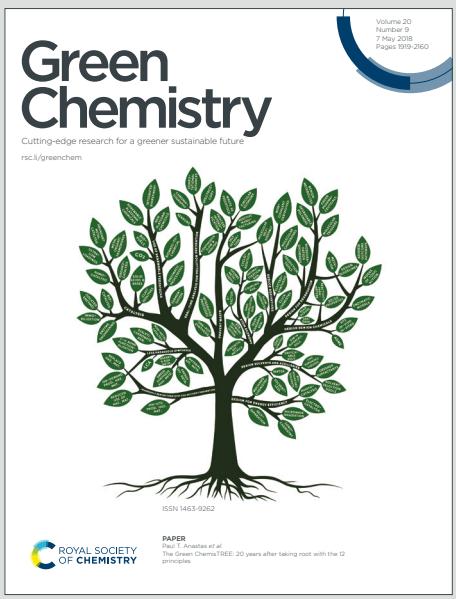

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Green Foundation

1. Our work has developed a direct and efficient methodology to construct valuable *δ*-trifluoromethyl-*δ*-hydroxyketone scaffolds. In contrast, previous works involve multiple reaction steps, sensitive or toxic reagents, harsh conditions, or limited substrate scopes.

2. Trifluoromethylated compounds are ubiquitous structural motifs found in numerous pharmaceuticals, agrochemicals, and materials. The new developed methods may serve as useful tools for the synthesis of *δ*-trifluoromethyl-*δ*-hydroxyketones in a 100% atom-economic and green manner. The reaction could proceed smoothly with the assistance of air, without adding any additional additives. The catalyst can be efficiently reused, indicating its potential for catalytic recycling.

3. It will be beneficial for organic chemists to access pharmaceuticals and natural products involving functionalized CF_3-substituted tertiary alcohols, therefore, making contributions to the new drug development. To make our work greener, improving the number of cycles and integrating solid-phase catalysis and continuous flow operation for sustained product formation should be considered. In addition, we should employ even more environmentally friendly reaction conditions to construct *δ*-trifluoromethyl-*δ*-hydroxyketone compounds, including photoreactions and electrochemical reactions.

Mn-Catalyzed Hydroxyalkylation of α-Trifluoromethylstyrenes with Cyclopropanols: Facile Synthesis of δ-Trifluoromethyl-δ-Hydroxyketones

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δ-Trifluoromethyl-δ-hydroxyketones are challenging to construct from simple starting materials. A highly efficient, concise hydroxyalkylation has been successfully achieved, in which the cyclopropanols and α-(trifluoromethyl)alkenes can be utilized for construction of valuable δ-trifluoromethyl-δ-hydroxyketone scaffolds in an economic and green manner. The reaction proceeded efficiently under mild, additive-free reaction conditions using ambient air as a benign oxidant, aligning with green chemistry principles such as atom economy, step economy and waste minimization. This transformation without competitive β-fluoride elimination, exhibits a broad substrate scope, excellent functional group compatibility, and scalability, demonstrating significant potential for practical applications. The recyclability of the catalytic system further underscores the sustainability of this transformation.

Introduction

Trifluoromethylated compounds are ubiquitous structural motifs found in numerous pharmaceuticals, agrochemicals, and materials due to their unique electronegativity, lipophilicity, metabolic stability, and bioavailability.[1] The widespread application of organic fluorine compounds has spurred the development of diverse synthetic methodologies. Of particular interest is the pursuit of green synthetic strategies.[2] Despite progress with reagents such as hypervalent iodine reagents and Umemoto's reagent,[3] their poor atom economy and stoichiometric waste generation necessitate the development of more efficient and atom-economical alternatives. Concurrently, the construction of quaternary carbon centers remains a persistent challenge in organic chemistry.[4] The combination of a trifluoromethyl group and a quaternary carbon center results in a unique structural motif – the trifluoromethylated quaternary carbon center – which exhibits both high steric hindrance and strong electron-withdrawing effects. Among them, CF_3-substituted tertiary alcohols and their derivatives are particularly notable for their presence in various therapeutic drugs and synthetic intermediates (Scheme 1a).[5] Several synthetic approaches have been developed to access tertiary trifluoromethyl alcohol-substituted ketones. Although synthetic routes to β,β- and γ,γ-disubstituted ketones featuring a tertiary trifluoromethyl alcohol moiety are well-established,[6] efficient strategies for constructing the δ,δ-disubstituted analogues remain underdeveloped (Scheme 1b).[7] General synthetic approaches involve the construction of the C5 skeleton utilizing either: (a) trifluoroacetic anhydride, 2-ethoxy-3,4-dihydro-2H-pyran, and a Grignard reagent, followed by oxidation with Jones reagent,[7a] or (b) an aldol reaction between an allyl aryl ketone and trifluoromethyl acetophenone, followed by hydrogenation.[7b] The present tactics rely on a linear synthesis strategy, which requires prior construction of the C5 skeleton followed by redox adjustments. Therefore, the development of highly efficient and direct convergent synthesis strategies to approach these exquisite scaffolds in one step from readily available building blocks remains highly sought after, as it would provide a novel, modular, and complementary pathway to access δ-trifluoromethyl-δ-hydroxyketones.

