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Silver-Catalyzed Radical Transformation of Aliphatic Carboxylic Acids to Oxime Ethers

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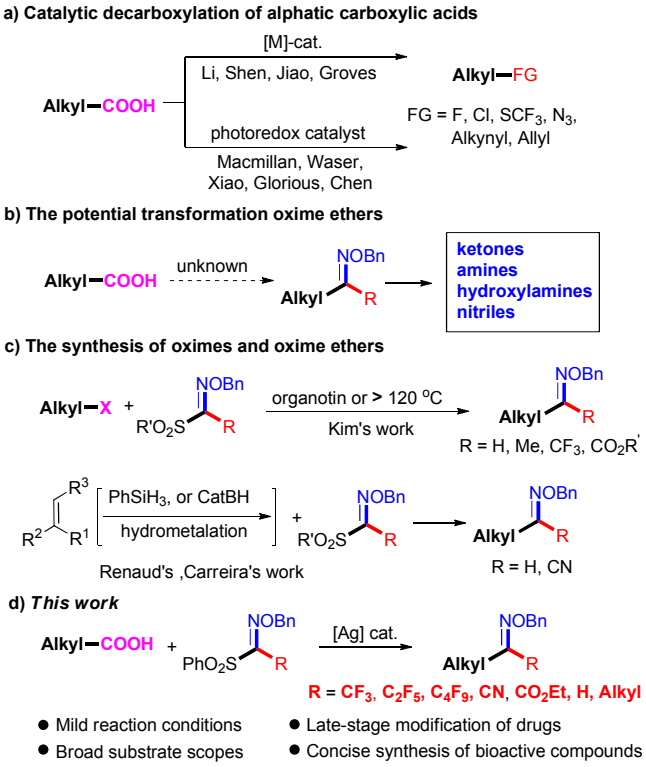
ABSTRACT. Oximes and oxime ethers are privileged building blocks, and could be conveniently converted to ketones, amines, hydroxylamines, and nitriles. We describe the catalytic decarboxylation of aliphatic carboxylic acids to oxime ethers. With $AgNO_3$ as the catalyst, the valuable oxime ethers bearing various substituents could be easily obtained. The broad substrate scope, easy accessibility of aliphatic carboxylic acids, mild reaction conditions make this strategy immediately applicable to the synthesis, late-stage functionalization and modification of biologically active compounds. Experimental studies show the reaction undergoes a radical process.

KEYWORDS. Radical, Decarboxylation, Aliphatic Carboxylic Acids, Oxime Ether, Late-Stage Functionalization.

INTRODUCTION:

Carboxylic acids are basic synthetic materials because they are stable, inexpensive and easily available.[1] Among the abundant transformations of carboxylic acids, the decarboxylative functionalization has been widely applied for the construction of new chemical bond. Traditional named reactions such as Hunsdiecker reaction,[2] Cristol-Firth reaction,[3] and Kochi reaction[4] reported decarboxylative halogenation of aliphatic carboxylic acids with stoichiometric metal (Ag, Hg, Pb) reagents. As a milestone, Goossen and coworkers disclosed the Pd/Cu co-catalyzed decarboxylative cross coupling reaction of aromatic carboxylic acids.[5] Based on this tremendous work, various decarboxylative functionalization reactions of aromatic,[6] alkenyl,[7] α-ketone,[8] and alkynyl[9] carboxylic acids were developed.

Compared to the above success, the catalytic decarboxylative functionalization of aliphatic carboxylic acids remains a challenging subject except for the special α-amino acids or carboxylates as the substrates.[10] In 2012, Li and coworkers innovatively disclosed Ag-catalyzed decarboxylative chlorination[11a] of aliphatic carboxylic acids which opened up the window of catalytic decarboxylations of aliphatic carboxylic acids (Scheme 1a). Up to now, the fluorination,[11b] alkynylation,[11c] trifluoromethylthiolation,[11d] allylation,[11e] and azidation[11f-g] of aliphatic carboxylic acids were successfully achieved using the decarboxylative strategy. With efficient photo-catalysts, the groups of Macmillan,[12a] Glorious,[12b] Waser,[12c] Xiao,[12d] and Chen[12e] developed the decarboxylative functionalization of aliphatic carboxylic acids. Groves and coworkers successfully realized decarboxylative fluorination of aliphatic carboxylic acids catalyzed by the well-designed Mn-catalyst.[13]



Scheme 1. The Decarboxylative Functionalization of Carboxylic Acids.

