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Convenient and efficient decarboxylative aldol reaction of malonic acid half esters with trifluoromethyl ketones

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ABSTRACT

A convenient and efficient decarboxylative ketone aldol condensation of malonic acid half esters was reported. In the presence of catalytic amount of triethylamine, a series of aromatic and alkyl trifluoromethyl ketones were transformed into the desired adducts in 61–99% yields. In a preliminary experiment, a moderate stereoselectivity was obtained. Direct reduction of the aldol product with $LiAlH_4$ afforded trifluoromethylated 1,3-diol.

Aspiring to imitate the enzymatic activation of malonic acid half thioesters (MAHTs) in the biosynthesis of polyketides and fatty acids,[1–6] organic chemists have succeeded in developing many decarboxylative carbon–carbon bond-forming reactions, such as Claisen condensations,[7–12] Mannich reactions,[13–17] Michael additions,[18–22] and Knoevenagel transformations.[23–27] Among the most widely used mimic decarboxylative transformations for the construction of carbon–carbon bonds are decarboxylative aldol reactions. A lot of examples of decarboxylative aldol condensations have been reported;[16,28–34] however, in most cases, the use of aldehydes to achieve successful results was necessary. Accordingly, little attention has been paid to exploring ketone compounds as electrophilic substrates. The lack of progress may be attributed to the intrinsic poor reactivity of simple ketones. In comparison with aldehydes, activated ketone electrophiles are necessary for reasonable reaction rates. One example of decarboxylative ketone aldol reactions came from Fagnou and co-workers, who reported a triethylamine-promoted reaction of malonic acid half esters with α-ketoesters to afford the tertiary alcohol in modest to good yields.[35,36] Nakamura and co-workers disclosed an asymmetric organocatalytic decarboxylative addition of malonic acids half thioesters to isatins to yield enantiomerically enriched adducts.[37] We recently found that trifluoromethyl ketones are suitable substrates for this decarboxylative aldol reaction, the products of which are the precursors of trifluoromethylated 1,3-diols. Herein, we report our preliminary results on this subject.

Initially, the condensation of malonic acid half thioester **1a** with 2,2,2-trifluoroacetophenone **2a** was explored as a model reaction. The reaction did not proceed in toluene at room temperature with stoichiometric triethylamine. This result prompted us to screen other solvents including chloroalkanes, esters, ethers, and alcohols. It was found that this decarboxylative transformation is highly dependent on the solvent used, and no reaction occurred in most cases. Tetrahydrofuran (THF) was shown to be the best solvent for this reaction. Notably, this decarboxylative ketone aldol condensation can be carried out in the presence of catalytic triethylamine (10 mol %) for 60 h to afford the desired product in a 95% yield. In addition, no precautions for the use of inert atmosphere are required since the reactions can be performed at room temperature in an open flask. Malonic acid half oxyester (MAHO) **1b**, when used instead of malonic acid half thioester **1a**, do participate in the catalytic aldol reaction to give the adduct **3a** in a quantitative yield over a shorter reaction time (16 h). Subsequently, malonic acid half oxyesters will be employed as the reactants for the generation of ester enolate equivalents under very mild reaction conditions (Scheme 1).

With the optimal conditions established, the scope of the reaction was then probed. The results were listed in Table 1.[38] For the MAHOs with electron-withdrawing groups on the aromatic ring, a relatively prolonged reaction time was required to get high yields (entries 2 and 3 vs entry 1). For a series of aromatic trifluoromethyl ketones with electron-withdrawing groups on aromatic rings were used, the decarboxylative aldol reactions proceeded smoothly to give the desired adducts **3e–i** in 90–98% yields (entries 4–8). However, the presence of electron-donating substituents on aromatic

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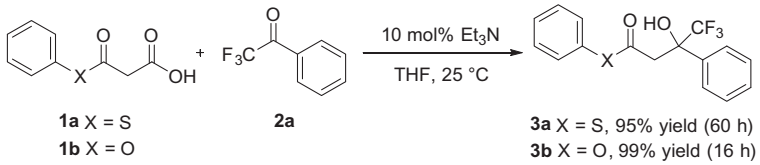
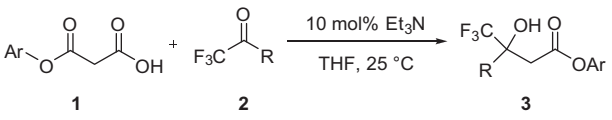


Scheme 1. Decarboxylative aldol condensation of malonic acid half esters **1** with 2,2,2-trifluoroacetophenone **2a**.

