

Organocatalyzed Decarboxylative Trifluoromethylation of β -Ketoacids

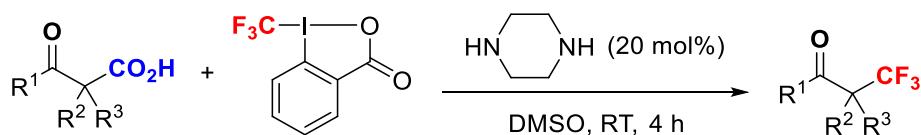
Rui Zhang¹ · Chuanfa Ni¹ · Zhengbiao He¹ · Jinbo Hu¹

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Abstract

A new protocol has been developed for the synthesis of α -trifluoromethyl ketones via organocatalyzed decarboxylative trifluoromethylation of β -ketoacids with Togni's reagent. Among various simple amine catalysts, primary amines and secondary amines were identified to be more effective than tertiary amines, with piperazine being the most effective. Mechanistic investigations suggested that the primary or secondary amine-catalyzed reactions proceed mainly through trifluoromethylation of an enamine intermediate, which is more effective than the tertiary amine-catalyzed pathway that involves an enol intermediate. By using piperazine as the optimal organocatalyst, various β -ketoacids, including the sterically hindered α, α -disubstituted ones, were converted into the corresponding α -trifluoromethyl ketones in good yields. This research not only provides a useful strategy for the efficient synthesis of a wide range of α -trifluoromethyl ketones under mild conditions, but also constitutes one of the few studies on decarboxylative alkylation of β -ketoacids, which can intrigue further exploitation on organocatalyzed asymmetric decarboxylative alkylation reactions.

Graphical Abstract



Keywords Organocatalysis · Trifluoromethylation · Carboxylic acids · Decarboxylation · β -Ketoacids · α -Trifluoromethyl ketones · Togni's reagent · Piperazine

1 Introduction

Trifluoromethylated compounds are of great significance in pharmaceutical and agrochemical research owing to the unique role of the CF_3 group in enhancing the bioactivity

In memory of Professor George A. Olah (1927–2017)

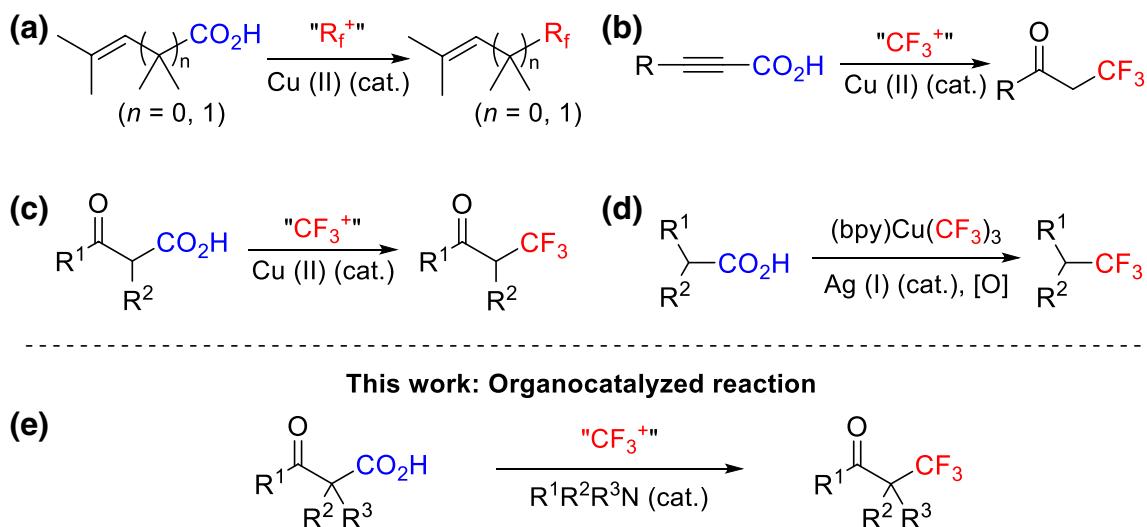
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✉ Jinbo Hu
jinbohu@sioc.ac.cn

¹ Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

of organic molecules [1–5]. Thus, trifluoromethylation has attracted increasing attention as an effective strategy for selective introduction of the CF_3 group [6–12]. In the past 5 years, encouraged by the rapid development of the aromatic trifluoromethylation [13–18], the aliphatic trifluoromethylation witnessed a renaissance [18–23]. A number of new synthetic methods beyond the traditional nucleophilic trifluoromethylation [6] were developed for the construction of $\text{C}(\text{sp}^3)\text{—CF}_3$ bond, such as electrophilic trifluoromethylation of carbon acids and their derivatives with Umemoto's reagents [8] or Togni's reagents [9], radical trifluoromethylation of alkenes with various CF_3 radical precursors [10, 20, 21, 24–26], and oxidative trifluoromethylation of alkylboronic acids [27] or terminal alkenes [28] with Ruppert–Prakash reagent. A common feature of these methods is the regioselective incorporation of the CF_3 group. Moreover, decarboxylative trifluoromethylation of carboxylic acids has

Previous work: Transition-metal catalyzed reactions



Scheme 1 Methods for decarboxylative fluoroalkylation of various carboxylic acids

emerged as a novel method for site-specific $\text{C}(\text{sp}^3)-\text{CF}_3$ bond formation [29–33].