Oximes and oxime ethers are privileged building blocks and are present in many biologically active compounds.[14] They could be easily converted to carbonyl and nitro compounds, amines, hydroxylamines, or nitriles (Scheme 1b).[15] Thus, the development of efficient approaches to oximes and oxime ethers has drawn many chemists' attention. Recently, Kim and coworkers innovatively reported the radical coupling of alkyl halide with oxime ether reagent bearing a sulfonyl group to build oxime ethers (Scheme 1c). However, stoichiometric organotin reagents are required during the radical initiation process, or employed AIBN instead of organotin at high temperature (>120 ^{o}C), which limited their wide application.[16] The synthesis of aldoxime ethers from olefins with sulfonyl oximes was reported by Renaud et al. which avoided the use of organotin reagents but suffered from a two-step workup (Scheme 1c).[17] Recently, Carreira and coworkers successfully realized the reductive coupling reaction of olefins and sulfonyl oximes (R = H, CN) catalyzed by well-

designed Co-catalyst (Scheme 1c).[18] Despite the significance of these methods, the direct synthesis of oximes and oxime ethers from easily available aliphatic carboxylic acids is not realized yet (Scheme 1b).

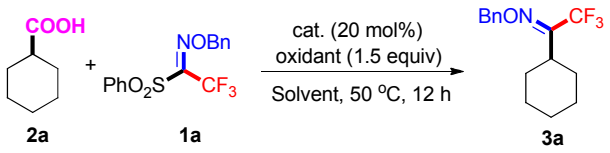
As our continuous interest in developing radical reactions[19] and decarboxylations,[9d, 11g] herein, we report the Ag-catalyzed decarboxylative cross coupling of aliphatic carboxylic acid with sulfonyl oximes **1** to synthesize oxime ethers which features the following advantages compared to the previous reports (Scheme 1d): 1) the aliphatic carboxylic acids are easily available and widespread in drugs and natural products; 2) the oxime ethers bearing many functional groups especially C_nF_{2n+1}, which shows privileged roles in drug candidates, were prepared; 3) the mild reaction conditions make this novel transformation immediately applicable to the synthesis and late-stage functionalization of bioactive molecules. Furthermore, this reaction enriched the decarboxylative cross coupling of aliphatic carboxylic acids with sulfonyl radical reagents.

RESULTS AND DISCUSSION:

The electron withdrawing property of trifluoromethyl group (CF_3) could protect drugs from in vivo metabolism by cytochrome P450 oxidases. Thus, the introduce of CF_3 group into drug candidates plays a privileged role in drug discovery.[20] In the last few years, the radical trifluoromethylation[21] reactions have gain remarkable progress. The CF_3-substituted oxime ethers, the equivalents of CF_3-substituted ketones or amines, could be easily prepared from CF_3-substituted reagent **1a** with alkyl radicals. With this purpose, we chose cyclohexanecarboxylic acid **2a** as the model substrate and **1a** as the reagent to explore the reaction conditions (Table 1). With $AgNO_3$ (20 mol%) in CH_3CN/H_2O (1:1) under argon atmosphere at 50 ^oC, several oxidants were tested (entries 1-4). No oxime ether product was detected with PIDA or TBHP as the oxidant (entries 1-2). To our delight, the oxime ether **3a**

was obtained in good yield when $Na_2S_2O_8$ (64%, entry 3) or $K_2S_2O_8$ (71%, entry 4) was used. Screening of silver salts showed their solubility has great influence in this reaction. Similar yield was obtained when changing $AgNO_3$ to the soluble AgOTf (69%, entry 5). On the contrary, the insolvable AgI afforded only trace product (entry 6). Other metal catalysts such as $CuCl_2$, $FeCl_2$ and $MnBr_2$ are less active (entries 7-9). Lower yields were obtained when the reaction carried out in other solvents such as THF/H_2O or DMSO/H_2O (entries 10-11).