Table 1
Scope of the decarboxylative aldol condensation of malonic acid half ester **1b** with trifluoromethyl ketones **2**[a]



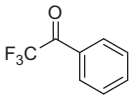
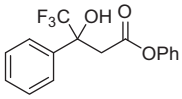
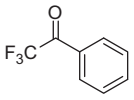
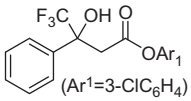
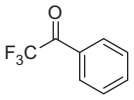
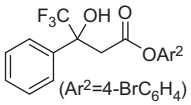
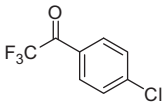
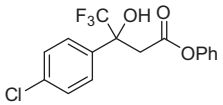
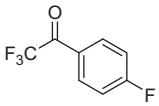
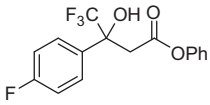
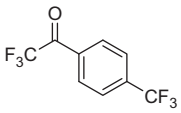
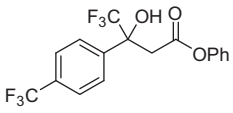
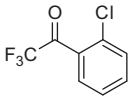
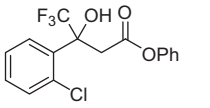
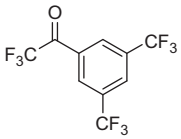
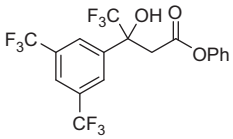
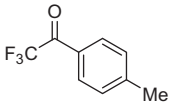
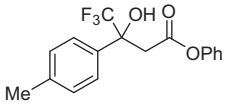
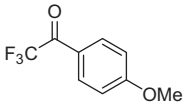
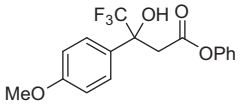
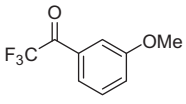
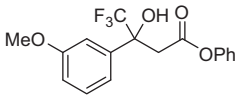
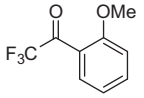
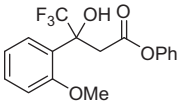
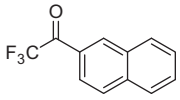
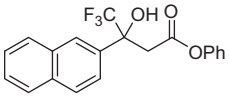
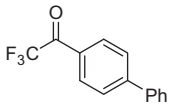
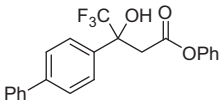
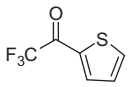
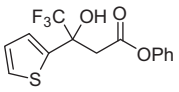
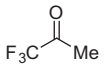
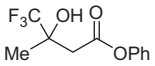
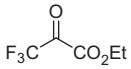
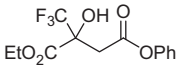
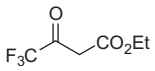
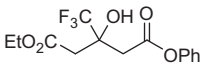
Entry	Ketone	Time (h)	Product **3**		Yield[b] (%)
1		16		**3b**	99
2		60	 (Ar^1=3-ClC_6H_4)	**3c**	99
3		60	 (Ar^2=4-BrC_6H_4)	**3d**	97
4		16		**3e**	96
5		16		**3f**	93
6		12		**3g**	96
7		60		**3h**	90
8		12		**3i**	98
9		72		**3j**	95
10		120		**3k**	61
11		120		**3l**	65

Table 1 (*continued*)

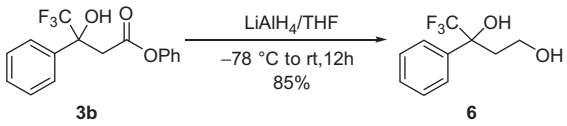
Entry	Ketone	Time (h)	Product **3**		Yield[b] (%)
12		120		**3m**	64
13		16		**3n**	86
14		16		**3o**	80
15		16		**3p**	98
16		12		**3q**	95
17		12		**3r**	98
18		24		**3s**	89

[a] Unless otherwise noted, the reaction was carried out with malonic acid half ester **1b** (1.5 mmol) with trifluoromethyl ketones **2** (1.0 mmol) in the presence of triethylamine (0.1 mmol) in THF (2.0 mL) at 25 °C.
[b] Isolated yield.

