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Catalytic aerobic oxidative decarboxylation of α-trifluoromethyl-α-hydroxy acids to trifluoromethyl ketones

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Abstract—The oxidative decarboxylation of α-trifluoromethyl-α-hydroxy acids to trifluoromethyl ketones is carried out under mild catalytic aerobic conditions using a cobalt(III) complex in the presence of pivalaldehyde.

1. Introduction

In the last two decades there has been an increasing interest in developing new catalytic processes for the oxidation of organic substrates that use oxygen as terminal oxidant. One of the most interesting approaches for this purpose employs transition metal complexes as catalysts.[1] In this context, our group has synthesised a number of transition metal complexes with bis-*N*,*N*′-disubstituted oxamides and related ligands that have been successfully applied in the oxidation of different functional groups.[2] Among these, we have reported the aerobic oxidative decarboxylation of α-hydroxy acids catalyzed by the Co(III) *ortho*-phenylene-bis(*N*′-methyloxamidate) complex (**1**) (Fig. 1), in the presence of pivalaldehyde under very mild conditions, and the application of this reaction in an umpoled synthesis of aryl alkyl ketones.[3]

On the other hand, the chemistry of fluorine containing compounds has received much attention because the incorporation of fluorine into organic molecules often results in profound modifications of their physical and chemical properties as well as of their biological activity profile.[4] In this article we describe the catalytic aerobic decarboxylation of α-trifluoromethyl-α-hydroxy acids to trifluoromethyl ketones with our catalytic procedure. Trifluoromethyl ketones are a well documented class of enzymatic inhibitors[5,6] and building blocks for trifluoromethyl heterocycles.[7] A number of methods for the synthesis of this kind of fluorocompounds have appeared in the literature in the last years.[8]

Keywords: decarboxylation; catalysts; fluorine compounds; cobalt; complexes.

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2. Results and discussion

α-Trifluoromethyl-α-hydroxyesters **3** can be prepared by the addition of $TMSCF_3$ to α-keto esters induced by fluoride.[9] However, this procedure is limited to a number of readily available α-keto esters, and in some cases the hydrolysis of the silyl ether intermediate poses difficulties. In the present work we have prepared compound **3** by reaction between Grignard reagents **2** and ethyl trifluoropyruvate as the source of the trifluoromethyl group at −78°C (Scheme 1). The procedure was applicable to both aromatic and aliphatic Grignard reagents and proceeded with fair to good yields (Table 1).

Saponification of compounds **3** with ethanolic potassium hydroxide followed by acidic work up afforded the corresponding α-trifluoromethyl-α-hydroxy acids **4** in almost quantitative yields. This reaction proceeded readily at room temperature with the aromatic derivatives (5–6 h) while the aliphatic derivatives required longer saponification times (overnight) or reflux temperatures for 2–3 h.

The oxidative decarboxylation of these α-trifluoromethyl-α-hydroxy acids to give the corresponding trifluoromethyl

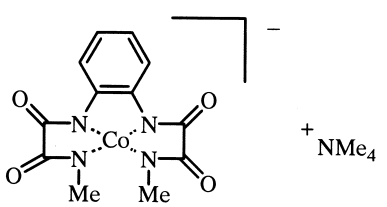

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Figure 1. Complex **1**.

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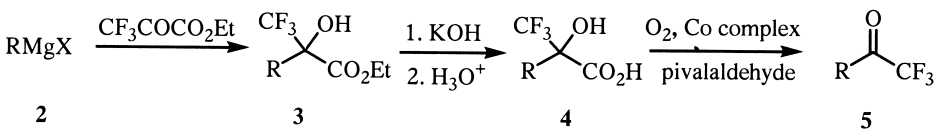
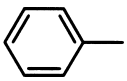
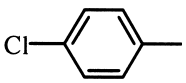
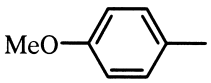
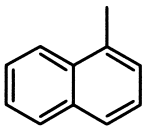
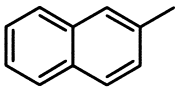
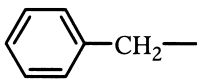
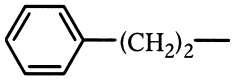
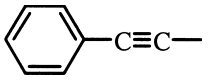
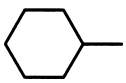


Scheme 1. Synthesis and decarboxylation of α-trifluoromethyl-α-hydroxy acids.

ketones **5** was achieved using the catalytic procedure developed in our laboratory for the decarboxylation of α-hydroxy acids.[3] A solution of compounds **4**, pivalaldehyde, and complex **1** in dichloromethane was stirred in an oxygen atmosphere at room temperature. The progress of the reaction was monitored by TLC. The application of this catalytic system to compounds **4** gave rise to a clean oxidative decarboxylation leading to trifluoromethyl ketones **5**. One of the problems found in this reaction was the removal of the excess of pivalaldehyde and pivalic acid formed during the reaction. Elimination of pivalaldehyde under reduced pressure was not possible since many trifluoromethyl ketones were volatile. On the other hand, chromatographic separation was not easy because of the R_f similarities of pivalaldehyde and non polar trifluoromethyl ketones. To solve this problem, we decided to allow the reaction to proceed until a complete oxidation of pivalaldehyde to pivalic acid, which was then removed by extraction with aqueous $NaHCO_3$. Careful elimination of the solvent under reduced pressure followed by a fast filtration through a short pad of silica gel to remove traces of the catalyst permited the obtention of almost pure trifluoromethyl ketones **5**.