Table 1. Examination of Reaction Conditions.[a]



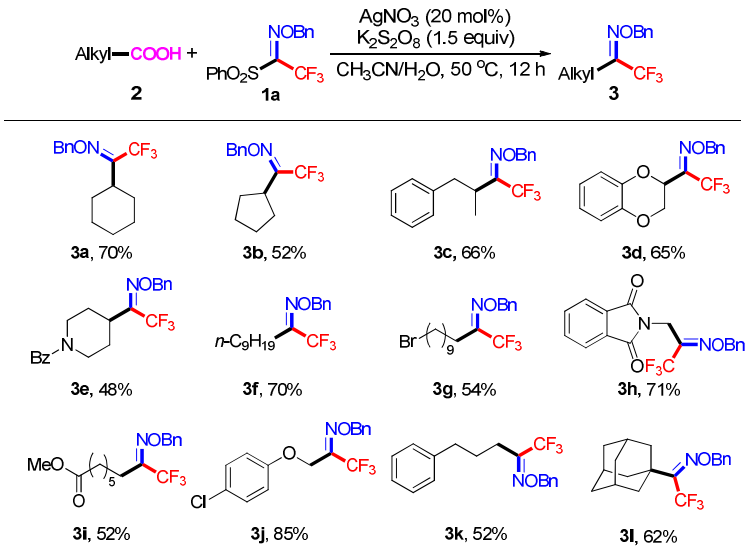
2a **1a** **3a**

entry	Oxidant	cat. (20 mol%)	Solvent	yields (%)[b]
1	PIDA	$AgNO_3$	CH_3CN/H_2O	n.d.
2	TBHP	$AgNO_3$	CH_3CN/H_2O	n.d.
3	$Na_2S_2O_8$	$AgNO_3$	CH_3CN/H_2O	64
4	$K_2S_2O_8$	$AgNO_3$	CH_3CN/H_2O	71 (70)[c]
5	$K_2S_2O_8$	AgOTf	CH_3CN/H_2O	69
6	$K_2S_2O_8$	AgI	CH_3CN/H_2O	trace
7	$K_2S_2O_8$	$CuCl_2$	CH_3CN/H_2O	trace
8	$K_2S_2O_8$	$FeCl_2$	CH_3CN/H_2O	trace
9	$K_2S_2O_8$	$MnBr_2$	CH_3CN/H_2O	trace
10	$K_2S_2O_8$	$AgNO_3$	THF/H_2O	12
11	$K_2S_2O_8$	$AgNO_3$	$DMSO/H_2O$	64

[a] Reaction conditions: **2a** (0.2 mmol), **1a** (0.3 mmol), catalyst (0.04 mmol), oxidant (0.3 mmol), solvent (2 mL), stirred at 50 °C under argon atmosphere for 12 h. [b] Yield was determined by ^1H NMR analysis of the crude reaction mixture using $Cl_2CHCHCl_2$ as an internal standard. [c] Isolated yield.

With the optimum conditions in hand, we next explored the scope of carboxylic acid **2** with reagent **1a** (Scheme 2). A series of CF_3-substituted oxime ethers **3** were synthesized by the present decarboxylation strategy. The secondary (**3a-e**), primary (**3f-k**), or tertiary (**3l**) aliphatic carboxylic acids are reactive in this transformation. Cyclic and branched carboxylic acid were tolerated to afford **3a-c** in moderate to good yields (52-70%). Besides, the reaction of heterocyclic carboxylic acids proceed smoothly to afford the corresponding oxime ether **3d**

and **3e** in 65% and 48% yields, respectively. In addition, the primary carboxylic acids, which showed lower reactivity in previous radical decarboxylative reactions,[11] performed well to give aim products in moderate to good yields (**3f-k**, 52-85%) with the tolerance of halo, amide, or ester groups. Similar phenomenons were reported in MacMillan's work.[12a] Among them, **3j** was isolated in 84% yield, showing the carbon radical next to the oxygen atom is stable.