α-(Trifluoromethyl)alkenes have emerged as important building blocks for the synthesis of structurally diverse fluorinated compounds.[8] The construction of trifluoromethyl-substituted quaternary carbon centers faces two major challenges: first, the significant steric hindrance must be overcome; second, due to the strong electron-withdrawing nature of the trifluoromethyl group, if classical carbanion-based strategies are employed, issues such as fluoride elimination[9] and undesired hydrogen atom abstraction[10] must be circumvented. Accordingly, manipulation of reaction mode to form a trifluoromethylated quaternary carbon center is of great significance. Recently, various difunctionalizations of α-(trifluoromethyl)alkenes have been developed to access densely functionalized CF_3-substituted tertiary alcohols,[11] but these radical addition process is not compatible with alkyl groups, which restricts the broader utility of this method. This limitation arises from the fact that radicals stabilized by functional groups such as carbonyl and sulfonyl exhibit highly stability, while alkyl radicals derive only limited stabilization from hyperconjugation effects. The generation of unstabilized alkyl radicals under mild conditions, while maintaining control and selectivity over the subsequent reactions, has long posed a significant challenge in synthetic chemistry.[12]

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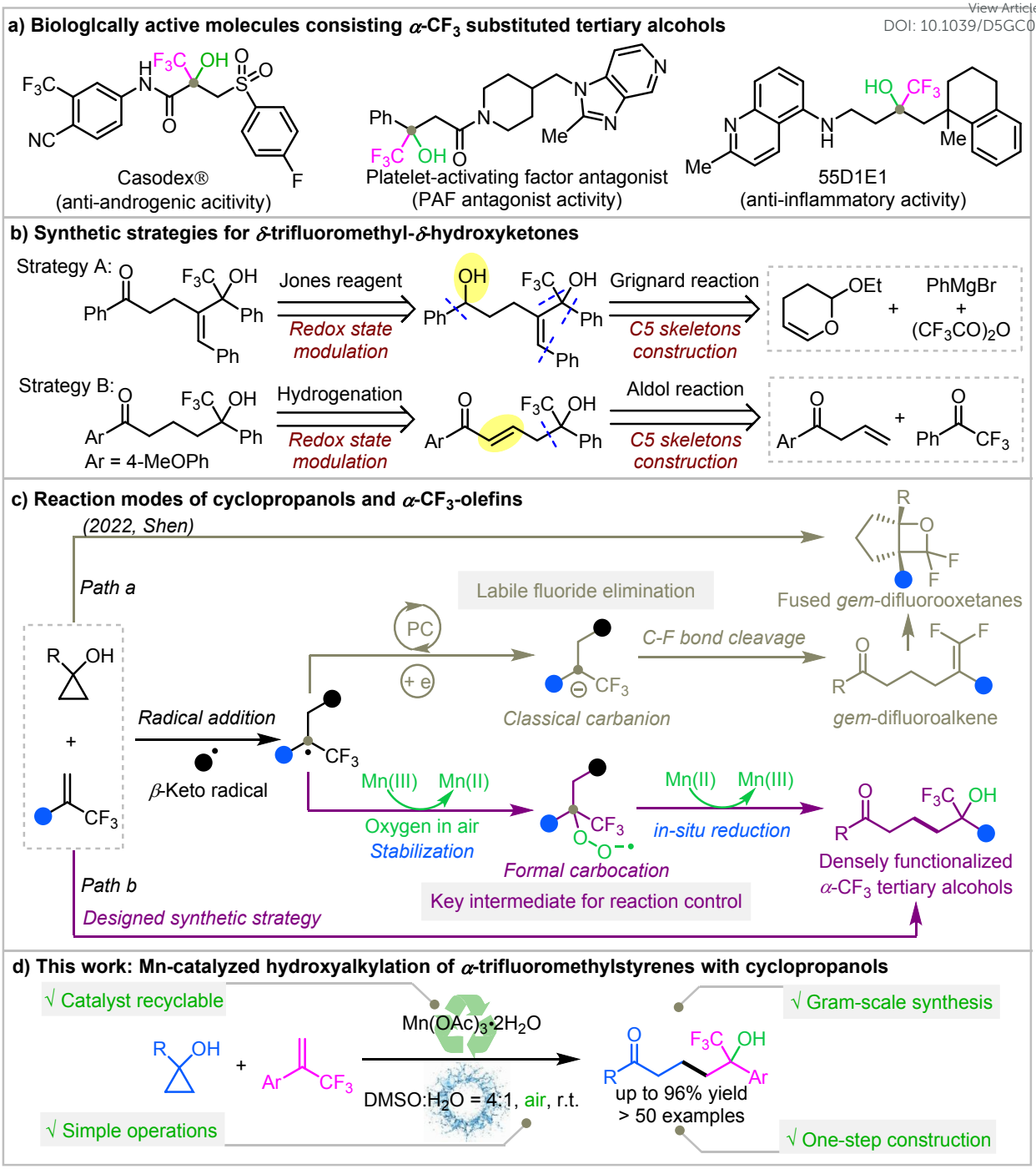