Table 1. Synthesis of α-trifluoromethyl-α-hydroxyesters **3** from **2**, and oxidative decarboxylation of the corresponding α-trifluoromethyl-α-hydroxy acids **4** to trifluoromethyl ketones **5**

Entry	R	Yield (%) (**3**)	Yield (%) (**5**)[a]
a		83	87
b		80	85
c		80	85
d		90	86
e		87	90
f		94	–[b]
g		97	95
h		79	81
i		65	82
j	$CH_3(CH_2)_9-$	85	85
k	$H_2C{=}CH-(CH_2)_9-$	80	80
l	MEM–O–$(CH_2)_{11}-$	45	80
m[c]	HO–$(CH_2)_{11}-$	–	85

Hydrolysis of compounds **3** to **4** were almost quantitative.
[a] Starting from **4**.
[b] Complex reaction mixture.
[c] Hydroxyester **3m** was prepared from **3l**.

The results for the oxidative decarboxylation of α-hydroxy acids **4** are shown in Table 1. The decarboxylation of aromatic acids **4** was complete in 4–5 h and the yields of aromatic trifluoromethyl ketones ranged from 85 to 90% (entries a–e). Aliphatic acids required some longer reaction times (7 h) and the yields of aliphatic trifluoromethyl ketones were slightly lower ranging from 80 to 85% (entries g–m), except in the case of compound **5g** which was obtained in 95%. It is remarkable that in this case no products arising from benzylic oxidation were obtained. In contrast decarboxylation of compound **4f** gave rise to the formation of a complex reaction mixture because of benzylic oxidation of the resulting benzyl trifluoromethyl ketone. In this compound the benzyl carbon is doubly activated toward oxidation by the phenyl and the trifluoroacetyl groups. Despite this result, the oxidative decarboxylation was shown to be compatible with other potentially oxidisable groups in the molecule. Thus, selective decarboxylation could be achieved in the presence of a triple bond (entry h) allowing the preparation of ketone **5h** in 81% yield. It is worth remarking that the preparation of this compound by TBAF catalysed addition of $TMSCF_3$ to methyl phenylpropynoate[8c] fails because of extensive polymerisation under the reaction conditions. The reaction could also be achieved in the presence of a double bond with less than 5% of epoxidation of the double bond after stirring the reaction mixture overnight at room temperature (entry k). The reaction was also successful in the presence of a hydroxyl group either protected as a MEM group (entry l) or free (entry m).

In summary, we have developed a procedure for the oxidative decarboxylation of α-trifluoromethyl-α-hydroxy acids to trifluoromethyl ketones with oxygen in the presence of pivalaldehyde and a cobalt(III) complex **1**, under mild conditions. The procedure is also compatible with the presence of other oxidisable groups.

3. Experimental

3.1. General

Solutions of Grignard reagents **2a**–**2c**, **2f**–**2j** (X=Cl) were commercially available, while solutions of **2d**, **2e**, **2k** and **2l**

(X=Br) in THF–toluene were prepared from the corresponding bromides and magnesium following the entrainment procedure with I_2–dibromoethane.[10] IR were recorded as liquid film in NaCl for oils and as KBr discs for solids. NMR were run at 300 MHz for ^1H and 75 MHz for ^{13}C using the solvent as internal standard, and at 282 MHz for ^{19}F NMR using $CFCl_3$ as internal standard. The carbon type was determined by DEPT experiments. Mass spectra were run by electron impact at 70 eV or by chemical ionisation using methane as ionising gas. Complex **1** was prepared according to our procedure.[2a]

3.2. Synthesis of α-trifluoromethyl-α-hydroxyesters 3

A solution of the Grignard reagent (6.45 mmol) was added dropwise to a solution of ethyl trifluoropyruvate (1 g, 5.87 mmol) in dry THF (13 mL) at −78°C under argon. After 1 h at this temperature, the reaction was quenched with 2 M HCl (3.5 mL) and water (100 mL), extracted with CH_2Cl_2 (5×50 mL) and washed with brine (2×50 mL). The organic layer was dried with $MgSO_4$, concentrated under reduced pressure and chromatographed on silica gel.