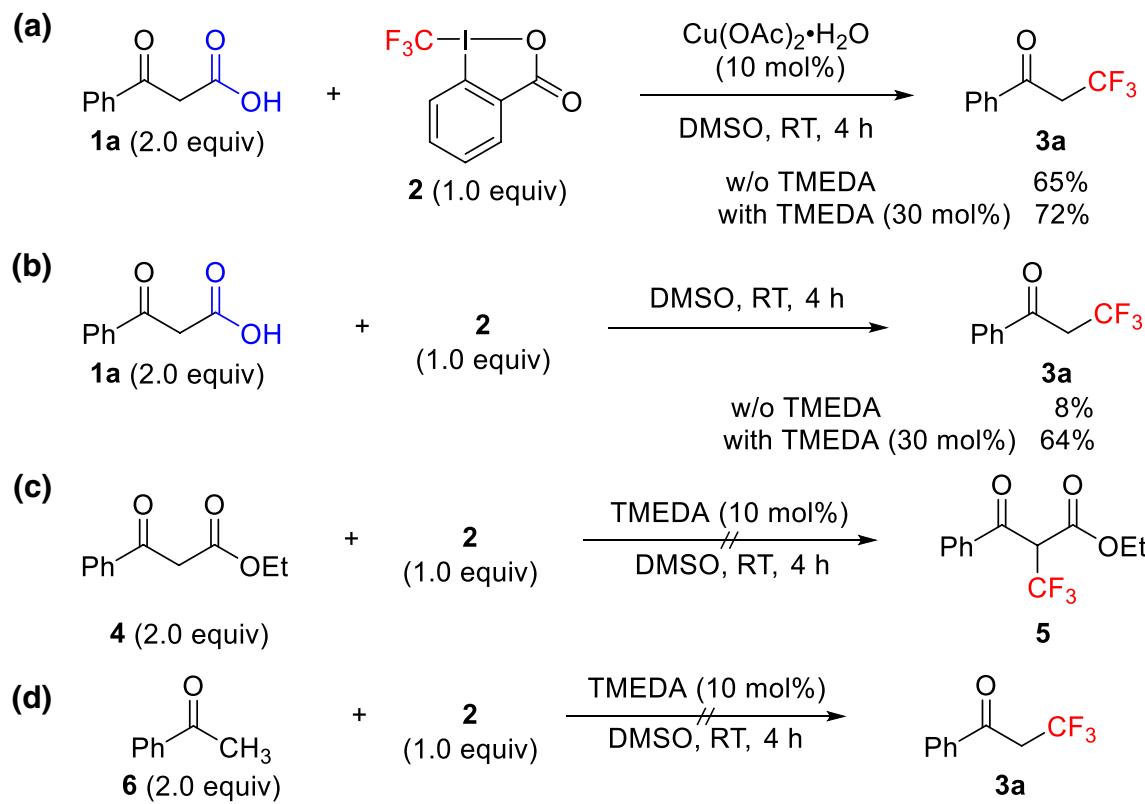
Recently, we first described the copper-catalyzed decarboxylative di- and trifluoromethylation of α,β - [34] and β,γ -unsaturated carboxylic acids [29, 30] with Togni-type electrophilic fluoroalkylating agents, which provides a rapid access to various organofluorine compounds bearing di- and trifluoromethyl groups at vinylic and allylic positions, respectively (Scheme 1a). Thereafter, many efforts have been devoted to decarboxylative fluoroalkylation of α,β -unsaturated carboxylic acids by others [35–44]. We also demonstrated that the copper-mediated decarboxylative trifluoromethylation of substituted propiolic acids [31] using Togni reagent in the presence of water gave α -trifluoromethyl ketones (Scheme 1b). During the preparation of this manuscript, Xu, He and coworkers reported a copper-catalyzed decarboxylative trifluoromethylation of β -ketoacids [32] with Togni reagent (Scheme 1c). Meanwhile, Li and coworkers reported a silver-catalyzed decarboxylative trifluoromethylation of saturated aliphatic carboxylic acids [33] with $(\text{bpy})\text{Cu}(\text{CF}_3)_3$ ($\text{bpy} = 2,2'$ -bipyridine) (Scheme 1d).

Although several methods have been developed for decarboxylative trifluoromethylation of aliphatic carboxylic acids, all these methods rely on metal catalysis or mediation [29–34]. β -Ketoacids can readily undergo decarboxylation and are widely used as promising precursors for the generation of ketone enolate equivalents under organocatalysis; however, their synthetic application mainly concentrates on addition reactions to unsaturated systems such as aldehydes, imines, and Michael acceptors [45–49]. Herein, as an extension of our previous work

on decarboxylative fluoro-functionalization of unsaturated aliphatic carboxylic acids [29–31, 34, 50], we report an *organocatalyzed* decarboxylative trifluoromethylation of β -ketoacids with Togni's reagent (Scheme 1e). This metal-free protocol supplements the reported copper-catalyzed method and acts a useful strategy for the efficient synthesis of a wide range of α -trifluoromethyl ketones under mild conditions [32].