Scheme 1. Significance and synthetic strategies of α-CF_3 tertiary alcohols. a) Biologically active molecules consisting α-CF_3 substituted tertiary alcohols. b) Synthetic strategies for δ-trifluoromethyl-δ-hydroxyketones. c) Reaction modes of cyclopropanols and α-CF_3-olefins. d) Mn-catalyzed hydroxyalkylation of α-trifluoromethylstyrenes with cyclopropanols.

Cyclopropanols serve as readily available C3 synthons, and versatile homoenolates or radical precursors owing to their intrinsic ring strain.[13] It has been known that alkoxyl radicals generated from cyclopropanols could undergo radical β-carbon elimination to generate alkyl radicals.[14] In 2022, Shen and colleagues reported a photocatalytic cascade reaction involving α-(trifluoromethyl)alkenes and cyclopropanols. This approach enabled the successful addition of alkyl radicals to α-(trifluoromethyl)alkenes, followed by facile fluoride elimination, leading to the formation of *gem*-difluorooxetane-fused products.[15] To avoid the C–F bond cleavage, an appropriate way need to be find to stabilize the trifluoromethyl radicals. To date, the chemistry of transition-metal-catalyzed cyclopropanol ring-opening for C–C bond construction has been extensively investigated.[13a,16] Driven by a commitment to green chemistry and sustainable development, non-precious metal catalysts are gaining increasingly attention.[17] Among them, as the third most abundant transition metal, manganese has been successfully exploited as a low-toxicity and low-cost catalyst for a

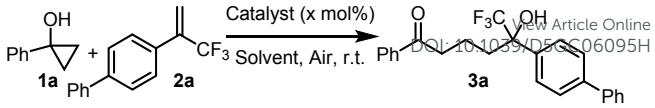
variety of practical transformations.[18] Manganese's capability to readily cycle through its numerous oxidation states (from −3 to +7) underpins its key role in redox chemistry, allowing it to act as an oxidant, reductant or catalyst, which demonstrates significant potential in the ring-opening of cyclopropanols.[19] As an unstable, intermediate-state, single-electron oxidant, Mn(III)[20] readily abstracts an electron from cyclopropanol, forms a β-ketone radical and the more stable Mn(II) to initiate the radical reaction.[19e-g] The subsequently formed trifluoromethyl-substituted alkyl radical is rapidly captured by oxygen, yielding a relatively stable peroxy radical. Resonance effects render the entire structure relatively rigid. This process rapidly consumes the highly reactive carbon-centered radical and avoids C–F bond cleavage. Concurrently, the peroxides generated in the system can re-oxidize Mn(II) back to Mn(III), closing the catalytic cycle (Scheme 1c). In this process, the choice of oxidant is critical. Previously reported methodologies often require stoichiometric or catalytic amounts of oxidants, such as *tert*-butyl hydroperoxide (TBHP) or potassium persulfate ($K_2S_2O_8$).[11d,21] Inspired by recent advances in aerobic oxidation,[11c,22] we recognized the potential of employing air (O_2) as a green, readily available, cost-effective, and sustainable oxidant, which has gained considerable attention in recent years.[23] This led us to select air as the green oxidant for our proposed methodology.

Herein, we report a manganese-catalyzed ring-opening of cyclopropanols that enables radical addition for the straightforward synthesis of δ-trifluoromethyl-δ-hydroxyketones. This strategy employs aerial oxygen as a benign oxidant[19] under mild and concise conditions to stabilize radical intermediates and facilitate their conversion to formal carbocation species without C–F bond cleavage. The process demonstrates green chemistry advantages, including excellent atom economy[25] and step economy[26] through a one-pot transformation, and recyclability[27] of the manganese catalyst, offering an efficient and sustainable route to these valuable fluorinated structures (Scheme 1d).

