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# Organocatalytic Decarboxylative Cyanomethylation of Difluoromethyl and Trifluoromethyl Ketones

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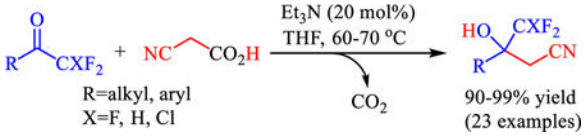
## Abstract

An efficient organocatalytic method for the synthesis of difluoromethyl and trifluoromethyl substituted β-hydroxynitriles is introduced. The decarboxylative cyanomethylation of fluorinated ketones with readily available cyanoacetic acid gives a variety of tertiary alcohols in high yields and without concomitant water elimination. The reaction occurs in the presence of catalytic amounts of triethylamine, can be upscaled and applied to chlorofluoromethyl ketones and difluoromethyl ketimines.

## Graphical Abstract




### Keywords

Cyanomethylation; Organocatalysis; Organofluorines; β-hydroxynitriles; Cyanoacetic acid

In stark contrast to the wealth of reports on the Henry reaction and other variations of the aldol reaction, relatively few methods that accomplish efficient cyanomethylation of carbonyl substrates exist. The formation of the synthetically versatile β-hydroxynitrile motif often requires large excess of acetonitrile and is in some cases accompanied by the loss of the hydroxy group due to uncontrolled elimination toward unsaturated nitrile derivatives. Substantial progress has been made with regard to the cyanomethylation of aldehydes and imines by the introduction of $Me_3SiCH_2CN$ or other α-cyano carbananion precursors[1] and through the development of mild transition metal catalyzed procedures that address the challenging low acidity of acetonitrile (pKa 31.3 in DMSO).[2] In addition, decarboxylative cyanomethylation and superbase catalyzed acetonitrile additions have emerged as a practical alternative.[3,4]

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The unique chemical and pharmacological properties of fluorinated compounds continues to receive considerable attention from synthetic and medicinal chemists.[5] The vital role of the C-F moiety in today's drug design and discovery programs has motivated the introduction of a large variety of organofluorines that either show therapeutic potential in clinical trials or are already in use.[6] Synthetic methods that accomplish C-C bond formation with trifluoromethyl or difluoromethyl ketones or derivatives thereof have become particularly important. The trifluoromethyl group is a key structural motif in several anticonvulsants,[7] metalloproteinase inhibitors,[8] CJ-17,493,[9] a Neurokinin 1 receptor antagonist, ZK (+)-216348,[10] a potent glucocorticoid receptor agonist, and HIV drugs such as Efavirenz.[11] Examples of therapeutics exhibiting a difluoromethylene or difluoromethyl group are the HIV-1 protease inhibitor A-79285[12] and Eflornithine,[13] an inhibitor of ornithine decarboxylase used for the treatment of facial hirsutism and African sleeping sickness. In recent years, we have developed an interest in catalytic nucleophilic addition reactions with trifluoromethyl ketone substrates.[14] We now report the first organocatalytic decarboxylative cyanomethylation of trifluoromethyl and difluoromethyl ketones. This method is applicable to aromatic and aliphatic substrates, operationally simple and it avoids the previously prevailing problem with concurrent water elimination (Scheme 1).[15]

We began our search for a practical method for the synthesis of trifluoromethylated β-hydroxynitriles by screening the reaction of 2,2,2-trifluoroacetophenone, **1a**, and cyanoacetic acid, **2**, in the presence of various organic and inorganic bases. We found that **1a** is converted to the desired 4,4,4-trifluoro-3-hydroxy-3-phenylbutanenitrile, **3a**, in 49% yield at room temperature after 42 hours when three equivalents of **2** and 50 mol% of DBU are employed in THF (Table 1, entry 1). Importantly, we did not observe formation of by-products under these conditions. The prospect of mild cyanomethylation of **1a** without subsequent dehydration encouraged us to test several amines, DMAP, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton's base), $K_2CO_3$ and $Cs_2CO_3$. The results show that similar yields can be obtained with triethylamine and Barton's base (Table 1, entries 2–9). When the reaction was carried out in the absence of base no product was formed (Table 1, entry 10).