3.2.1. Ethyl 3,3,3-trifluoro-2-hydroxy-2-phenylpropanoate (3a). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.208 g (83%) of **3a**.[9]

3.2.2. Ethyl 2-(*p*-chlorophenyl)-3,3,3-trifluoro-2-hydroxypropanoate (3b). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.324 g (80%) of **3b**: oil; IR (NaCl) ν 3483, 1740 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 7.73 (2H, d, J=7.1 Hz), 7.36 (2H, d, J=7.1 Hz), 4.41 (2H, m), 4.35 (1H, s), 1.36 (3H, t, J=7.5 Hz); ^{13}C NMR (δ, $CDCl_3$) 168.5 (C), 135.8 (C), 131.2 (C), 128.3 (CH), 128.2 (CH), 122.8 (CF_3, q, $^1J_{C-F}$=284 Hz), 77.4 (C, q, $^2J_{C-F}$=30 Hz), 64.6 (CH_2), 13.9 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −76.6 (s); MS (EI) m/z 284, 282 (M^+, 10, 30), 211 (58), 209 (100), 141 (43), 139 (93); HRMS 282.0262, $C_{11}H_{10}ClF_3O_3$ required 282.0271.

3.2.3. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(*p*-methoxyphenyl)propanoate (3c). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.305 g (80%) of **3c**: oil; IR (NaCl) ν 3480, 1741 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 7.69 (2H, d, J=6.5 Hz), 6.90 (2H, d, J=6.5 Hz), 4.38 (2H, m), 4.32 (1H, s), 3.80 (3H, s), 1.35 (3H, t, J=7.0 Hz); ^{13}C NMR (δ, $CDCl_3$) 169.1 (C), 160.4 (C), 128.1 (CH), 124.8 (C), 123.1 (CF_3, q, $^1J_{C-F}$=284 Hz), 113.7 (CH), 77.4 (C, q, J_{C-F}=30 Hz), 64.2 (CH_2), 55.22 (CH_3), 13.8 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −77.2 (s); MS (EI) m/z 278 (M^+, 36), 205 (85), 135 (100); HRMS 278.0771, $C_{12}H_{13}F_3O_4$ required 278.0766.

3.2.4. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-naphthyl)propanoate (3d). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.574 g (90%) of **3d**: mp 47–50°C (hexane–EtOAc); IR (KBr) ν 3472, 1741 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 8.13 (1H, m), 7.89 (1H, d, J=8.0 Hz), 7.85 (1H, m), 7.78 (1H, m), 7.46 (3H, m), 4.49 (1H, s, OH), 4.32 (1H, m), 4.19 (1H, m), 1.08 (3H, t, J=7.0 Hz); ^{13}C NMR (δ, $CDCl_3$) 170.4 (C), 134.4 (C), 130.9 (C), 130.7 (CH), 129.2 (CH), 128.5 (C), 126.1 (CH, q, $^3J_{C-F}$=3.3 Hz), 125.8 (CH), 125.1 (CF_3, q, $^1J_{C-F}$=283 Hz), 124.5 (CH), 124.2 (CH), 79.9 (C, q, $^2J_{C-F}$=29 Hz), 64.2 (CH_2), 13.6 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −73.2 (s); MS (EI) m/z 298 (M^+, 40), 225 (100), 155 (40); HRMS 298.08165, $C_{15}H_{13}F_3O_3$ required 298.0817.

3.2.5. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-naphthyl)propanoate (3e). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.520 g (87%) of **3e**: mp 40–42°C (hexane–EtOAc); IR (KBr) ν 3483, 1739 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 8.32 (1H, s), 7.80–7.95 (4H, m), 7.57–7.46 (2H, m), 4.49 (1H, s, OH), 4.44 (2H, qq, J=7.2, 3.6 Hz), 1.38 (3H, t, J=7.2 Hz); ^{13}C NMR (δ, $CDCl_3$) 168.9 (C), 133.5 (C), 132.7 (C), 130.1 (C), 128.6 (CH), 127.5 (CH), 127.1 (CH), 126.9 (CH, q, $^3J_{C-F}$=0.8 Hz), 126.5 (CH), 123.6 (CH, q, $^3J_{C-F}$=1.7 Hz), 123.5 (CF_3, q, $^1J_{C-F}$=284 Hz), 77.9 (C, q, $^2J_{C-F}$=30 Hz), 64.5 (CH_2), 13.9 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −76.4 (s); MS (EI) m/z 298 (M^+, 41), 225 (100), 155 (50), 128 (57); HRMS 298.0812, $C_{15}H_{13}F_3O_3$ required 298.0817.

3.2.6. Ethyl 2-hydroxy-3-phenyl-2-trifluoromethylpropanoate (3f). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.446 g (94%) of **3f**: oil; IR (NaCl) ν 3490, 1740 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 7.20 (5H, br s), 4.23 (2H, m), 3.81 (1H, s, OH), 3.26 (1H, d, J=13.7 Hz), 3.16 (1H, d, J=13.7 Hz), 1.27 (3H, t, J=7.2 Hz); ^{13}C NMR (δ, $CDCl_3$) 168.8 (C), 132.9 (C), 130.4 (CH), 128.2 (CH), 127.5 (CH), 123.4 (CF_3, q, $^1J_{C-F}$=284 Hz), 78.1 (C, q, $^2J_{C-F}$=29 Hz), 63.7 (CH_2), 37.5 (CH_2), 13.8 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −78.8 (s); MS (EI) m/z 262 (M^+, 1), 244 (25), 141 (12), 91 (100); HRMS 262.0803, $C_{12}H_{13}F_3O_3$ required 262.0817.