Results and discussion

Reaction Design and Optimization. We started our study with an investigation of reaction conditions using 1-phenylcyclopropan-1-ol **1a** and 4-(3,3,3-trifluoroprop-1-en-2-yl)-1,1'-biphenyl **2a** as the model substrates (Table 1; see the Supporting Information for details). Firstly, the influence of the metal salts on the reaction was evaluated. Among various metal salts including copper, silver, iron and manganese, manganese-based catalysts demonstrated the highest catalytic performance for the reaction, with $Mn(OAc)_3{\cdot}2H_2O$ proving to be the most effective (entries 1–5). The yield was greatly affected by the solvent and DMSO was the optimal solvent for this reaction (entries 6–9). Notably, an appropriate amount of water was beneficial to secure a high yield, but an excess of water resulted in a lower yield due to the lower solubility of **2a** (entries 10, 11). Decreasing the amount of $Mn(OAc)_3{\cdot}2H_2O$ to 5 mol% would maintain a considerable yield of **3a** by prolonging the reaction time (entries 12, 13).

Table 1. Optimization of conditions[a].



Entry	Catalyst (x mol%)	Solvent	Yield[b] (%)
1	$Mn(acac)_2$ (30)	DMSO	78
2	$Mn(OAc)_3{\cdot}2H_2O$ (30)	DMSO	80
3	$Mn(dpm)_3$ (30)	DMSO	60
4	$Mn(CO)_5Br$ (30)	DMSO	68
5	$Mn_2(CO)_{10}$ (30)	DMSO	78
6	$Mn(OAc)_3{\cdot}2H_2O$ (15)	DMSO	84
7	$Mn(OAc)_3{\cdot}2H_2O$ (15)	DMF	61
8	$Mn(OAc)_3{\cdot}2H_2O$ (15)	CH_3CN	46
9	$Mn(OAc)_3{\cdot}2H_2O$ (15)	THF	64
10	$Mn(OAc)_3{\cdot}2H_2O$ (15)	DMSO/H_2O = 4/1	94
11	$Mn(OAc)_3{\cdot}2H_2O$ (15)	DMSO/H_2O = 1/1	46
12[c]	$Mn(OAc)_3{\cdot}2H_2O$ (5)	DMSO/H_2O = 4/1	93 (92)[e]
13[d]	$Mn(OAc)_3{\cdot}2H_2O$ (2.5)	DMSO/H_2O = 4/1	81

a) Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), catalyst, solvent (1 mL), air, r.t., 8 h. b) Yield determined by ^{19}F NMR using (trifluoromethoxy)benzene as an internal standard. c) 18 h was used. d) 24 h was used. e) Isolated yield.

Substrate Scope. Upon optimization of the reaction conditions, using $Mn(OAc)_3{\cdot}2H_2O$ (5 mol%) as the catalyst, the mixture of DMSO/H_2O [4/1 (v/v)] as the reaction solvent, the desired product **3a** was successfully furnished in 92% isolated yield for 18 h. The structure of **3a** was confirmed by X-ray analysis (CCDC 2483414).[28] With the optimized conditions established, we next evaluated the substrate scope by examining a range of cyclopropanols and α-(trifluoromethyl)alkenes (Scheme 2). A wide range of substituted cyclopropanols was subsequently examined. To our delight, the substituents on the phenyl ring and their positions of cyclopropanols did not present an obvious negative effect on the reaction efficiency, giving **3a–3m** in moderate to excellent yields. Naphthyl substrate was isolated with satisfying yield (**3n**). Thiophene- and furan-containing cyclopropanols were also competent reaction partners (**3o** and **3p**). Aliphatic-substituted cyclopropanols participate in the transformation to provide **3q–3s** with good yields. It is notable that the cyclopropanol without any substituents proved to be a suitable substrate for this transformation, and further cyclize to form six-membered lactone compound, affording **3t** in 68% yield. Next, we sought to examine the generality of this reaction by exploring a wide range of trifluoromethyl alkenes. Transformation of the diverse substrates proceeded without compromising efficiency, delivering the corresponding products in yields ranging from 62% to 96% (**3u–3ar**). Both electron-donating and electron-withdrawing substituents in the *para* positions of the benzene ring worked well in our catalytic system (**3z–3ar**). Owing to steric hindrance, the *ortho*-substituent on the benzene ring led to a lower reaction yield than the *meta* and *para* substituents. (**3av**). Reactive functional groups, such as a free amine (**3x**), a carboxylic acid (**3aq**) and a hydroxyl group (**3ar**) were well tolerated under the standard conditions. Heterocyclic substrates bearing thiophene (**3as**) and quinolone (**3at**) substituents were also compatible with the reaction conditions, affording the corresponding products in good yields. The conjugated 2-trifluoromethyl-1,3-enyne could generate the desired product (**3au**) in 60% yield. Both 1- and 2-naphthyl substrates (**3av** and **3aw**) were suitable for this transformation in excellent yields. Notably, this transformation was successfully extended beyond trifluoromethyl

alkenes to include pentafluoro-, α-difluoromethyl-, and α-fluoro-substituted alkenes, affording the corresponding products in moderate yields (**3ax–3az**). The non-fluorinated alkene also proceeded efficiently, yielding product **3ba** in 82% yield.