We then continued with the optimization of solvent, temperature and loading of triethylamine which was chosen because it is commonly present in synthetic laboratories and less expensive than DBU and Barton's base (see Table 1 and SI). The use of dichloromethane, dioxane, toluene, acetonitrile, methanol and water as solvent did not improve the results. High yields of **3a**, albeit with concomitant formation of by-products, were achieved under solvent-free microwave conditions using 10 mol% of $Et_3N$ at 100 °C (entry 17). Because milder conditions were considered more promising with regard to a procedure having a wide functional group tolerance we decided to further investigate ambient temperatures using THF as solvent. Finally, we were able to produce **3a** in 98% yield after 21 hours using two equivalents of **2** and 20 mol% of $Et_3N$ in THF (entry 20).

With the optimized reaction conditions in hand, we continued with exploring the substrate scope and organocatalytic decarboxylative cyanomethylations were carried out with a series of trifluoromethyl ketones (Scheme 2). The reactions with aromatic trifluoromethyl ketones **1a**–**1c** proceeded quantitatively and gave the benzyl alcohols **3a**–**3c** in 97–98% yield. Halogen substituents in *ortho* or *para* positions of the trifluoroacetophenones **1d**–**1g** were

well tolerated and we isolated **3d**–**3g** in 93–99% yield. The reaction is also applicable to the trifluoroacetophenones **1h**–**1l** carrying a wide range of electron-withdrawing or electron-donating groups. The corresponding tertiary alcohols **3h**–**3l** were obtained in 93–99% yield and side reactions, for example at the ester group, were not observed. Importantly, heteroaryl and aliphatic trifluoromethyl ketones can be used. 4,4,4-Trifluoro-3-hydroxy-3-(thiophen-2-yl)butanenitrile, **3m**, was produced with excellent yield and the enolizable trifluoromethyl ketone **1n** underwent decarboxylative cyanomethylation to the aliphatic tertiary alcohol **3n** in 92% yield. To further demonstrate the general utility of the triethylamine catalyzed decarboxylative cyanomethylation we performed the reaction between **1a** and **2** on a gram scale using otherwise essentially the same reaction conditions as described in Scheme 2. In this case, the β-hydroxynitrile **3a** was obtained in 93% yield after 24 hours.

We then extended our decarboxylative cyanomethylation method to difluormethyl substrates. First, a series of difluoromethyl ketones was synthesized by following previously reported literature protocols.[16] After minor changes of the reaction procedure described above, we were able to prepare the β-difluoromethyl-β-hydroxynitriles **5a**–**5h** (Scheme 3). The cyanomethylation of the phenyl, tolyl, and 2-napthyl ketones **4a**–**4c** gave **5a**–**5c** in 92–99% yield. Again, other functional groups are well tolerated and we obtained the 2-nitro, 4-fluoro and 6-chloro derivatives **5d**–**5f** in 92–99% yield. Excellent results were also achieved with heteroaromatic difluoromethyl ketones and **5g** and **5h** carrying a 2-furyl and 2-thienyl ring, respectively, were formed in 90–94% yield.

Finally, we employed chlorodifluoromethyl ketone **6** in our reaction protocol (Scheme 4). As expected, the cyanomethylated alcohol **7** was produced in high yield, which proves that other halogens on the alkyl side chain are tolerated. Alternatively, we attempted to prepare **7** by careful addition of one equivalent of $LiCH_2CN$, which was prepared by deprotonation of acetonitrile with *n*-BuLi at −78 °C, to ketone **6**. Under these conditions, **7** was obtained in only 74% yield due to formation of byproducts.[17] We were pleased to find that our protocol is compatible with the use of activated imines. The diastereoselective Mannich reaction with enantiomerically pure *tert*-butylsulfinyl imide **8** gave **9** with 82% yield and 89:11 diastereoselectivity.[18] If desired, ethyl malonic acid, **10**, can be employed in the same protocol to produce **11** in high yields.