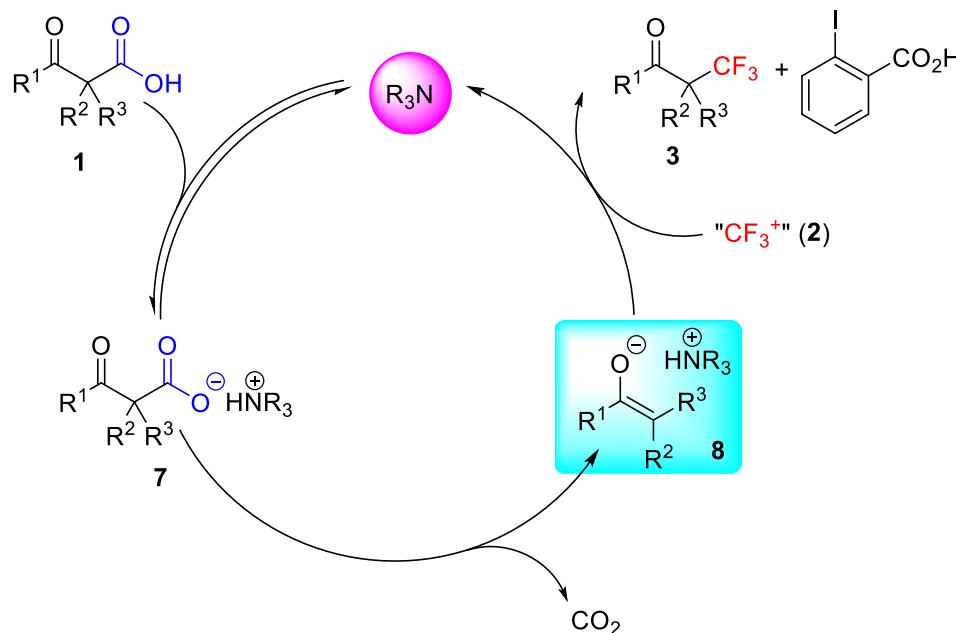
2 Results and Discussion

This study was initiated by our independent research on copper(II)-catalyzed decarboxylative trifluoromethylation of β -ketoacids **1** with Togni's reagent (Scheme 2a; for details, see the supplementary material). During our investigation on the role of the additive tetramethylethylenediamine (TMEDA), we serendipitously found that TMEDA itself could promote the reaction, albeit the yield of **3a** was somewhat lower than in the copper-catalyzed reaction (Scheme 2b). However, in the absence of TMEDA and a copper catalyst, the decarboxylation of **1a** led only low yield of **3a**, with the formation of acetophenone (**6**) as the major side product. Control experiments with either the ethyl ester **4** or ketone **6** failed to give any trifluoromethylation product (Scheme 2c–d), indicating that product **3a** was formed through the trifluoromethylation of the enolate intermediate **8** *in-situ* generated from the amine-promoted decarboxylation of **1a** (Scheme 3). It is possible that the amine served as both the stabilizer of **1a** and the catalyst for the formation of the highly reactive intermediate **8**, [48] thus facilitating the trifluoromethylation reaction. Inspired by



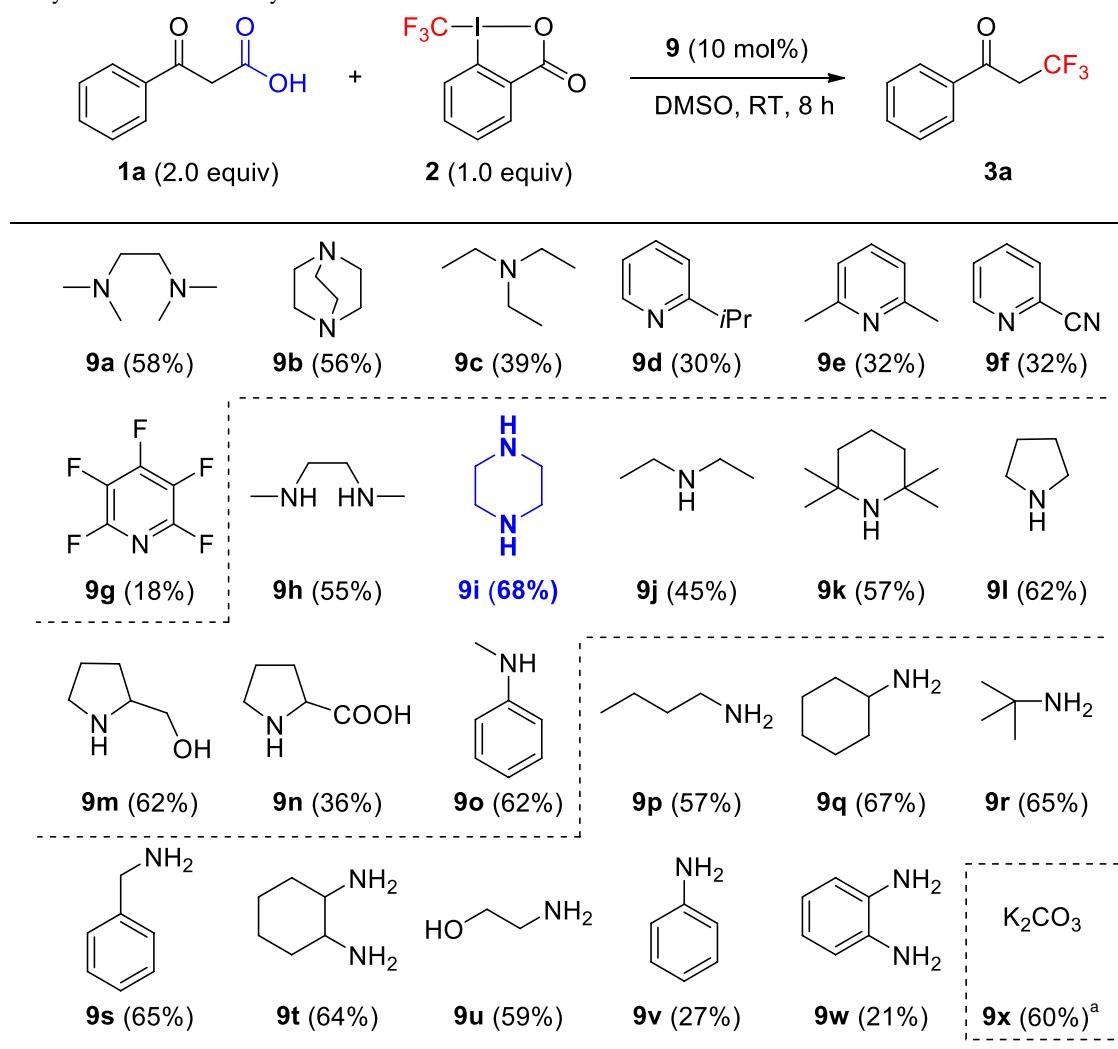
Scheme 2 Copper-catalyzed decarboxylative trifluoromethylation of β -ketoacid **1a** and the control experiments. Yields were determined by ^{19}F NMR spectroscopy analysis with PhOCF_3 as an internal standard

Scheme 3 Proposed mechanism for tertiary amine-catalyzed decarboxylative trifluoromethylation of β -ketoacid **1**



these preliminary results, we set out to develop an effective method for organocatalyzed decarboxylative trifluoromethylation of β -ketoacids. We speculated that amines should

promote the trifluoromethylation by enhancing the reactivity of the intermediate resulting from the decarboxylation of the β -ketoacids.