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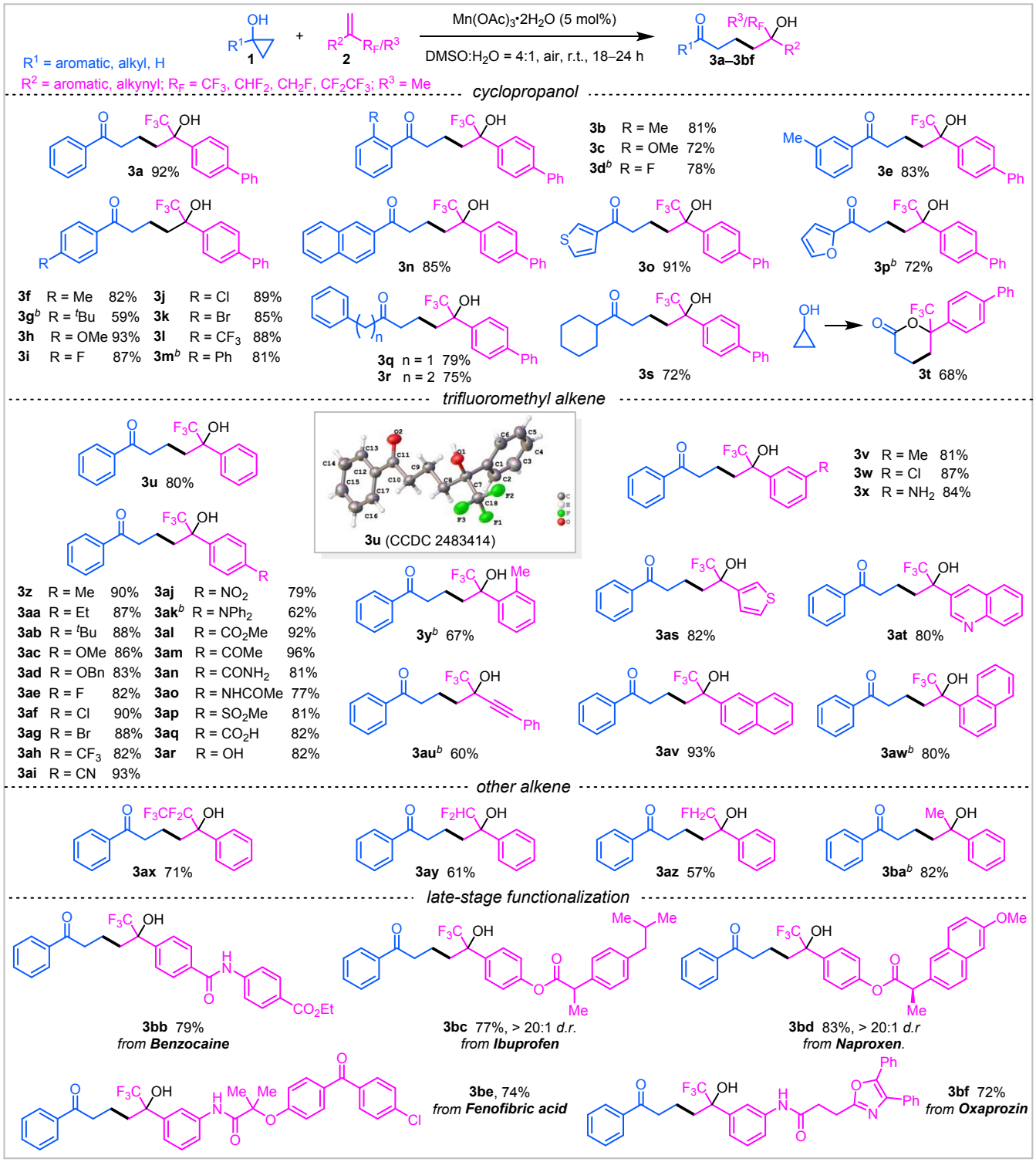
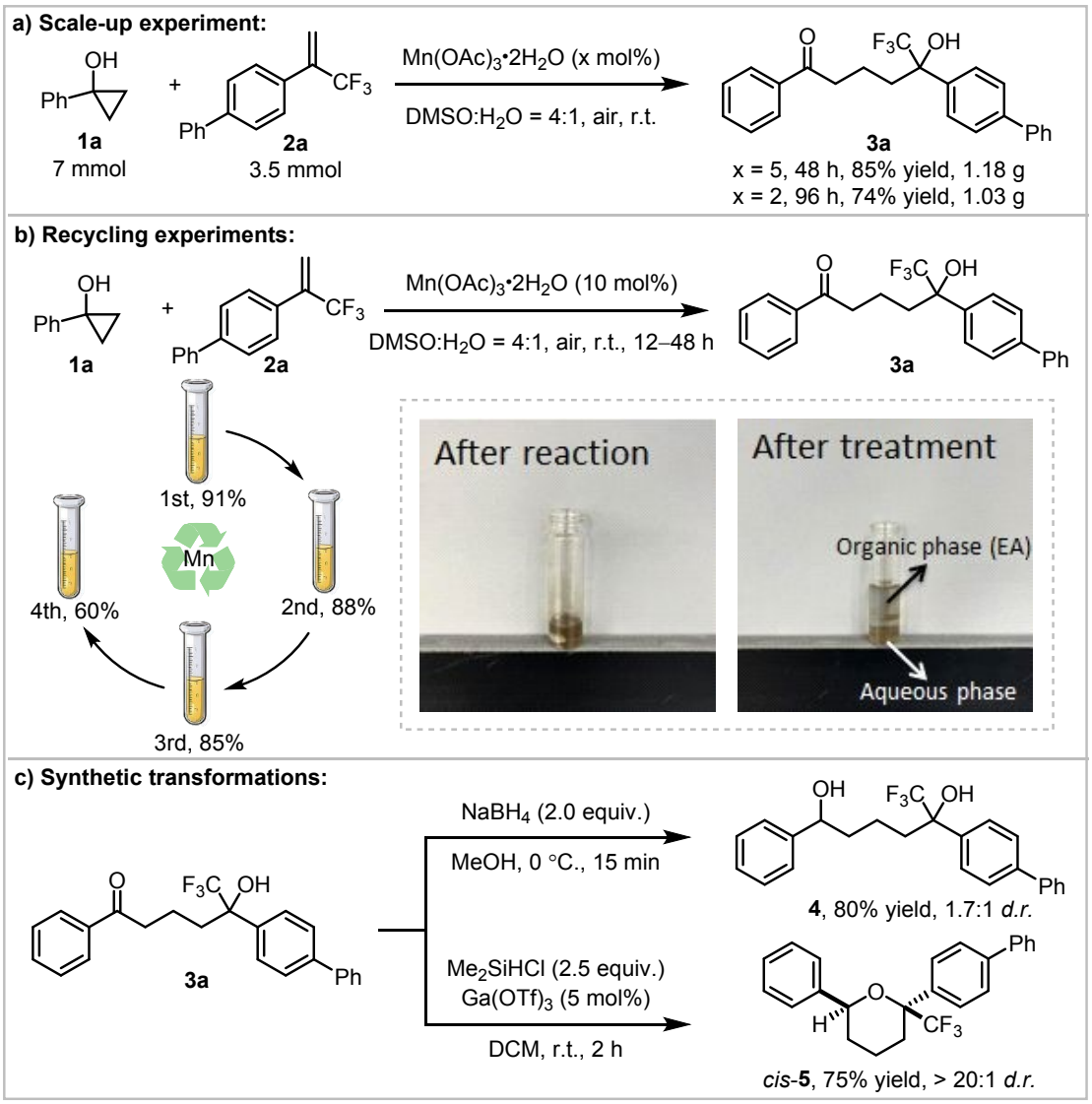