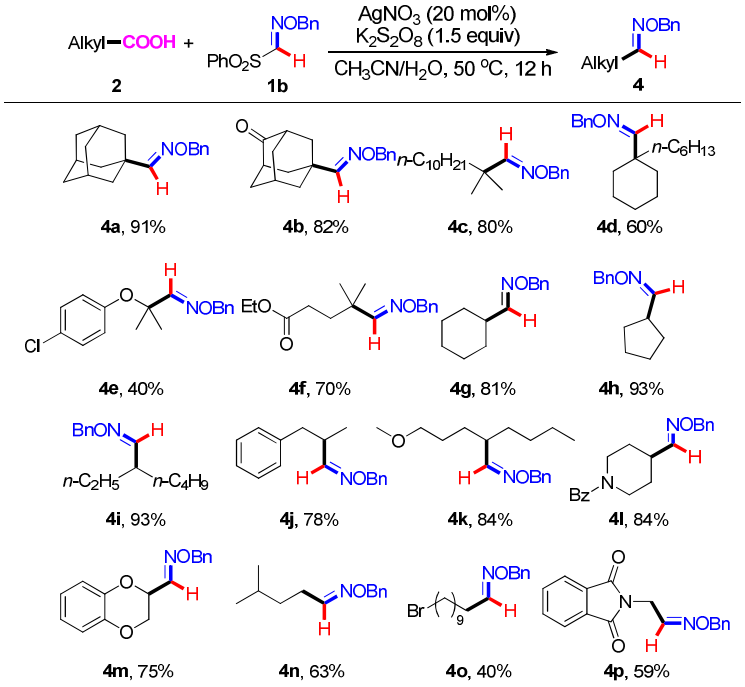


Scheme 2. Transformation of Aliphatic Carboxylic Acids to CF_3-substituted Oxime Ethers[a]

[a] Reaction conditions: see entry 4 in Table 1. Isolated yields.

The aldoximes could be easily synthesized from the decarboxylative cross coupling of aliphatic carboxylic acid **2** with reagent **1b** (Scheme 3). The adamantane-1-carboxylic acid and 4-oxoadamantane-1-carboxylic acid reacted well to give **4a** and **4b** in 91% and 82% yields, respectively. Surprisingly, the sterically hindered carboxylic acids reacted smoothly to give oxime ether **4c** (80%) and **4d** (60%). The 2-(4-chlorophenoxy)-2-methylpropanoic acid, which contains a halogen group and an ether group, reacted efficiently to provide **4e** in synthetic useful yield (40%). Oxime ether **4f** bearing ester group was obtained in 70% yield.

Furthermore, the decarboxylative cross coupling of secondary alkyl carboxylic acids with **1b** proceeded to deliver the cyclic (**4g-h**) and branched product (**4i-k**) in high yields (78-93%). Moreover, the oxime ether products (**4k-p**) were isolated in good yields (40-84%), showing the reaction is tolerable to various functional groups. It is worthy to mention that several primary carboxylic acids were conveniently converted to the corresponding oxime ether products (**4n-p**) which could not be prepared from reagent **1b** with olefins reported by Renaud[17] and Carreira.[18]