3.2.7. Ethyl 2-hydroxy-4-phenyl-2-trifluoromethylbutanoate (3g). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.570 g (97%) of **3g**: oil; IR (NaCl) ν 3490, 1745 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 7.20 (2H, t, J=7.5 Hz), 7.10 (3H, m), 4.17 (2H, m), 3.91 (1H, d, J=1.3 Hz, OH), 2.77 (1H, td, J=11.7, 5.0 Hz), 2.50–2.00 (3H, m), 1.32 (3H, t, J=7.1 Hz); ^{13}C NMR (δ, $CDCl_3$) 169.7 (C), 140.1 (C), 128.5 (CH), 126.3 (CH), 123.4 (CF_3, q, $^1J_{C-F}$=284 Hz), 77.6 (C, q, $^2J_{C-F}$=29 Hz), 63.8 (CH_2), 33.1 (CH_2), 28.7 (CH_2), 13.9 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −78.9 (s); MS (EI) m/z 276 (M^+, 30), 172 (100), 144 (67); HRMS 276.0975, $C_{13}H_{15}F_3O_3$ required 276.0973.

3.2.8. Ethyl 2-hydroxy-4-phenyl-2-trifluoromethyl-3-butynoate (3h). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.262 g (79%) of **3h**: oil; IR (NaCl) ν 3472, 2336, 1751 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 7.49 (2H, d, J=7.5 Hz), 7.34 (3H, m), 4.47 (2H, m), 4.27 (1H, s, OH), 1.39 (3H, t, J=7.1 Hz); ^{13}C NMR (δ, $CDCl_3$) 166.5 (C), 132.1 (CH), 129.6 (CH), 128.4 (CH), 121.5 (CF_3, q, $^1J_{C-F}$=285 Hz), 120.6 (C), 87.1 (C), 79.6 (C), 71.7 (C, $^2J_{C-F}$=33 Hz), 65.0 (CH_2), 13.8 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −78.7; MS (EI) m/z 272 (M^+, 16), 199 (100), 129 (78); HRMS 272.0662, $C_{15}H_{11}F_3O_3$ required 272.0660.

3.2.9. Ethyl 2-cyclohexyl-3,3,3-trifluoro-2-hydroxypropanoate (3i). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 970 mg (65%) of **3i**: oil; IR (NaCl) ν 3499, 1742 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.31 (2H, m), 3.72 (1H, s, OH), 2.04 (1H, br t, J=8 Hz), 1.95–1.55 (5H, m),

1.31 (3H, t, J=6.0 Hz), 1.40–1.00 (6H, m); ^{13}C NMR (δ, $CDCl_3$) 170.5 (C), 123.6 (CF_3, q, $^1J_{C-F}$=286 Hz), 80.3 (C, q, $^2J_{C-F}$=28 Hz), 63.7 (CH_2), 40.3 (CH), 26.2 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 23.8 (CH_2), 13.9 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −73.4 (s); MS (CI) m/z 255 (M^++1, 63), 217 (24), 183 (100); HRMS 255.1198, $C_{11}H_{18}F_3O_3$ required 255.1208.

3.2.10. Ethyl 2-hydroxy-2-trifluoromethyldodecanoate (3j). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.556 g (85%) of **3j**: oil; IR (NaCl) ν 3509, 1741 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 4.36 (2H, m), 3.79 (1H, s), 1.91 (2H, m), 1.23 (18H, m), 0.86 (3H, t, J=4.8 Hz); ^{13}C NMR (δ, $CDCl_3$) 170.0 (C), 123.5 (CF_3, q, $^1J_{C-F}$=284 Hz), 77.4 (C, q, $^2J_{C-F}$=30 Hz), 63.7 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.7 (CH_2), 22.4 (CH_2), 14.1 (CH_3), 13.9 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −79.2 (s); MS (CI) m/z 313 (M^++1, 100), 246 (66), 172 (34); HRMS 313.2003, $C_{15}H_{28}F_3O_3$ required 313.1991.

3.2.11. Ethyl 2-hydroxy-2-trifluoromethyl-12-tridecenoate (3k). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.521 g (80%) of **3k**: oil; IR (NaCl) ν 3490, 1740 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 5.78 (1H, ddq, J=6.8, 10.2, 16.5 Hz), 5.1–4.8 (2H, m), 4.34 (2H, qq, J=7.0, 1.5 Hz), 3.80 (1H, s, OH), 1.98 (2H, m), 1.81 (1H, td, J=12.5, 4.5 Hz), 1.60–0.80 (15H, m), 1.32 (3H, t, J=7.0 Hz); ^{13}C NMR (δ, $CDCl_3$) 170.0 (C), 139.2 (CH), 123.5 (CF_3, q, $^1J_{C-F}$=285 Hz), 114.1 (CH_2), 77.7 (C, q, $^2J_{C-F}$=29 Hz), 63.7 (CH_2), 33.8 (CH_2), 31.3 (CH_2), 29.4 (CH_2), 29.3 (2CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 22.3 (CH_2), 13.9 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −79.1 (s); MS (EI) m/z 324 (M^+, 4), 306 (2), 286 (10), 172 (34); HRMS 324.1908, $C_{16}H_{27}F_3O_3$ required 324.1908.