Scheme 2. Investigation of substrate scope[a]. a) Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (5 mol%), DMSO (0.8 mL), H_2O (0.2 mL), air, r.t., 18–24 h. Isolated yield. b) 15 mol% of $Mn(OAc)_3 \cdot 2H_2O$ was used.

On the basis of the good functional group tolerance, we tried to carry out the reactions for late-stage functionalization of structural complex molecules to show its potential applicability.[9e-g,29], Five trifluoromethyl alkenes derived from benzocaine (**3bb**), ibuprofen (**3bc**), naproxen (**3bd**), fenofibric acid (**3be**) and oxaprozin (**3bf**) proceeded smoothly to obtain the products in good yields.

Synthetic Applications and Mechanistic Studies. Based on the perspective of green chemistry, we analyzed major green chemistry

metrics[3b,23c,30] between our work and the previously reported work (Scheme 1b, strategy B): atom economy (AE), atom efficiency (AEF), reaction mass efficiency (RME), *E*-factor, process mass intensity (PMI), turnover number (TON), and turnover frequency (TOF). It should be acknowledged that strategy B constitutes a commendable green and enantioselective route, offering distinct synthetic value. Our analysis aimed to compare the intrinsic green chemistry performance of the core scaffold construction, recognizing that such a comparison has certain inherent limitations. The subsequent hydrogenation in strategy B was excluded from this calculation, as its yield was unknown and not integral to the initial scaffold construction. The metrics showed notably high values, with AE (75%), AEF (69%), and RME (69%), compared to the previously reported method, demonstrating improved atom and resource efficiency. The solvent-inclusive metrics, *E*-factor (29.9) and PMI (30.9), were comparable to the previous work, showing a modest improvement. On a broader perspective, our catalyst demonstrated significantly higher catalytic activity, with a TON of 18.4 and a TOF of 1.02 h^{-1}, these values are substantially greater than those reported for the prior system (TON = 9.3, TOF = 0.3 h^{-1}), indicating superior catalytic performance. Taken together, these results demonstrated that our system also represented a viable alternative for the scaffold construction.