Table 1 Survey of various amine catalysts

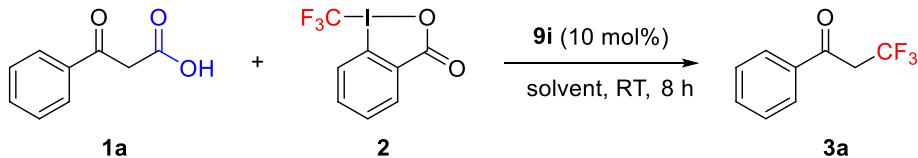
Conditions: **1a** (0.4 mmol), **2** (0.2 mmol), **9** (0.02 mmol), DMSO (2 mL). Yields were determined by ^{19}F NMR spectroscopy with PhOCF_3 as an internal standard

^a**1a** (0.2 mmol), **2** (0.4 mmol), **9** (0.04 mmol), DMSO (2 mL)

We first examined the catalytic reactivity of various tertiary amines and pyridines, with the assumption that an organic base may stabilize the corresponding enol intermediates by slowing down its tautomerization to ketones, thus facilitating the trifluoromethylation reaction. As is shown in Table 1, TMEDA (**9a**) and 1,4-diazabicyclooctane (DABCO, **9b**) worked equally well to afford **3a** in moderate yields. However, tertiary amine **9c** and pyridines **9d–f** were found to be less efficient. To further improve the reaction, we turned our attention to the use of primary and secondary amines. It has been established that these amines can promote the decarboxylation of β -ketoacids through the conversion of β -iminoacids to enamines [51–54]. Because enamines are more nucleophilic than the corresponding enols due to its enhanced electron-rich character, we assumed that the use of a primary or secondary amine should be able to catalyze the electrophilic trifluoromethylation

process. A screening of structurally diverse secondary and primary amines showed that a number of *N*-alkyl substituted ones were capable of promoting the decarboxylative trifluoromethylation of **3a**, with piperazine (**9i**) being the most effective. In the case of proline (**9n**), an additional carboxylic group was found to be detrimental to the reaction. Besides, primary aromatic amines such as aniline (**9v**) and *o*-phenylenediamine (**9w**) were less effective than secondary aromatic amines such as *N*-methylaniline (**9o**). Interestingly, when the inorganic base K_2CO_3 (**9x**) was used, the reaction also proceeded smoothly, producing comparable yield to TMEDA-catalyzed reaction.¹

¹ It was found that when 1 equiv of K_2CO_3 was used, the yield of **3a** dropped dramatically to 13%, indicating that the carboxylate anion of **1a** itself is not the reactive species for trifluoromethylation. In this context, we rationalized that **1a** and its salt worked together to pro-

Table 2 Survey of reaction conditions

Entry	Solvent	1a/2	Conversion (2, %)	Yield (3a, %)
1 ^a	DMF	2.0:1.0	15	Trace
2	MeNO ₂	2.0:1.0	11	0
3	MeOH	2.0:1.0	27	13
4	THF	2.0:1.0	100	11
5	Et ₂ O	2.0:1.0	100	37
6	1,4-dioxane	2.0:1.0	100	0
7	DME	2.0:1.0	100	Trace
8	CHCl ₃	2.0:1.0	13	0
9	CH ₂ Cl ₂	2.0:1.0	18	0
10	MeCN	2.0:1.0	22	0
11	DMSO	2.0:1.0	78	68
12 ^b	DMSO	1.0:2.0	59	74

Reactions were performed on 0.2-mmol scale

In all cases, the conversions of **1a** were 100%. Conversions of **2** and Yields of **3a** were determined by ¹⁹F NMR spectroscopy with PhOCF₃ as an internal standard

^a**9i** (5 mol%)

^b**9i** (20 mol%)

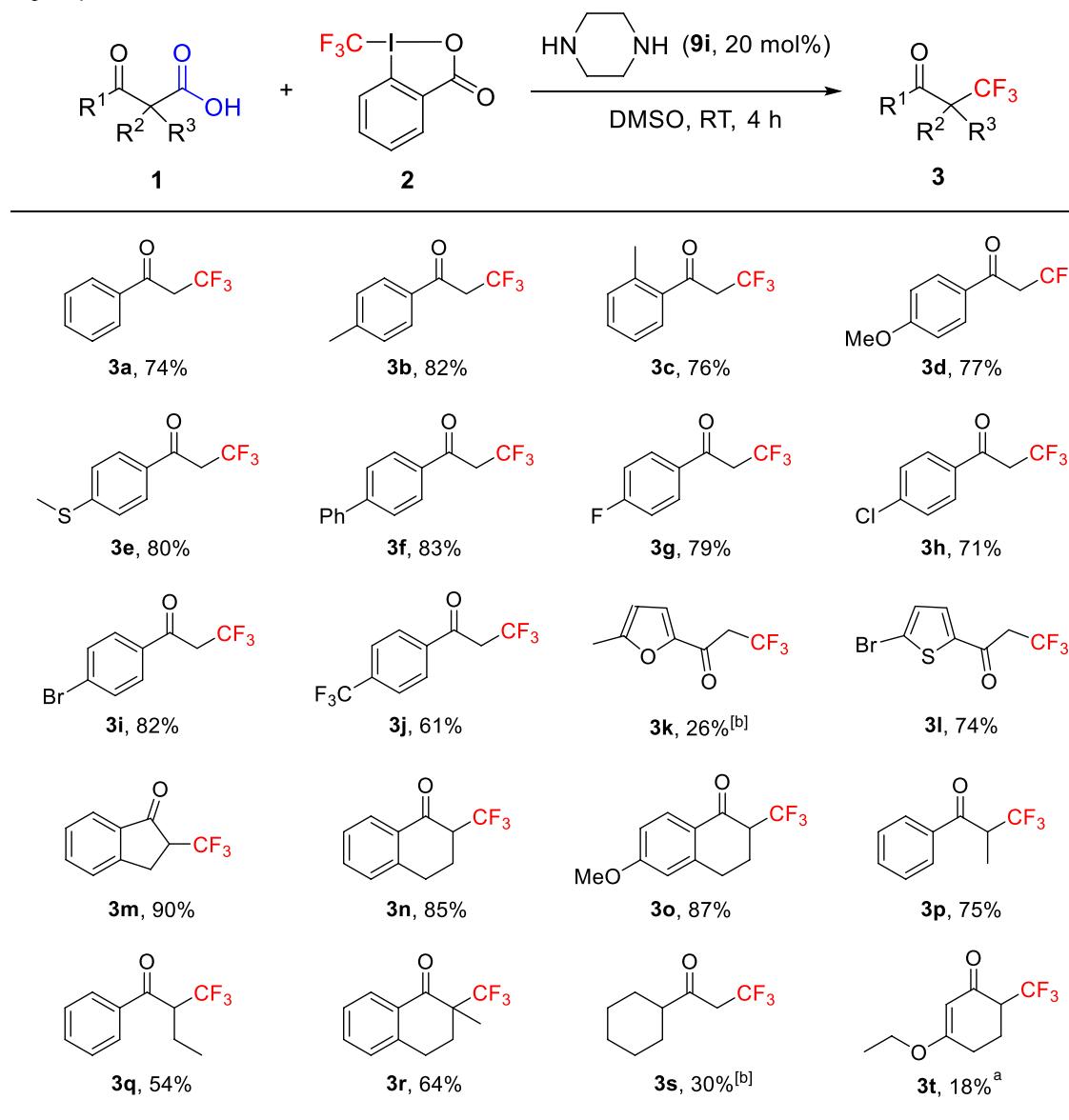
With piperazine (**9i**) as the optimal catalyst, we then investigated the proper reaction conditions (Table 2). First, the influence of solvent was examined (Table 2, entries 1–11). For this purpose, 10 mol% of **9i** (in respect to the limiting reactant) was used. When the reaction was conducted in solvents other than DMSO, a significant decrease of the yields of **3a** was observed owing to the ready decomposition of **1a** to acetophenone (**6**). In the ethereal solvents, the instability of Togni's reagent **2** may also attribute to the low yields of **3a** (Table 2, entries 4–7). Then the molar ratio of the reactants was investigated. A survey of the reaction in DMSO showed the yield of **3a** could be improved to 74% when **1a** and **2** were used in a molar ratio of 1:2 with a 20 mol% loading of **9i** (Table 2, entry 12). Having identified the optimal reaction conditions (Table 2, entry 12), we further examined the scope of this trifluoromethylation reaction (Table 3). Generally, β -aryl-substituted β -ketoacids reacted smoothly to give α -trifluoromethyl ketones in moderate to good yields, and no aromatic C–H trifluoromethylation occurred (**3a**–**3j**). Various substituents on the aryl ring at