3.2.12. Ethyl 2-hydroxy-13-methoxyethoxymethoxy-2-trifluoromethyltridecanoate (3l). From 1 g (5.87 mmol) of ethyl trifluoropyruvate was obtained 1.136 g (45%) of **3l**: oil; IR (NaCl) ν 3490, 1747 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 4.67 (2H, s), 4.31 (2H, qd, J=7.2, 1.4 Hz), 3.84 (1H, br s, OH), 3.65 (1H, dd, J=6.5, 4.3 Hz), 3.52 (2H, t, J=6.5 Hz), 3.51 (1H, dd, J=6.5, 4.3 Hz), 3.36 (3H, s), 1.93 (1H, td, J=12.1, 4.7 Hz), 1.79 (1H, td, J=12.1, 4.7 Hz), 1.62–0.90 (18H, m), 1.28 (3H, t, J=7.2 Hz); ^{13}C NMR (δ, $CDCl_3$) 169.9 (C), 123.5 (CF_3, q, $^1J_{C-F}$=285 Hz), 95.4 (CH_2), 77.6 (C, q, $^2J_{C-F}$=29 Hz), 71.8 (CH_2), 67.9 (CH_2), 66.6 (CH_2), 63.6 (CH_2), 58.9 (CH_3), 31.3 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (2 CH_2), 29.3 (CH_2), 29.2 (2 CH_2), 26.1 (CH_2), 22.3 (CH_2), 13.9 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −78.9 (s); MS (EI) m/z 429 (M^+−1, 10), 371 (21), 355 (34), 3441 (32), 325 (100); HRMS 429.2463, $C_{20}H_{36}F_3O_6$ required 429.2464.

3.2.13. Ethyl 2,3-dihydroxy-2-trifluoromethyltridecanoate (3m). A solution of compound **3l** (200 mg, 0.49 mmol) in dry CH_2Cl_2 at 0°C under argon was treated with a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.98 mL, 0.98 mmol). The mixture was stirred at this temperature for 6 h. Then 10% NH_4OH was added, and the mixture was extracted with CH_2Cl_2, washed with brine and dried. Evaporation of the solvent followed by column chromatography (hexane–EtOAc 6:4) afforded 98 mg (60%) of compound **3m**: mp 63–64°C (hexane–EtOAc); IR (KBr) ν 3475, 3206, 1752 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 4.31 (2H, qd, J=7.1, 1.0 Hz), 3.58 (2H, t, J=6.8 Hz), 2.80 (1H, br s, OH), 1.93 (1H, td, J=12.0, 4.5 Hz), 1.80 (1H, td, J=12.0, 4.5 Hz), 1.55–0.90 (18H, m), 1.29 (3H, t, J=7.1 Hz); ^{13}C NMR (δ, $CDCl_3$) 169.9 (C), 123.5 (CF_3, q, $^1J_{C-F}$=285 Hz), 77.7 (C, q, $^2J_{C-F}$=29 Hz), 63.6 (CH_2), 62.9 (CH_2), 32.6 (CH_2), 31.4 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (2 CH_2), 29.2 (2 CH_2), 25.6 (CH_2), 22.3 (CH_2), 13.9 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −79.3 (s); MS (EI) m/z 343 (M^++1, 3), 312 (17), 276 (34), 258 (34), 172 (100); HRMS 343.2096, $C_{16}H_{30}F_3O_4$ required 343.2096.

3.3. Synthesis of α-trifluoromethyl-α-hydroxy acids 4

The α-trifluoromethyl-α-hydroxyesters **3** (1 mmol) was treated with 5% ethanolic KOH (2.5 mL, 2 mmol) at room temperature until complete reaction of the starting material (TLC). The solution was poured into ice and acidified with 1 M HCl until pH ≈2. The aqueous mixture was extracted with EtOAc (3×60 mL), the organic layers were washed with brine until neutrality was reached, dried, filtered and concentrated under reduced pressure to give the α-trifluoromethyl-α-hydroxyacids **4**.

3.3.1. 3,3,3-Trifluoro-2-hydroxy-2-phenylpropanoic acid (4a). From 1 g (4.03 mmol) of **3a** was obtained 869 mg (98%) of **4a**.[11]

3.3.2. 2-(*p*-Chlorophenyl)-3,3,3-trifluoro-2-hydroxypropanoic acid (4b). From 1 g (3.54 mmol) of **3b** was obtained 880 mg (98%) of **4b**: mp 94–96°C (EtOH); IR (KBr) ν 3463, 3500–2400, 1740 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.74 (2H, d, J=8.6 Hz), 7.38 (2H, d, J=8.6 Hz), 6.5 (2H, br s); ^{13}C NMR (δ, $CDCl_3$) 172.0 (C), 136.3 (C), 130.5 (C), 128.8 (CH), 128.3 (CH), 122.8 (CF_3, q, $^1J_{C-F}$=284 Hz), 77.6 (C, q, $^2J_{C-F}$=30 Hz); ^{19}F NMR (δ, $CDCl_3$) −76.6 (s); MS (EI) m/z 256, 254 (M^+, 7, 20), 211 (25), 209 (83), 141 (35), 139 (100); HRMS 253.9959, $C_9H_6ClF_3O_3$ required 253.9958.