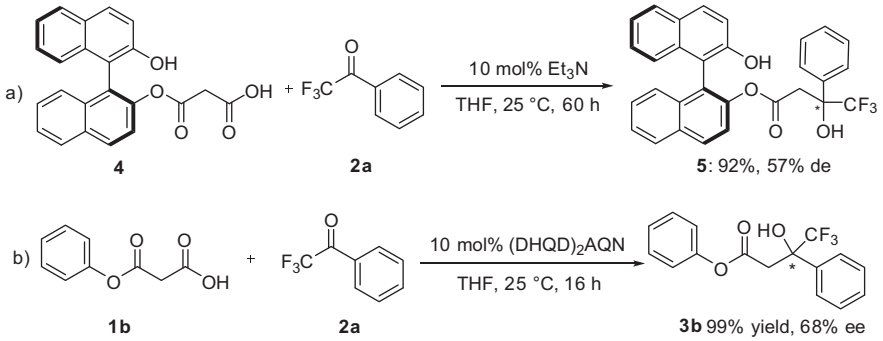
rings of ketones decreased the reaction rate, and relatively lower yields were obtained (products **3j**–**m**, entries 9–12). Accordingly, the decarboxylative aldol reactions worked well with biphenyl, 2-naphthyl, and 2-thiophenyl trifluoromethyl ketones under our current conditions to give the aldol products **3n**–**p** in good yields (entries 13–15). In addition, we also investigated the aldol reaction of the MAHO **1b** with alkyl trifluoromethyl ketones, including 1,1,1-trifluoropropan-2-one, ethyl 3,3,3-trifluoro-2-oxopropanoate,[35] and ethyl 4,4,4-trifluoro-3-oxobutanoate. These electrophilic ketones are also viable substrates in this decarboxylative transformation, affording the products **3q**–**s** in 89–98% yields (entries 16–18). Furthermore, the products derived from the self-condensation and keto-enol tautomerization of ethyl 4,4,4-trifluoro-3-oxobutanoate have not been observed in the reaction system, demonstrating the mildness and selectivity of MAHOs activation under the organic base conditions.

This methodology was further extended to the chiral (*S*)-1,1′-binaphthyl-2,2′-diol-derived malonic acid half ester **4** to illustrate the application of the decarboxylative ketone aldol reaction (Scheme 2a).[39] We found that in the presence of 10 mol % of triethylamine the aldol adduct **5** was obtained in a 92% yield with 57% de. The described decarboxylative ketone aldol condensation of malonic acid half esters could also, in principle, be extended to a catalytic enantioselective reaction. Screening of a series of available cinchona alkaloids (see Supplementary data) indicated that $(DHQD)_2AQN$ gave the best performance in terms of both the yield and the enantioselectivity (Scheme 2b).

In addition, these aldol adducts are useful synthetic intermediates and can be readily transformed into trifluoromethyl-substituted 1,3-diol derivatives. For example, direct reduction of **3b** in the presence of $LiAlH_4$ gave 4,4,4-trifluoro-3-phenylbutane-1,3-diol **6** in an 85% isolated yield (Scheme 3).[40]



Scheme 3. Synthetic transformation of the aldol adduct **3b** into the product **6**.



Scheme 2. Asymmetric decarboxylative aldol condensation.

In summary, we have developed a decarboxylative ketone aldol reaction of malonic acid half esters by using triethylamine as an efficient organocatalyst. A series of aromatic and alkyl trifluoromethyl ketones were transformed into the aldol adducts in 61–99% yields. In a preliminary experiment, moderate stereoselectivities were obtained. Further improvement of enantioselectivity of this transformation as well as additional mechanistic studies are ongoing in our laboratory and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.053.