A plausible mechanism of the decarboxylative cyanomethylation is presented in Scheme 5. Initial deprotonation of cyanoacetic acid generates dianionic intermediate **I**. Nucleophilic addition to a halogenated ketone then forms intermediate **II**. The carbon-carbon bond formation step is then followed by decarboxylation which affords the β-hydroxy nitrile product and regenerates the amine catalyst. This reaction course is in agreement with literature reports on decarboxylative additions with malonic acids.[19]

In conclusion, we have introduced a practical organocatalytic method for the synthesis of difluoromethyl and trifluoromethyl substituted β-hydroxynitriles. The decarboxylative cyanomethylation of fluorinated ketones with cyanoacetic acid occurs under mild conditions in the presence of 20 mol% of inexpensive triethylamine and affords a wide variety of multifunctional tertiary alcohols in 90–99% yield without concomitant water elimination.

The general reaction protocol was successfully upscaled and extended to an asymmetric Mannich reaction with a *tert*-butylsulfinyl ketimine derivative.

## Experimental Section

### Representative Procedure for the Organocatalytic Cyanomethylation of Trifluoromethyl Ketone.

To a solution of 2,2,2-trifluoro-1-phenylethan-1-one (52 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in THF (1.0 mL) was added triethylamine (20 mol%). The resulting mixture was stirred at 60 °C for 24 hours and the reaction was monitored by $^{19}$F NMR for the disappearance of the trifluoromethyl ketone. The crude product was purified by flash chromatography on silica gel using hexanes-ethyl acetate as mobile phase to give 4,4,4-Trifluoro-3-hydroxy-3-phenylbutanenitrile (**3a**) as a colorless solid in 98% yield (63 mg, 0.294 mmol). Mp. 75.1–75.9 °C; $R_f$ = 0.2 (hexanes/EtOAc, 8:2); $^1$H NMR (400 MHz, Chloroform-*d*) δ = 7.61 – 7.52 (m, 2H), 7.52 – 7.42 (m, 3H), 3.25 – 3.12 (m, 2H), 3.12 (s, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ = 134.3, 129.8, 128.9, 125.9 (q, $J_{C\text{-}F}$ = 1.3 Hz), 124.1 (q, $J_{C\text{-}F}$ = 286.0 Hz), 114.8, 75.2 (q, $J_{C\text{-}F}$ = 29.7 Hz), 26.9 (q, $J_{C\text{-}F}$ = 1.7 Hz); $^{19}$F NMR (376 MHz, Chloroform-*d*) δ = −79.5; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_8F_3NO$ 215.0558, found 215.0553.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