the β -position, both electron-donating (**3b**–**3e**, and **3o**) and electron-withdrawing (**3f**–**3j**), are well tolerated in this reaction. The reaction is also amenable with β -heteroaryl substituents such as 5-bromothiophen-2-yl (**3l**). However, in the case of an electron-rich heteroaryl substituted β -ketoacid, its reaction afforded the desired α -CF₃ ketone in low yield due to the limited stability of the substrate (**3k**). Moreover, α -substituted β -ketoacids are also suitable substrates. Both the cyclic (**3m**–**3o**) and acyclic ones (**3p**–**3q**) were trifluoromethylated to deliver the corresponding ketones in good yields (54–90%). Of note the α,α -disubstituted ketoacid **1r**, which contains no α -hydrogen, could be converted into α -CF₃ ketone **3r** in 64% isolated yield, indicating that this decarboxylative trifluoromethylation proceeded through CO₂ release followed by CF₃ incorporation. Besides, fully aliphatic substrates could also be used in the reaction, albeit the yields of α -CF₃ ketones were lower (**3s** and **3t**).

To further understand the mechanism of piperazine-catalyzed reactions, we compared the catalytic performances of TMEDA (**9a**) and piperazine (**9i**) in the decarboxylative trifluoromethylation of α,α -disubstituted ketoacid **1r**. As is shown in Scheme 4a, piperazine is superior to TMEDA in catalyzing the trifluoromethylation. Considering that TMEDA (pK_a = 10.40) is more basic than piperazine (pK_a = 9.73) [55], we conclude that the piperazine-catalyzed

Footnote 1 (continued)

mote the trifluoromethylation, where the salt of **1a** plays a similar role as TMEDA, for a plausible explanation, see the supplementary material.

Table 3 Scope of β -ketoacids

Conditions: **1** (0.5 mmol), **2** (1.0 mmol), **9i** (0.1 mmol), DMSO (5.0 mL). Unless otherwise noted, isolated yields were given.