3.3.3. 3,3,3-Trifluoro-2-hydroxy-2-(*p*-methoxyphenyl)-propanoic acid (4c). From 1 g (3.59 mmol) of **3c** was obtained 900 mg (100%) of **4c**: mp 114–116°C (EtOH); IR (KBr) ν 3495, 3500–2400, 1734 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 7.70 (2H, d, J=6.8 Hz), 6.91 (2H, d, J=6.8 Hz), 5.82 (2H, br s), 3.81 (3H, s); ^{13}C NMR (δ, $CDCl_3$) 172.1 (C), 160.5 (C), 128.1 (CH, C overlaped), 122.9 (CF_3, q, $^1J_{C-F}$=284 Hz), 124.2 (C), 113.9 (CH), 77.6 (C, q, $^2J_{C-F}$=30 Hz), 55.3 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −76.9 (s); MS (EI) m/z 250 (M^+, 68), 205 (100), 135 (65); HRMS 250.0457, $C_{10}H_9F_3O_4$ required 250.0453.

3.3.4. 3,3,3-Trifluoro-2-hydroxy-2-(1-naphthyl)propanoic acid (4d). From 1 g (3.36 mmol) of **3d** was obtained 905 mg (100%) of **4d**: mp 93–95°C (EtOH); IR (KBr) 3500–2400, 1736; ^{1}H NMR (δ, d_6-DMSO) 8.19 (1H, m), 8.00 (1H, d, J=8.5 Hz), 7.98 (1H, m), 7.83 (1H, d, J=7.4 Hz), 7.6–7.4 (3H, m); ^{13}C NMR (δ, d_6-DMSO) 170.3 (C), 134.2 (C), 131.4 (C), 130.9 (C), 130.3 (CH), 129.2 (CH), 126.5 (CH), 126.1 (CH, q, $^3J_{C-F}$=3.4 Hz), 125.9 (CH), 125.1 (CH, q, $^3J_{C-F}$=3.0 Hz), 124.6 (CH, q, $^1J_{C-F}$=280 Hz), 79.5 (C, q, $^2J_{C-F}$=27 Hz); ^{19}F NMR (δ, d_6-DMSO) −72.5 (s); MS (EI) m/z 270 (M^+, 70), 225 (100), 155 (77), 128 (93); HRMS 270.0514, $C_{13}H_9F_3O_3$ required 270.0504.

3.3.5. 3,3,3-Trifluoro-2-hydroxy-2-(2-naphthyl)propanoic acid (4e). From 1 g (3.36 mmol) of **3e** was obtained 900 mg (99%) of **4e**: mp 164–166°C (EtOH); IR (KBr) ν 3410, 3500–2400, 1740 cm^{-1}; ^1H NMR (δ, d_6-DMSO) 8.22 (1H, s), 8.02–7.89 (3H, m), 7.76 (1H, d, J=8.7 Hz), 7.60–7.50 (2H, m); ^{13}C NMR (δ, d_6-DMSO) 169.6 (C), 133.3 (C), 132.6 (C), 132.5 (C), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.3 (CH), 127.0 (CH), 126.3 (CH), 124.3 (CH, q, $^1J_{C-F}$=284 Hz), 124.0 (CH), 78.3 (C, q, $^2J_{C-F}$=28 Hz); ^{19}F NMR (δ, d_6-DMSO) −74.6 (s); MS (EI) *m/z* 270 (M^+, 75), 225 (100), 155 (88), 128 (70); HRMS 270.0514, $C_{13}H_9F_3O_3$ required 270.0504.

3.3.6. 2-Hydroxy-3-phenyl-2-trifluoromethylpropanoic acid (4f). From 1 g (3.82 mmol) of **3f** was obtained 875 mg (98%) of **4f**: mp 118–120°C (EtOH); IR (KBr) ν 3437, 3411, 3400–2800, 1747 cm^{-1}; ^1H NMR (δ, d_6-DMSO) 7.27 (5H, br s), 3.20 (1H, d, J=13.5 Hz), 3.01 (1H, d, J=13.5 Hz); ^{13}C NMR (δ, d_6-DMSO) 169.4 (C), 134.3 (C), 130.8 (CH), 128.2 (CH), 127.2 (CH), 127.8 (CF_3, q, $^1J_{C-F}$=286 Hz), 78.0 (C, q, $^2J_{C-F}$=26 Hz), 38.1 (CH_2); ^{19}F NMR (δ, d_6-DMSO) −76.1 (s); MS (EI) *m/z* 234 (M^+, 6), 216 (11), 91 (100); HRMS 234.0510, $C_{10}H_9F_3O_3$ required 234.0504.