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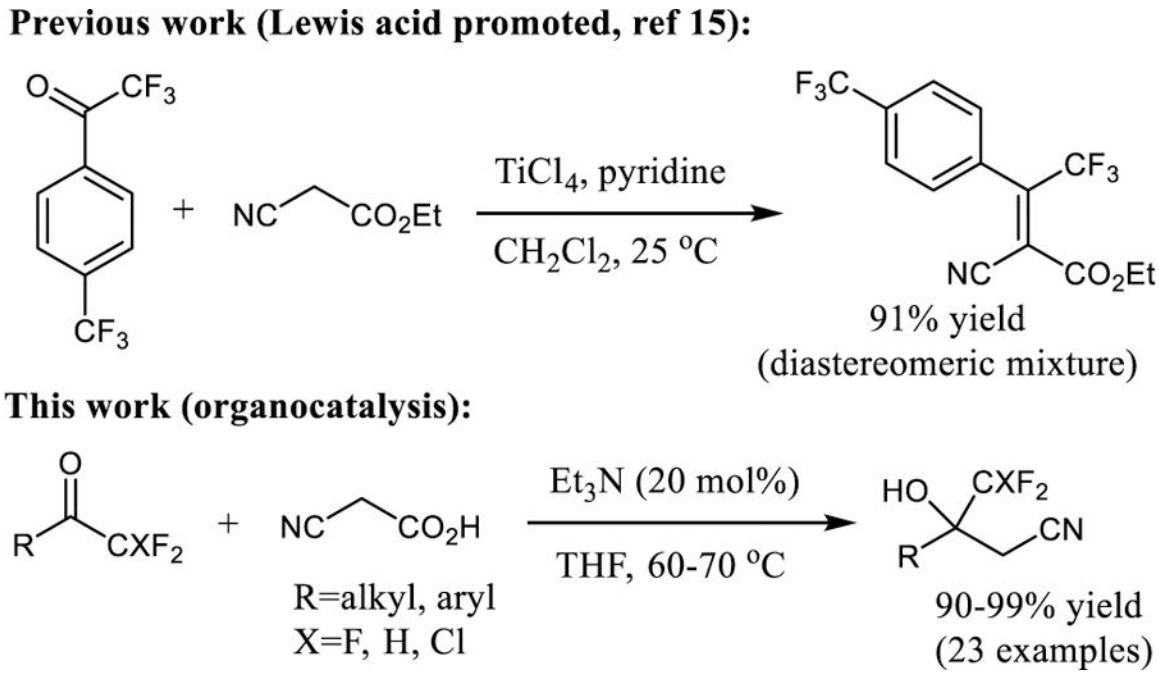