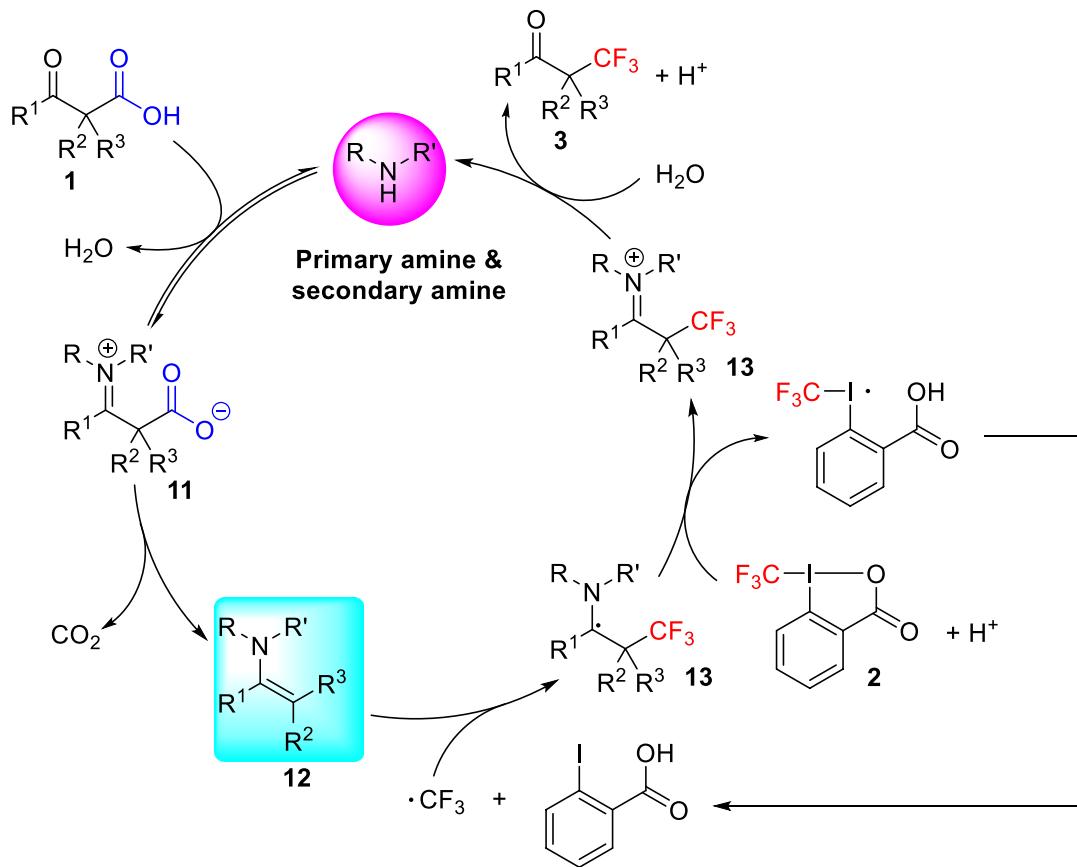
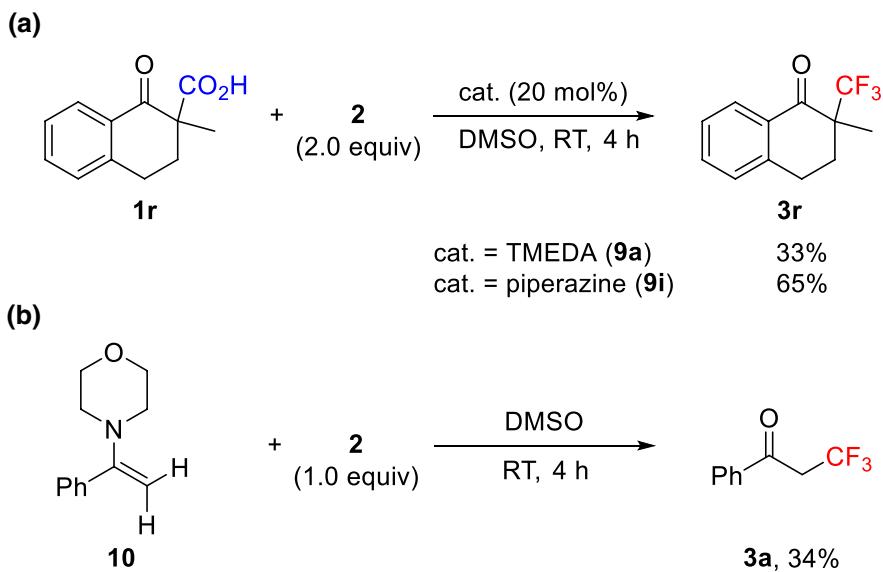
^aYields were determined by ¹⁹F NMR spectroscopy analysis with PhOCF₃ as an internal standard

reaction may take place in a different way from the TMEDA-catalyzed reaction (see Scheme 3). The latter may involve the reaction between reagent **2** and an enol intermediate; however, the former probably proceeded through the reaction of an enamine intermediate. Previous reports have showed that primary and secondary amines can catalyze the decarboxylation of β -ketoacids through enamine intermediates [52–54]. The viability for the trifluoromethylation of enamines is verified by the smooth reaction between enamine **10** and reagent **2** (Scheme 4b). Moreover, control experiments in the presence of known radical scavengers 1,1-diphenylethylene or butylated hydroxytoluene (BHT) showed that the reaction was totally inhibited, suggesting

the involvement of a radical pathway in the decarboxylative trifluoromethylation.

Based on above results and discussion, the proposed mechanism for decarboxylative trifluoromethylation with a primary or secondary amine catalyst is depicted in Scheme 5. First, a reversible condensation reaction of the amine (RR'NH) with β -ketoacids **1** affords the β -iminoacids **11**, which undergo irreversible decarboxylation to form the enamine intermediates **12**. Then enamines **12** react with the electrophilic trifluoromethylation reagent **2** to give α -CF₃ iminium intermediate **13**, most probably proceeding through single electron-transfer from the enamine to reagent **2** followed by CF₃ radical addition

Scheme 4 Mechanistic investigations. Yields were determined by ^{19}F NMR spectroscopy analysis with PhOCF_3 as an internal standard. **a** Comparison of TMEDA- and piperazine-catalyzed reaction. **b** Trifluoromethylation of enamine with reagent **2**. The low yield of **3a** is attributed to the ready hydrolysis of **10** by adventitious water



Scheme 5 Proposed mechanism for primary and secondary amine-catalyzed decarboxylative trifluoromethylation of β -ketoacids **1**

to the radical cation species of the enamine. Finally, the hydrolysis of intermediate **13** delivers $\alpha\text{-CF}_3$ ketones; meanwhile, the amine catalyst (such as piperazine) is regenerated. However, because the primary and secondary

amines can also serve as bases, we cannot rule out the possibility for the involvement of an enol intermediate, which may occur as a minor pathway.

3 Conclusions

In summary, a new protocol has been achieved for the synthesis of α -trifluoromethyl ketones via organocatalyzed decarboxylative trifluoromethylation of β -ketoacids with Togni's reagent. Among various simple amine catalysts examined, primary amines and secondary amines were found to be more effective than tertiary amines, and piperazine was identified as the most effective catalyst. Mechanistic investigations suggested that the primary or secondary amine-catalyzed reactions proceed mainly through the trifluoromethylation of an enamine intermediate, which is distinct from the tertiary amine-catalyzed reactions. By using piperazine as the optimal organocatalyst, various β -ketoacids, including the sterically hindered α,α -disubstituted ones, could be converted into the corresponding α -trifluoromethyl ketones in good yields. This research not only provides a useful strategy for the efficient synthesis of a wide range of α -trifluoromethyl ketones under mild conditions, but also constitutes one of the few studies on decarboxylative alkylation of β -ketoacids [56–60], which may intrigue further exploitation on organocatalyzed asymmetric reactions.