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38. *General procedure for the catalytic decarboxylative aldol reaction of malonic acid half esters with trifluoromethyl ketones*: To a Schlenk tube were added monophenyl malonate **1b** (270 mg, 1.2 mmol), 1-(4-chlorophenyl)-2,2,2-trifluoroethanone (208 mg, 1.0 mmol), triethylamine (10 mg, 0.1 mmol), and THF (2.0 mL). The resulting mixture was stirred at room temperature with a hole pierced in the septum. After 16 h, the solvent was evaporated in vacuo and the reaction mixture was directly purified by flash column chromatography with ethyl acetate/petroleum ether (1/20 to 1/6) to get the white solid (**3e**, 330.2 mg). 96% yield, mp: 63–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (s, 2H), 4.97 (s, 1H), 6.91 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 5.6 Hz, 1H), 7.36–7.46 (m, 4H), 7.63 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 149.6, 135.4, 135.2, 129.6, 128.8, 128.0, 126.6, 124.3 (q, J_{C-F} = 284.5 Hz), 121.0, 75.3 (q, J_{C-F} = 29.5 Hz), 38.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.3 (s, 3F); MS (ESI) m/z 378.7 $[M+Cl-H]^-$; IR (KBr) ν 3348, 3075, 2946, 2855, 1714, 1600, 1495, 1436, 1359, 1235, 1097, 1041, 1163, 970, 794, 686 cm^{-1}.
39. *Procedure for an asymmetric decarboxylative aldol reaction of malonic acid half ester* ***4*** *with 2,2,2-trifluoroacetophenone* ***2a***: To a Schlenk tube were added **4** (186 mg, 0.5 mmol), 2,2,2-trifluoroacetophenone **2a** (131 mg, 0.75 mmol), triethylamine (5.1 mg, 0.05 mmol), and THF (2.0 mL). The resulting mixture was stirred at room temperature with a hole pierced in the septum. After 60 h, the solvent was evaporated in vacuo and the reaction mixture was directly purified by flash column chromatography with ethyl acetate/petroleum ether (1/20 to 1/4) to get the light yellow solid (**5**, 231 mg). mp 70–72 °C; yield 92%, de 57% (determined by ^{19}F NMR); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (d, J = 16.5 Hz, 1H), 3.12 (d, J = 16.5 Hz, 1H), 4.48 (s, 1H), 6.94–7.00 (m, 1H), 7.12–7.14 (m, 1H), 7.20–7.26 (m, 2H), 7.37–7.48 (m, 7H), 7.50–7.53 (m, 2H), 7.88–8.00 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 151.7, 147.1, 136.6, 133.5, 133.4, 132.6, 131.6, 131.1, 131.0, 130.9, 129.3, 129.2, 128.7, 128.5, 128.4, 127.9, 127.1, 126.9, 126.6, 126.3, 126.0, 124.6 (q, J_{C-F} = 283.7 Hz), 124.5, 123.9, 121.2, 118.3, 113.3, 75.3 (q, J_{C-F} = 28.9 Hz), 38.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.34 (s, 3F), −80.58(s, 3F); MS (ESI) m/z 536.5 $[M+Cl-H]^-$; IR (KBr) ν 3620, 3483, 3060, 2963, 2927, 1735, 1619, 1596, 1508, 1431, 1381, 1206, 1162, 1072, 1023, 974, 816, 750 cm^{-1}.
40. *General procedure for the reduction of the aldol product*: To a solution of **3b** (155.0 mg, 0.5 mmol) in 10 mL of THF was added $LiAlH_4$ (19.5 mg, 0.5 mmol) in one portion at 0 °C. The resultant mixture was stirred over night at room temperature (monitored by TLC). The mixture was evaporated in vacuum, added water (5 mL), extracted with dichloromethane (5 mL × 3), washed with brine and dried over $MgSO_4$. Concentration and flash chromatography (ethyl acetate/hexane: 1/15 to 1/5 as eluant) afforded the white solid (**6**, 93.5 mg, 85% yield). Mp: 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.6 Hz, 2H), 7.45–7.39 (m, 3H), 4.98 (s, 1H), 3.98–3.95 (m, 1H), 3.73–3.68 (m, 1H), 2.56–2.46 (m, 1H), 2.40–2.31 (m, 1H), 1.99 (t, J = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 128.5, 128.4, 126.6, 125.2 (q, J = 283.0 Hz), 78.03 (q, J = 28.2 Hz), 59.5, 35.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.17 (s, 3F); MS (ESI) m/z 242.3 $[M+Na-H]^+$; IR (KBr) ν: 3418, 3215, 2970, 2906, 1451, 1267, 1169, 1134, 1038, 977, 706 cm^{-1}.