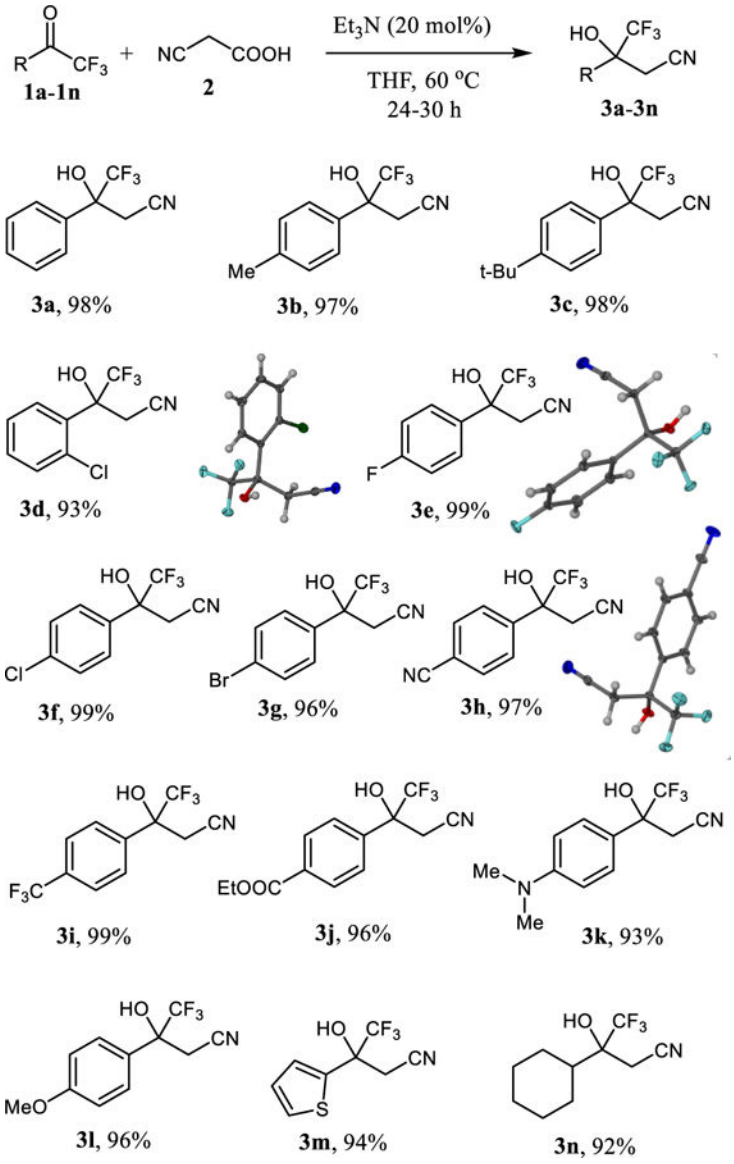
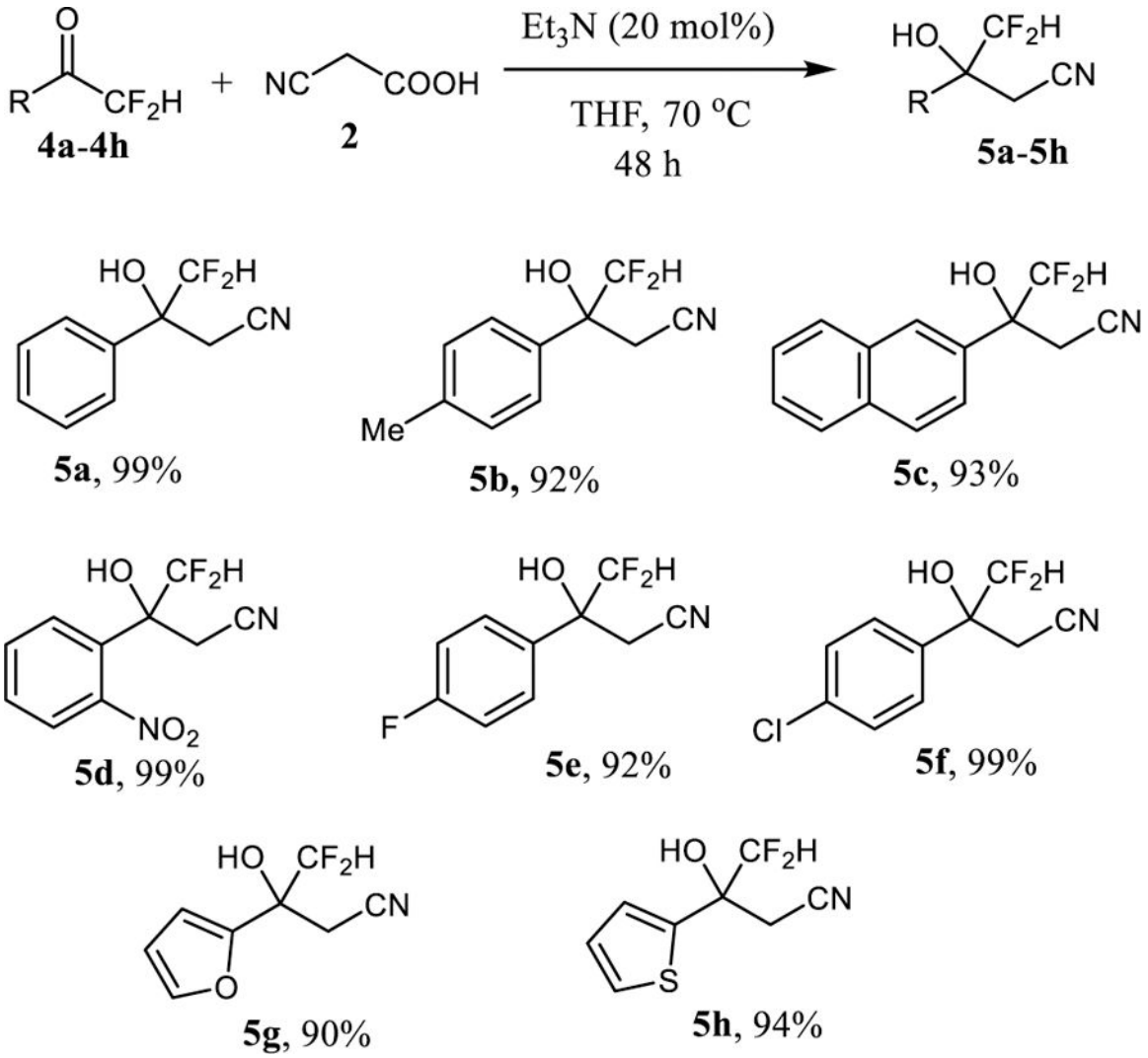