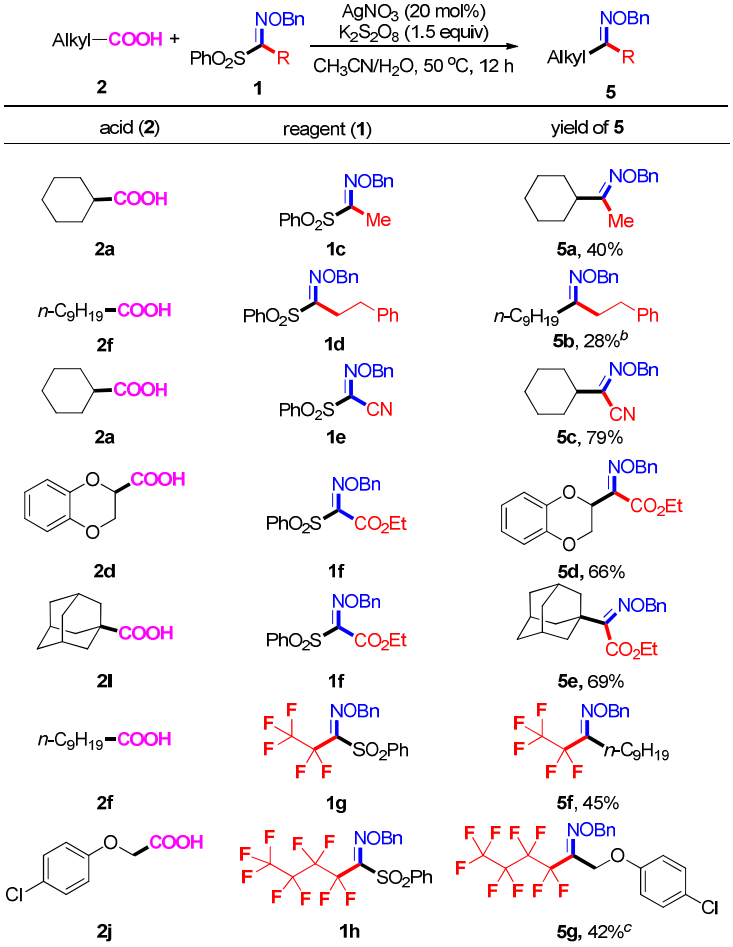


Scheme 3. Transformation of Aliphatic Carboxylic Acids to Aldoxime Ethers.[a]

[a] Reaction conditions: Reaction conditions: **2** (0.2 mmol), **1b** (0.4 mmol), $AgNO_3$ (0.04 mmol), $K_2S_2O_8$ (0.3 mmol), CH_3CN/H_2O (1 mL/1 mL), stirred at 50 °C under argon atmosphere for 12 h. Isolated yields.

As mentioned in Scheme 1c, the cross coupling of sulfonyl oximes **1** with alkyl halides or olefins afforded aldoxime ethers efficiently (R = H). The groups of Kim, Renaud, and Carreira reported the synthesis of oxime ethers bearing CF_3, Me, CO_2R', and CN substituent, respectively.[16-18] However, to the best of our knowledge, there is no one system that can

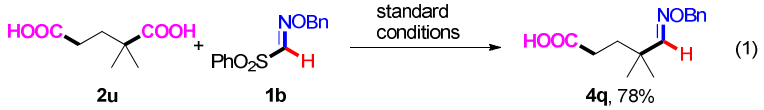
synthesize oxime ethers bearing diverse functional groups. Inspired by the above results, we synthesized several sulfonyl oxime reagents bearing other substituent groups (**1c-h**). Gratifyingly, the present transformation is applicable to all these sulfonyl oxime reagents (Scheme 4). Alkyl substituted sulfonyl reagents **1c-d** were compatible to give the corresponding dialkyl oxime ether **5a-b** in 40% and 28% yields, respectively. The CN-substituted sulfonyl oxime **1e** showed high reactivity to give **5c** in 79% yield. On the other hand, the ester-substituted reagent **1f** could react with acid to give modified α-amino acid product **5d-e** with moderate yields (66-69%). To be emphasized, the perfluoroalkyl substituted oxime ether **5f-g** were isolated when we used **1g-h** as reagents, showing this reaction could be used in the synthesis of multiple fluorine-containing compounds.



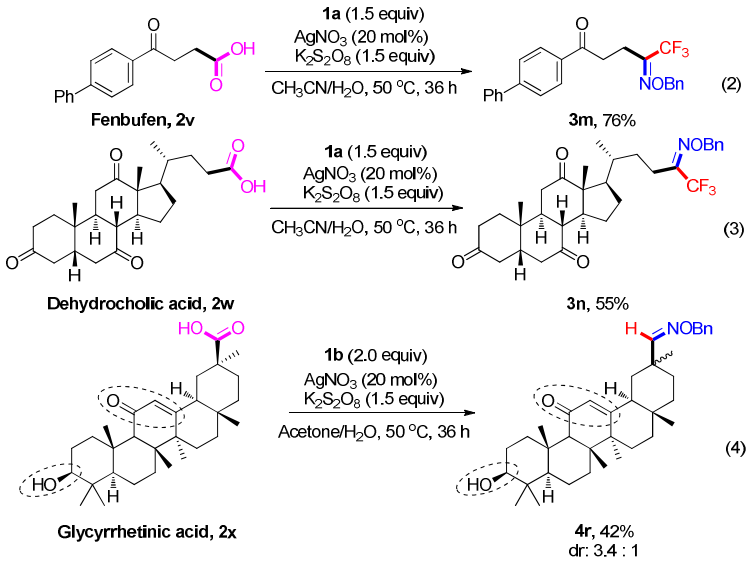
Scheme 4. Transformation of Aliphatic Carboxylic Acids to Substituted Oximes Ethers.[a]

[a] Reaction conditions: see entry 4 in Table 1. Isolated yields. [b] CH_3CN/H_2O (2 mL/2 mL) was used for 16 h. [c] 30 mol% $AgNO_3$ was used for 16 h.