3.3.7. 2-Hydroxy-4-phenyl-2-trifluoromethylbutanoic acid (4g). From 1 g (3.62 mmol) of **3g** was obtained 895 mg (100%) of **4g**: mp 105–106°C (EtOH); IR (KBr) ν 3431, 3500–2800, 1750 cm^{-1}; ^1H NMR (δ, d_6-DMSO) 7.29 (1H, d, J=8.1 Hz), 7.26 (1H, d, J=8.1 Hz), 7.20–7.10 (3H, m), 2.77 (1H, td, J=12.9, 4.5 Hz), 2.45 (1H, td, J=12.9, 4.5 Hz), 2.16 (1H, td, J=12.9, 4.5 Hz), 1.96 (1H, td, J=12.9, 4.5 Hz); ^{13}C NMR (δ, d_6-DMSO) 169.9 (C), 141.0 (C), 128.8 (CH), 128.6 (CH), 126.4 (CH), 124.8 (CF_3, q, J_{C-F}=285 Hz), 77.1 (C, q, J_{C-F}=27 Hz), 34.7 (CH_2), 28.9 (CH_2); ^{19}F NMR (δ, d_6-DMSO) −76.3; MS (EI) *m/z* 248 (M^+, 26), 202 (3), 144 (14), 105 (100), 91 (82); HRMS 248.0659, $C_{11}H_{11}F_3O_3$ required 248.0660.

3.3.8. 2-Hydroxy-4-phenyl-2-trifluoromethyl-3-butynoic acid (4h). From 950 mg (3.49 mmol) of **3h** was obtained 827 mg (97%) of **4h**: mp 96–98°C (EtOH); IR (KBr) ν 3406, 3073, 2244, 1759 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 7.49 (2H, dd, J=8.1, 1.5 Hz), 7.42–7.24 (3H, m), 5.57 (1H, br s, OH); ^{13}C NMR (δ, $CDCl_3$) 168.6 (C), 132.2 (CH), 129.8 (CH), 128.4 (CH), 121.6 (CF_3, q, $^1J_{C-F}$=285 Hz), 120.3 (C), 87.9 (C), 79.0 (C), 71.6 (C, q, $^2J_{C-F}$=33 Hz); ^{19}F NMR (δ, $CDCl_3$) −78.6 (s); MS (EI) *m/z* 244 (M^+, 21), 199 (43), 182 (60), 129 (100); HRMS 244.0350, $C_{11}H_7F_3O_3$ required 244.0347.

3.3.9. 2-Cyclohexyl-3,3,3-trifluoro-2-hydroxypropanoic acid (4i). From 800 mg (3.15 mmol) of **3i** was obtained 695 mg (98%) of **4i**: mp 109–111°C (EtOH); IR (KBr) ν 3434, 3500–2800, 1747 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 2.12 (1H, tt, J=11.0, 2.0 Hz), 2.00–1.00 (10H, m); ^{13}C NMR (δ, $CDCl_3$) 174.5 (C), 123.3 (CF_3, $^1J_{C-F}$=287 Hz), 80.7 (C, q, $^2J_{C-F}$=28 Hz), 40.4 (CH), 26.3 (CH_2), 25.8 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 25.4 (CH_2); ^{19}F NMR (δ, $CDCl_3$) −73.4 (s); MS (EI) *m/z* 226 (M^+, 0.2), 181 (3), 144 (16), 83 (100); HRMS 226.0810, $C_9H_{13}F_3O_3$ required 226.0817.

3.3.10. 2-Hydroxy-2-trifluoromethyldodecanoic acid (4j). From 1 g (3.20 mmol) of **3j** was obtained 892 mg (98%) of **4j**: mp 80–82°C (EtOH), IR (KBr) ν 3509, 1741 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 2.02 (1H, td, J=9.0, 2.6 Hz), 1.90 (1H, td, J=9.0, 3.3 Hz), 1.54 (1H, m), 1.24 (15H, m), 0.86 (3H, t, J=5.3 Hz); ^{13}C NMR (δ, $CDCl_3$) 173.7 (C), 123.3 (CF_3, q, $^1J_{C-F}$=284 Hz), 77.9 (C, q, $^2J_{C-F}$=28 Hz), 31.9 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.7 (CH_2), 22.4 (CH_2), 14.1 (CH_3); ^{19}F NMR (δ, $CDCl_3$) −79.0 (s); MS (CI) *m/z* 285 (M^++1, 0.1), 246 (100), 199 (66); HRMS 285.1674, $C_{13}H_{24}F_3O_3$ required 285.1678.