**Scheme 1.**
Decarboxylative cyanomethylation of halogenated ketones.

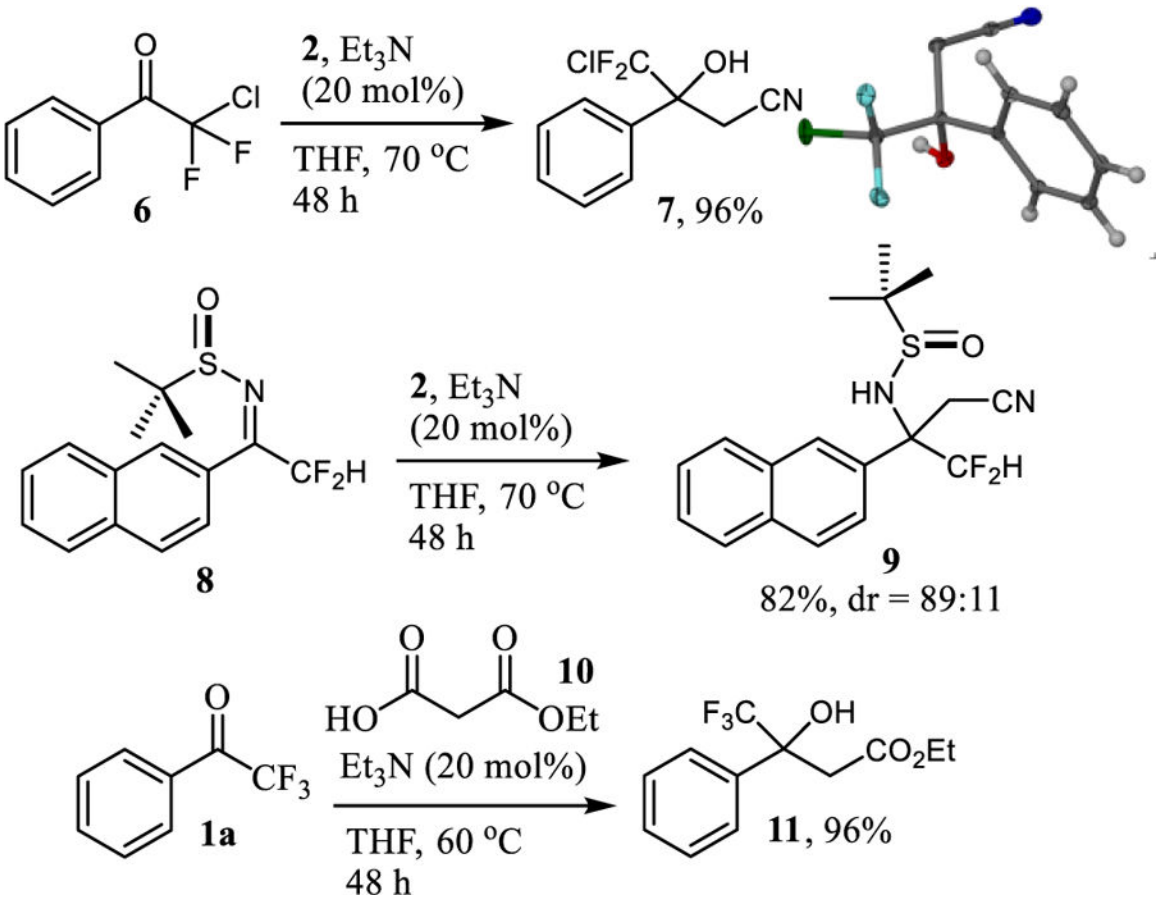



**Scheme 2.**

Substrate scope of the cyanomethylation of trifluorome-thyl ketones. Reaction conditions: All reactions were performed with trifluoromethyl ketone **1** (0.3 mmol), cyanoacetic acid **2** (0.6 mmol) and triethylamine (0.06 mmol) in 1 mL of THF at 60 °C. See SI for details.