It's worthwhile to mention that in several compounds such as **3f-g**, **3i**, **3k**, **4a-f**, there are only one geometric isomer, while in others, both E and Z isomers around the C=N bond are existed. Based on the experimental data, we speculate the steric hindrance of the substrates influences the E and Z configuration of products. Moreover, the present decarboxylative strategy showed excellent chemo-selectivity. For example, the reaction between reagent **1b** and di-acid **2u** proceeded smoothly to afford mono-decarboxylative product **4q** in 78% yield (Eq 1).



The synthesis and late-stage modification of bioactive molecules. The properties of the carboxylic acids make them widespread in drugs as well as some bioactive molecules. The simple and mild reaction conditions make it possible to apply the present system in the late-stage functionalization of bioactive molecules containing carboxylic acid group (Scheme 5). Under the standard conditions, fenbufen, the nonsteroidal antiinflammatory drug,[22] and dehydrocholic acid, the choleretic drug[23] could be modified to their oxime derivatives **3m-n** in 76% and 55% yields without the affecting of ketone group (Eq 2-3). Glycyrrhetinic acid, a natural product containing hydroxyl, carbonyl, and alkenyl groups reacted with **1b** to afford **4r** in 42% yield (Eq 4).

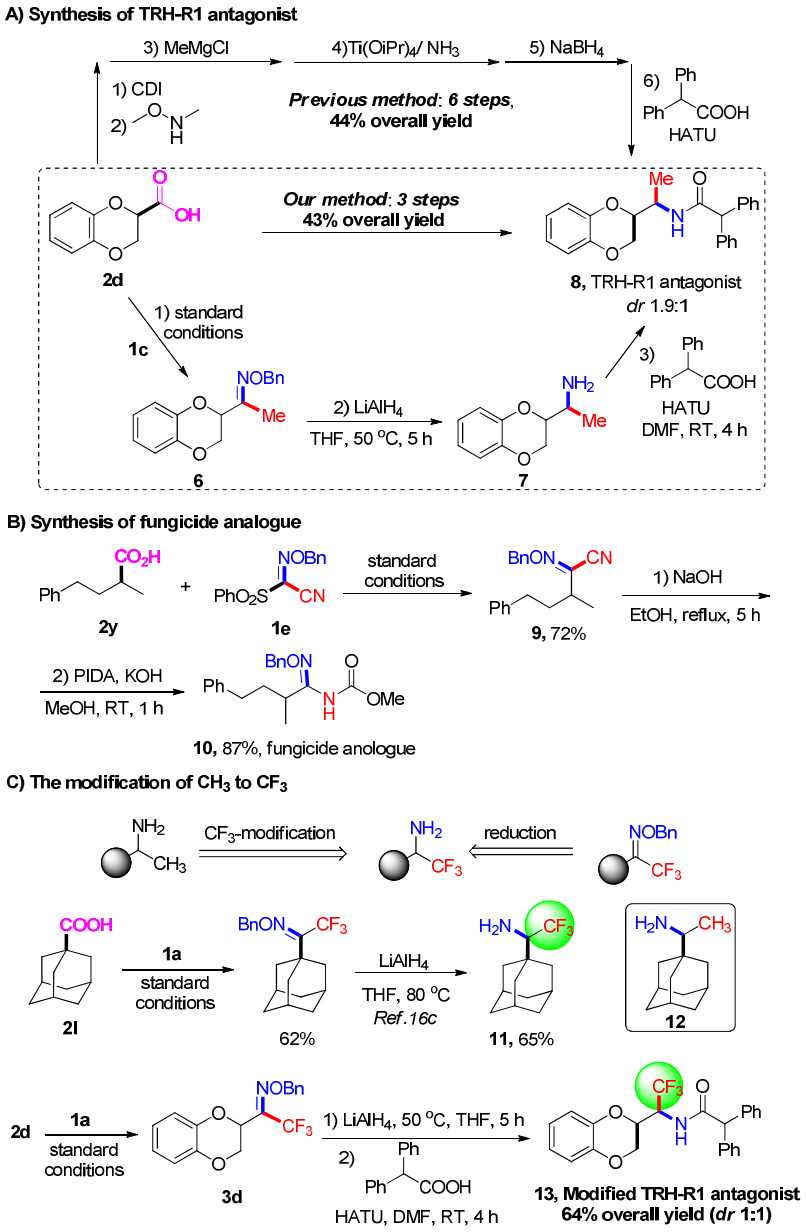


Scheme 5. The Late-stage Modification of Drugs and Natural Products.