4 Experimental

4.1 General Information

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. The solvents DMSO and DMF were distilled over CaH_2 . All the β -ketoacids were prepared according to reported procedures [61–63]. ^1H , ^{19}F , and ^{13}C NMR spectra were recorded on a Bruker AM-300 NMR, VarianMercury-300, or Agilent MR-400 NMR spectrometer. ^1H NMR chemical shifts were determined relative to internal $(\text{CH}_3)_4\text{Si}$ (TMS) at δ 0.0 or to the signal of a residual protonated solvent CDCl_3 at δ 7.26. ^{19}F NMR chemical shifts were determined relative to external CFCl_3 at δ 0.0. ^{13}C NMR chemical shifts were determined relative to internal $(\text{CH}_3)_4\text{Si}$ (TMS) at δ 0.0. MS (EI-MS) were obtained on an Agilent 5975C gas chromatography and HP5989A mass spectrometer. MS (ESI) were obtained on an AGILENT1100 mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI mode. HRMS(EI) were recorded on a Waters Micromass GCT Premier mass spectrometer.

4.2 Typical Procedure for Organocatalyzed Decarboxylative Trifluoromethylation of β -Ketoacids 1 with Togni's Reagent (2)

Into a 20-mL Schlenk flask equipped with a stirring bar were added β -ketoacid **1a** (82.0 mg, 0.5 mmol), and

1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (Togni's reagent, **2**) (316.0 mg, 1.0 mmol). Then piperazine (8.6 mg, 0.1 mmol) in DMSO (5 mL) was added via syringe. After stirring at room temperature for 4 h, water (20 mL) was added, and the resulting mixture was extracted by Et_2O (20 mL \times 3). The organic layer was washed by water and brine solution, dried with MgSO_4 , concentrated under reduced pressure, and purified using flash column chromatography (silica gel; petroleum ether/dichloromethane, 5:2, v/v) to give α -trifluoromethyl ketone **3a** as white solid (71.5 mg, 74% yield).

4.2.1 3,3,3-Trifluoro-1-phenylpropan-1-one (3a) [31]

71.5 mg, 74% yield, white solid. ^1H NMR (400 MHz, CDCl_3 /TMS): δ 7.95–7.93 (m, 2H), 7.64–7.62 (m, 1H), 7.53–7.50 (m, 2H), 3.80 (q, J = 10.0 Hz, 2H); ^{19}F NMR (376 MHz, CDCl_3 /CFCl₃): δ –62.07 (t, J = 10.0 Hz); MS (EI, m/z): 188 (M⁺, 27.13), 105 (100.00).

4.2.2 3,3,3-Trifluoro-1-(*p*-tolyl)propan-1-one (3b) [31]

82.8 mg, 82% yield, white solid. ^1H NMR (400 MHz, CDCl_3 /TMS): δ 7.83 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.76 (q, J = 10.1 Hz, 1H), 2.43 (s, 2H); ^{19}F NMR (376 MHz, CDCl_3 /CFCl₃): δ –62.05 (t, J = 10.1 Hz); MS (EI, m/z): 202 (M⁺, 28.19), 119 (100.00).

4.2.3 3,3,3-Trifluoro-1-(*o*-tolyl)propan-1-one (3c) [64]

76.9 mg, 76% yield, colorless oil. ^1H NMR (400 MHz, CDCl_3 /TMS): δ 7.61 (d, J = 7.7 Hz, 1H), 7.46–7.42 (m, 1H), 7.33–7.29 (m, 2H), 3.75 (q, J = 10.1 Hz, 2H), 2.54 (s, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ –62.13 (t, J = 10.0 Hz); MS (EI, m/z): 202 (M⁺, 34.52), 119 (100.00).

4.2.4 3,3,3-Trifluoro-1-(4-methoxyphenyl)propan-1-one (3d) [31]

84.0 mg, 77% yield. ^1H NMR (400 MHz, CDCl_3 /TMS) δ 7.93–7.89 (m, 2H), 6.97–6.95 (m, 2H), 3.88 (s, 3H), 3.73 (q, J = 10.1 Hz, 2H); ^{19}F NMR (376 MHz, CDCl_3 /CFCl₃) δ –62.10 (t, J = 10.1 Hz); MS (EI, m/z): 218 (M⁺, 28.19), 105 (100.00).

4.2.5 3,3,3-Trifluoro-1-(4-(methylthio)phenyl)propan-1-one (3e)

93.0 mg, 80% yield, white solid. ^1H NMR (400 MHz, CDCl_3 /TMS): δ 7.84 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 3.75 (q, J = 10.0 Hz, 2H), 2.53 (s, 3H); ^{19}F NMR (376 MHz, CDCl_3 /CFCl₃): δ –61.98 (t, J = 10.1 Hz); MS (EI, m/z): 234 (M⁺, 44.35), 151 (100.00). ^{13}C NMR (101 MHz, CDCl_3) δ

188.63 (d, $J=2.5$ Hz), 147.79 (s), 132.00 (d, $J=1.7$ Hz), 128.73 (s), 125.01 (s), 124.05 (q, $J=277.0$ Hz), 41.90 (q, $J=28.1$ Hz), 14.59 (s); MS (ESI, m/z, %): 165 ($M+Na^+$, 100). HRMS (EI): Calcd. For $C_{10}H_9OF_3S$: 234.0326; Found: 234.0324.

4.2.6 1-[(1,1'-Biphenyl)-4-yl]-3,3,3-trifluoropropan-1-one (3f) [31]

109.9 mg, 83% yield, white solid. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 8.00 (d, $J=8.5$ Hz, 2H), 7.71 (d, $J=8.6$ Hz, 2H), 7.63–7.59 (m, 1H), 7.51–7.44 (m, 2H), 7.41 (t, $J=7.3$ Hz, 1H), 3.81 (q, $J=10.0$ Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –61.97 (t, $J=10.0$ Hz); MS (EI, m/z): 264 (M^+ , 9.41), 181 (100.00).

4.2.7 3,3,3-Trifluoro-1-(4-fluorophenyl)propan-1-one (3g) [31]

81.4 mg, 79% yield, white solid. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 7.97 (dd, $J=7.9$, 5.6 Hz, 2H), 7.18 (t, $J=8.3$ Hz, 2H), 3.78 (q, $J=9.9$ Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –62.05 (t, $J=9.8$ Hz), –102.83 to –107.47 (m); MS (EI, m/z): 206 (M^+ , 35.11), 123 (100.00).