Scheme 3. Gram-scale operation and synthetic application. a) Scale-up experiment. b) Recycling experiments. c) Synthetic transformations.

To further assess the practical applicability of our developed method, we performed scale-up experiments. The gram-scale reaction of **1a** and **2a** smoothly delivered the product **3a** in 85% yield under standard conditions. Even at a reduced catalyst loading of 2 mol%, the model reaction still proceeded, affording product **3a** in 74% yield by extending the reaction time to 96 h (Scheme 3a). More importantly, during post-treatment process, the catalyst partitioned into the aqueous phase upon extraction, indicating its potential for recycling. To assess its recyclability, recycling experiments were conducted (Scheme 3b). Upon completion of each reaction, the upper organic phase was removed by extraction, and the aqueous phase containing the catalyst was directly used in the next cycle. Notably, the first three cycles showed consistent performance. However, by the fourth cycle, the yield of **3a** dropped to 60%. This

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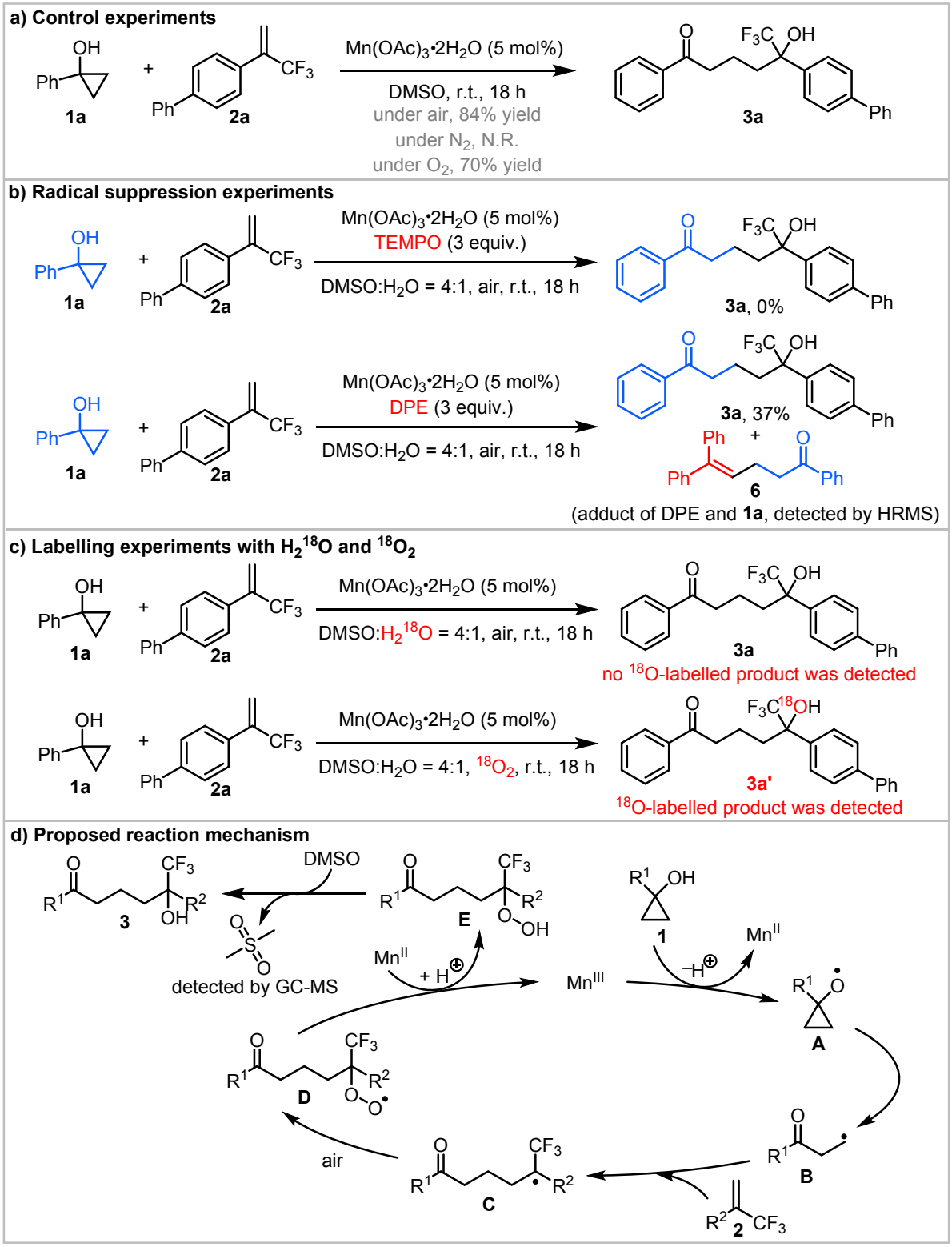
decline was likely caused by the challenging handling of DMSO over multiple runs, which led to substantial catalyst loss and incomplete recovery. These results point to the promising recyclability. Further derivatization of **3a** was showcased in Scheme 3c. We successfully performed a reduction of the carbonyl group on **3a** to readily obtain the diol derivative **4** in 80% yield.[31] Alternatively, alcohol-substituted ketone could be underwent a cascade of reduction and cyclization *via* an organosilane-Ga(OTf)$_3$ system,[32] leading to access trifluoromethyl-substituted tetrahydropyran derivative *cis*-**5**.