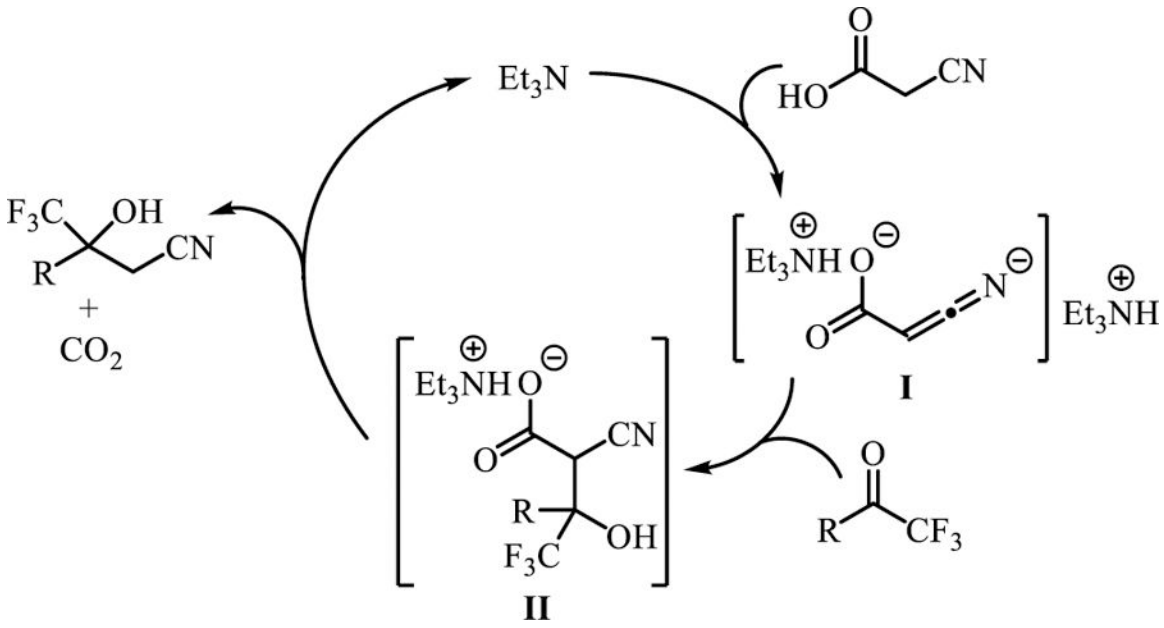



**Scheme 3.**
Decarboxylative cyanomethylation of difluoromethyl ketones.




**Scheme 4.**

Decarboxylative cyanomethylation of **6** and **8**, and conversion of **1a** to the ethyl ester **11**.




**Scheme 5.**
Proposed mechanistic pathway of the organocatalytic decarboxylative cyanomethylation.

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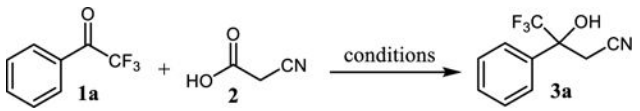
**Table 1.**

Optimization of the cyanomethylation of 2,2,2-trifluoroacetophenone.[a]




| Entry | Base (mol%) | Solvent | Time (h) | Temp (°C) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | DBU (50) | THF | 42 | 25 | 49 |
| 2 | $Et_3N$ (50) | THF | 42 | 25 | 45 |
| 3 | DIPEA (50) | THF | 42 | 25 | 29 |
| 4 | DABCO (50) | THF | 42 | 25 | 13 |
| 5 | TMEDA (50) | THF | 42 | 25 | 23 |
| 6 | DMAP (50) | THF | 42 | 25 | 36 |
| 7 | Barton's base (50) | THF | 42 | 25 | 42 |
| 8 | $K_2CO_3$ (50) | THF | 42 | 25 | <5 |
| 9 | $Cs_2CO_3$ (50) | THF | 42 | 25 | 9 |
| 10 | None | THF | 42 | 25 | nr |
| 11 | $Et_3N$ (50) | $CH_2Cl_2$ | 48 | 25 | <5 |
| 12 | $Et_3N$ (50) | 1,4-dioxane | 48 | 25 | 27 |
| 13 | $Et_3N$ (50) | toluene | 48 | 25 | <5 |
| 14 | $Et_3N$ (50) | $CH_3CN$ | 48 | 25 | 8 |
| 15 | $Et_3N$ (50) | $CH_3OH$ | 48 | 25 | <5 |
| 16 | $Et_3N$ (50) | $H_2O$ | 48 | 25 | nr |
| 17 | $Et_3N$ (10) | neat, MW | 0.75 | 100 | 89 |
| 18 | $Et_3N$ (50) | THF | 16 | 60 | 99 |
| 19 | $Et_3N$ (20) | THF | 21 | 60 | 98[d] |
| 20[c] | $Et_3N$ (20) | THF | 24 | 60 | 98[d] |
| 21[c] | $Et_3N$ (10) | THF | 36 | 60 | 91 |

[a]Conditions: 0.3 mmol of **1a**, 0.9 mmol of **2**, 1 mL of solvent.

[b] By NMR analysis.

[c] Two equivalents of **2** were used. The reaction is slow and takes 3 days with 1.5 equivalents of **2**.

[d] Isolated yields.