4.2.8 1-(4-Chlorophenyl)-3,3,3-trifluoropropan-1-one (3h) [31]

78.9 mg, 71% yield, white solid. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 7.90–7.86 (m, 1H), 7.51–7.48 (m, 1H), 3.77 (q, $J=9.9$ Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –62.03 (t, $J=9.9$ Hz); MS (EI, m/z): 222 (M^+ , 22.7), 139 (100.00).

4.2.9 1-(4-Bromophenyl)-3,3,3-trifluoropropan-1-one (3i) [64]

109.1 mg, 82% yield, white solid. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 7.80 (d, $J=8.6$ Hz, 2H), 7.66 (d, $J=8.7$ Hz, 2H), 3.76 (q, $J=9.9$ Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –62.03 (t, $J=9.9$ Hz); MS (EI, m/z): 266 (M^+ , 37.61), 185 (100.00).

4.2.10 3,3,3-Trifluoro-1-(4-(trifluoromethyl)phenyl)propan-1-one (3j) [31]

78.5 mg, 61% yield, white solid. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 8.05 (d, $J=8.3$ Hz, 1H), 7.79 (d, $J=8.3$ Hz, 1H), 3.83 (q, $J=9.8$ Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –62.04 (t, $J=10.0$ Hz), –63.38 (s); MS (EI, m/z): 256 (M^+ , 6.67), 173 (100.00).

4.2.11 1-(5-Bromothiophen-2-yl)-3,3,3-trifluoropropan-1-one (3l) [31]

95.3 mg, 74% yield, white solid. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 7.44 (d, $J=4.1$ Hz, 1H), 7.14 (d, $J=4.1$ Hz, 1H), 3.62 (q, $J=10.0$ Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –61.90 (t, $J=10.1$ Hz); MS (EI, m/z): 272 (M^+ , 32.52), 191 (100.00).

4.2.12 2-(Trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (3m) [65]

90.6 mg, 90% yield, white solid. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 7.83–7.81 (m, 1H), 7.68–7.64 (m, 1H), 7.53–7.51 (m, 1H), 7.45–7.42 (m, 1H), 3.49–3.28 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –67.80 (d, $J=9.6$ Hz); MS (EI, m/z): 200 (M^+ , 78.22), 131 (100.00).

4.2.13 2-(Trifluoromethyl)-3,4-dihydronaphthalen-1(2*H*)-one (3n) [66]

90.5 mg, 85% yield, white solid. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 8.06 (d, $J=7.9$ Hz, 1H), 7.54–7.50 (m, 1H), 7.36–7.33 (m, 1H), 7.28–7.26 (m, 1H), 3.33–3.22 (m, 1H), 3.16–3.03 (m, 2H), 2.54–2.47 (m, 1H), 2.33–2.22 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –67.58 (d, $J=8.8$ Hz); MS (EI, m/z): 214 (M^+ , 46.03), 118 (100.00).

4.2.14 6-Methoxy-2-(trifluoromethyl)-3,4-dihydronaphthalen-1(2*H*)-one (3o)

105.7 mg, 87% yield, white solid. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 8.04 (d, $J=8.8$ Hz, 1H), 6.85 (dd, $J=8.8$, 2.2 Hz, 1H), 6.70–6.70 (m, 1H), 3.86 (s, 3H), 3.27–3.17 (m, 1H), 3.11–2.97 (m, 2H), 2.49–2.42 (m, 1H), 2.30–2.20 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –67.33 (d, $J=9.0$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.84 (s), 164.18 (s), 145.67 (s), 130.35 (s), 125.48 (s), 125.23 (q, $J=280.0$ Hz), 113.73 (s), 112.48 (s), 55.51 (s), 50.51 (q, $J=25.3$ Hz), 27.83 (s), 23.48 (q, $J=2.6$ Hz); MS (EI, m/z): 244 (M^+ , 30.88), 148 (100.00). HRMS (EI): Calcd. For $C_{12}H_{11}O_2F_3$: 244.0700; Found: 244.0708.

4.2.15 3,3,3-Trifluoro-2-methyl-1-phenylpropan-1-one (3p) [66]

75.9 mg, 75% yield, colorless oil. 1H NMR (400 MHz, $CDCl_3/TMS$): δ 7.95 (d, $J=7.5$ Hz, 2H), 7.62 (t, $J=7.4$ Hz, 1H), 7.50 (t, $J=7.7$ Hz, 2H), 4.32–4.20 (m, 1H), 1.46 (t, $J=9.1$ Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –68.35 (d, $J=8.1$ Hz); MS (EI, m/z): 202 (M^+ , 5.34), 105 (100.00).

4.2.16 Phenyl-2-(trifluoromethyl)butan-1-one (3q) [67]

58.6 mg, 54% yield, colorless oil. ^1H NMR (400 MHz, CDCl_3/TMS) δ 7.96–7.94 (m, 2H), 7.64–7.59 (m, 1H), 7.52–7.48 (m, 2H), 4.16–4.06 (m, 1H), 2.17–2.05 (m, 1H), 1.99–1.88 (m, 1H), 0.94 (t, $J=7.5$ Hz, 2H); ^{19}F NMR (376 MHz, $\text{CDCl}_3/\text{CFCl}_3$) δ –66.22 (d, $J=8.3$ Hz); MS (EI, m/z): 216 (M^+ , 13.28), 105 (100.00).

4.2.17 2-Methyl-2-(trifluoromethyl)-3,4-dihydronaphthalen-1(2H)-one (3r) [66]

72.6 mg, 64% yield, colorless oil. ^1H NMR (400 MHz, CDCl_3/TMS): δ 8.07 (d, $J=7.8$ Hz, 1H), 7.52 (td, $J=7.5$, 1.3 Hz, 1H), 7.34 (t, $J=7.6$ Hz, 1H), 7.26 (d, $J=7.5$ Hz, 1H), 3.11–3.00 (m, 2H), 2.49–2.42 (m, 1H), 2.20–2.14 (m, 1H), 1.45 (s, 3H); ^{19}F NMR (376 MHz, $\text{CDCl}_3/\text{CFCl}_3$): δ –73.09 (s); MS (EI, m/z): 228 (M^+ , 36.91), 118 (100.00).

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