Scheme 4. Mechanistic investigation and the proposed mechanism.. a) Control experiments. b) Radical suppression experiments. c) Labelling experiments with $H_2{}^{18}O$. d) Proposed reaction mechanism.

To gain the mechanistic insights into this reaction, we performed a series of mechanistic experiments. Control experiments indicated that the atmospheric oxygen played a key role in the reaction, it did not work under nitrogen atmosphere (Scheme 4a). It was known that radical scavengers could trap the alkyl radical derived from the ring-opening of cyclopropanols. [19a,19d-f,33] The formation of **3a** was completely inhibited in the presence of the radical scavenger TEMPO. In addition, the yield of **3a** decreased significantly in the presence of DPE, and the radical-trapped adduct **6** was observed by HRMS. These results suggest that a radical process is involved in this transformation (Scheme 4b). The ^{18}O-labelling experiments were conducted to track the source of the hydroxyl group (Scheme 4c).[11f] Upon replacing $H_2{}^{16}O$ with $H_2{}^{18}O$, no ^{18}O-labelled product was detected, indicating that water did not contribute a hydroxyl group to the final product. Under $^{18}O_2$ atmosphere, the ^{18}O-labelled product **3a'** was obtained, demonstrating that the newly incorporated oxygen atom originated from molecular dioxygen.

On the basis of previous reports and mechanism investigation,[11c] a plausible mechanism was proposed in Scheme 4d. Initially, the reaction of $Mn(OAc)_3{\cdot}2H_2O$ with cyclopropanol **1** gives a Mn(II) species and an *O*-centered radical species **A**. The species **A** subsequently undergoes ring-opening isomerization to generate a *C*-centered radical species **B**, which is then intercepted by α-trifluoromethyl alkene **2** to furnish the radical intermediate **C**. Next, the radical intermediate **C** reacts with Mn(II) species and proton to give the peroxy radical **D**, leading to access the peroxide product **E** (detected by HRMS, see the Supporting Information for details) and Mn(III) species. Finally, the reduction of **E** by DMSO formed the product **3** and dimethyl sulfone which was detected by GC-MS.

Conclusions

In summary, we have developed an efficient Mn-catalyzed hydroxyalkylation of α-(trifluoromethyl)alkenes with cyclopropanols. This transformation proceeded smoothly under mild conditions and simple operations, aligning with green chemistry principles by employing air as the sole oxidant and offering good atom economy and energy efficiency. A wide range of substrates were tolerated, affording the products in moderate to excellent yields. The present methods may serve as useful tools for the synthesis of δ-trifluoromethyl-δ-hydroxyketones by one step, avoiding resource consumption and waste generation associated with multi-step syntheses. The synthetic potential of this protocol is underscored by late-stage pharmaceutical derivatizations, gram-scale preparations, recycling experiments, and product modifications. Further studies on the application of this methodology to access bioactive molecules are ongoing and will be reported in due course.

Author Contributions

Z.-X.D. and X.X. performed and analyzed the experiments. Z.-G. L., J.-Y. H., T.-Y. Z. and D. C. contributed to part experiments. X.X. and F.-E.C. discussed the results, contributed to writing the manuscript, and commented on the manuscript. X.X. and F.-E.C. conceived and designed the project. X.X. and F.-E.C. overall supervised the project. All authors prepared this manuscript.

Conflicts of interest

There are no conflicts to declare.

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28 CCDC-2483414 (**3a**): $C_{18}H_{17}F_3O_2$, MW = 322.32, monoclinic, space group $P2_1/n$, final R indices [I> 2σ(I)], R_1 = 0.1004, wR_2 = 0.2451, R indices (all data), R_1 = 0.1442, wR_2 = 0.3013, a = 6.5279 (14) Å, b = 11.063 (2) Å, c = 22.438 (5) Å, α = 90°, β = 96.638 (9)°, γ = 90°, V = 1609.5(6) Å^3, Z = 4, Reflections collected/unique: 8934/2936 (R(int) = 0.0904). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/ci.

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Data availability

The data supporting this article has been provided as part of the Supplementary Information. Crystallographic data for compound 3a has been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition number 2483414 and can be obtained from www.ccdc.cam.ac.uk/data_request/cif. For ESI and other electronic format, see DOI: XXX.