Inspired by the above work, we further demonstrated the synthetic utility of our strategy by preparation of two bioactive molecules (Scheme 6). The amide **8**, which is a thyrotropin-releasing hormone receptor type 1 (TRH-R1) antagonist,[24] is condensed from diphenyl acetic acid and secondary amine **7**. As alkyl substituted oxime ethers are the analogue of secondary amine, we speculated that our strategy could be applied in the concise synthesis of **8**. As our expected, the decarboxylative cross coupling of acid **2d** and **1c** afforded the oxime ether **6** in 67% yield. The reduction of **6** with $LiAlH_4$ delivered secondary amine which reacted with diphenyl acetic acid in the presence of HATU to afford TRH-R1 antagonist **8**. Compared to the traditional approach (6 steps), our method is more concise (3 steps) with similar yield (Scheme 6A). Furthermore, the amidoxime group is present in many biologically active compounds such as fungicides[25a] or insecticides.[25b] The CN-substituted reagent **1e** reacted with aliphatic carboxylic acid **2y** to afford CN-substituted oxime ether **9** which was easily transformed to product **10** in 87% yield over two steps (Scheme 6B).

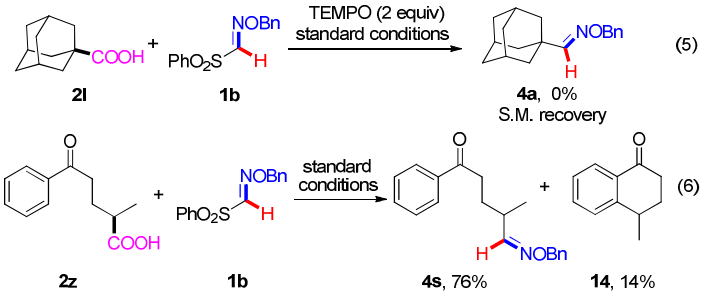
The modification of methyl group to CF_3 group may change the bioactive molecules' physicochemical properties such as dipole moments, metabolic rate, and pKa.[26] The methyl

substituted secondary amines show distinctive properties and are present in many bioactive molecules.[27] Our present chemistry may provide an efficient approach to corresponding CF_3 substituted secondary amines (Scheme 6c). For example, bioactive compounds **8** and **12** both contain the methyl substituted amine group. Employment of the present Ag-catalyzed decarboxylation strategy (Scheme 2) as the key step, followed by the reduction, CF_3 substituted product **11** and **13** were obtained in high yields. It is worthy to emphasize that the CF_3 substituted compound **13** may have potential bioactivity as it is an analogue of TRH-R1 antagonist **8**. This kind of compounds containing a CF_3 group has never been reported due to the limitations of traditional synthetic methods.

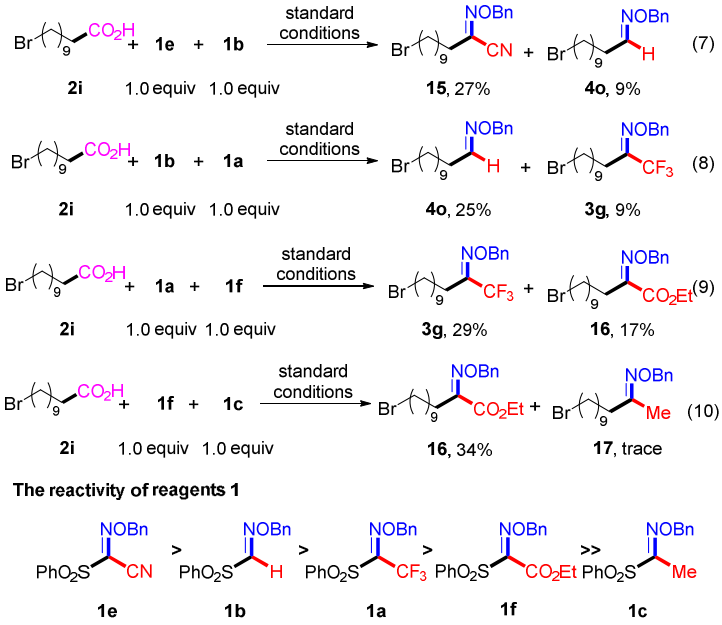


Scheme 6. Synthesis and CF_3-Modification of Biologically Active Compounds.

Mechanistic studies. To gain the insight mechanism of this reaction, we did several mechanistic experiments. When TEMPO (2 equiv) was added to the reaction of **2l** and **1b** under standard conditions, no decarboxylative product **4a** was detected and the substrate was recovered (eq 5). Secondly, when we used **2z** as the substrate, the cyclic byproduct **14** was obtained in 14% yield (eq 6), indicating the generation of carbon radical in this reaction. These results suggest the reaction undergoes a radical pathway.

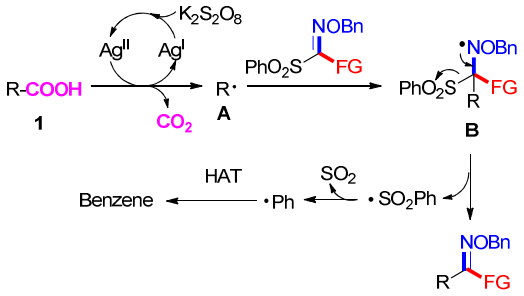


Furthermore, the competing experiment was conducted (Scheme 7). Using **2i** as the substrate, the reactivity of reagents **1a-c**, **1e-f** was compared. We found the CN substituted reagent **1e** is more reactive than reagent **1b**, giving the corresponding product **15** and **40** with an approximately 3:1 ratio (eq 7). The CF_3 substituted reagent **1a** is less reactive than reagent **1b** but more reactive than reagent **1f** (eq 8-9). Finally, the Me substituted reagent **1c** is less reactive. The yield of Me substituted product **17** was trace compared to the ester substituted product **16** (34%). In general, the reactivity of these reagents are **1e** > **1b** > **1a** > **1f** >> **1c**. These results indicate that the electron deficient oxime reagents are more reactive. On the other hand, the small steric hindrance may be the cause of the high reactivity of reagent **1b**.



Scheme 7. The Competing Experiments.

Based on the experiment results, we proposed a plausible mechanism involving the catalytic generation of carbon radical. As Scheme 8 showed, firstly, Ag^{I} was oxidized into Ag^{II} intermediate by $K_2S_2O_8$,[28] then the aliphatic carboxylic acids underwent an SET process to generate corresponding carbon radical **A** and release CO_2. The carbon radical then attacked sulfonyl reagents to afford the radical **B**, from which the aim product and sulfonyl radical was generated. The sulfonyl radical underwent a process of releasing SO_2 and generating aryl radical which was quenched by either H-abstraction or reduction-protonation sequence to generate the corresponding aromatic compound.[11g]



Scheme 8. Proposal Mechanism.

CONCLUSION :

In conclusion, we disclosed a novel and efficient Ag-catalyzed direct radical transformation of aliphatic carboxylic acids to oxime ethers. The present strategy provides an efficient and practical approach to oxime ethers with broad substrate scopes. The easy accessibility of aliphatic carboxylic acids, mild reaction conditions, high chemo-selectivity make this reaction very attractive, and successfully applied in the concise synthesis and late-stage modification of bioactive molecules. Mechanism studies showed the reaction undergoes a radical process. Further exploration of the synthetic utility of this transformation is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data for products, NMR spectra of products. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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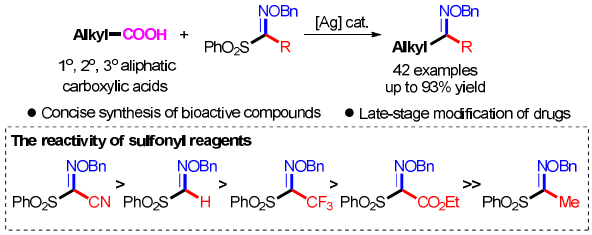
Alkyl—COOH
1°, 2°, 3° aliphatic carboxylic acids
NOBn
PhO2S
R
[Ag] cat.
Alkyl
42 examples
up to 93% yield
● Concise synthesis of bioactive compounds
● Late-stage modification of drugs
The reactivity of sulfonyl reagents
CN
H
CF3
CO2Et
Me