3.3.11. 2-Hydroxy-2-trifluoromethyl-12-tridecenoic acid (4k). From 1 g (3.09 mmol) of **3a** was obtained 890 mg (98%) of **4k**: mp 78–79°C (EtOH); IR (KBr) ν 3520, 3500–2800, 1740 cm^{-1}; ^1H NMR (δ, d_6-DMSO) 5.77 (1H, ddq, J=6.7, 10.3, 16.5 Hz), 4.96 (1H, br d, J=16.5 Hz), 4.91 (1H, br d, J=10.3 Hz), 1.99 (2H, q, J=6.8 Hz), 1.84 (1H, td, J=12.5, 4.4 Hz), 164 (1H, td, J=12.5, 4.4 Hz), 1.50–1.10 (14H, m); ^{13}C NMR (δ, d_6-DMSO) 169.9 (C), 138.9 (CH), 124.5 (CF_3, q, $^1J_{C-F}$=280 Hz), 114.6 (CH_2), 77.0 (C, q, $^2J_{C-F}$=27 Hz), 33.3 (CH_2), 32.3 (CH_2), 28.9 (CH_2), 28.8 (2 CH_2), 28.6 (CH_2), 28.3 (CH_2), 22.3 (CH_2), 13.9 (CH_3); ^{19}F NMR (δ, d_6-DMSO) −76.4 (s); MS (EI) *m/z* 255 ($M^+-C_3H_5$, 1), 200 (37), 55 (100); HRMS 255.1112, $C_{11}H_{18}F_3O_3$ required 255.1103.

3.3.12. 2-Hydroxy-13-methoxyethoxymethoxy-2-trifluoromethyltridecanoic acid (4l). From 1 g (2.33 mmol) of **3l** was obtained 895 mg (96%) of **4l**: mp 42–44°C (EtOH); IR (KBr) ν 3396, 1742 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.69 (2H, s), 3.68 (1H, dd, J=6.6, 3.9 Hz), 3.58 (1H, dd, J=6.6, 3.9 Hz), 3.53 (2H, t, J=6.6 Hz), 3.38 (3H, s), 1.96 (1H, td, J=12.6, 3.8 Hz), 1.80 (1H, td, J=12.6, 3.8 Hz), 1.62–1.00 (18H, m); ^{13}C NMR (δ, $CDCl_3$) 171.4 (C), 123.6 (CF_3, q, $^1J_{C-F}$=285 Hz), 95.1 (CH_2), 77.5 (C, q, $^2J_{C-F}$=29 Hz), 71.6 (CH_2), 68.2 (CH_2), 66.5 (CH_2), 58.7 (CH_3), 31.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 25.9 (CH_2), 22.3 (CH_2); ^{19}F NMR (δ, $CDCl_3$) −79.2 (s); MS (EI) *m/z* 401 (M^++1, 1), 343 (19), 313 (44), 251 (67), 59 (100); HRMS 401.2146, $C_{18}H_{32}F_3O_6$ required 401.2151.

3.3.13. 2,13-Dihydroxy-2-trifluoromethyltridecanoic acid (4m). From 200 mg (0.58 mmol) of **3m** was obtained 182 mg (99%) of **4m**: mp 74–76°C (EtOH); IR (KBr) ν 3446, 1741 cm^{-1}; ^1H NMR (δ, d_6-DMSO) 3.69 (1H, t, J=6.4 Hz), 1.85 (1H, td, J=12.4, 4.5 Hz), 1.60 (1H, td, J=12.4, 4.5 Hz), 1.50–1.00 (18H, m); ^{13}C NMR (δ, d_6-DMSO) 170.1 (C), 124.8 (CF_3, q, $^1J_{C-F}$=284 Hz), 77.2 (C, q, $^2J_{C-F}$=27 Hz), 60.9 (CH_2), 32.8 (CH_2), 32.5 (CH_2), 29.3 (CH_2), 29.2 (2 CH_2), 29.1 (CH_2), 29.0 (2 CH_2), 25.7 (CH_2), 22.5 (CH_2); ^{19}F NMR (δ, $CDCl_3$) −76.3 (s); MS (EI) *m/z* 313 (M^+-1, 5), 258 (28), 97 (48), 69 (80), 55 (100); HRMS 313.1638, $C_{14}H_{24}F_3O_4$ required 313.1627.

3.4. Synthesis of trifluoromethylketones

Pivalaldehyde (75 μL, 0.69 mmol) was added to a solution of Co(III) complex **1** (7.5 mg, 0.016 mmol) in 1.5 mL of CH_2Cl_2. After 5 min of stirring under an O_2 atmosphere, hydroxy acid **4** (0.35 mmol) was added all at once. The mixture was stirred at room temperature under O_2 until

consumption of the starting α-hydroxy acid as indicated by TLC. Stirring was continued overnight to ensure total oxidation of the excess pivalaldehyde. The reaction mixture was diluted with CH_2Cl_2, washed with $NaHCO_3$ (2×5 mL) and brine (5 mL), and dried with $MgSO_4$. After filtration, the solvent volume was reduced to ca. 2 mL in the rotavapor and filtered through a short pad of silica gel (1 cm). The pad of silica gel was washed with 5 mL of CH_2Cl_2 and the filtrates were concentrated under reduced pressure to give trifluoromethylketones **5**.

3.4.1. Phenyl trifluoromethyl ketone (5a). From 77 mg (0.35 mmol) of **4a** was obtained 53 mg (87%) of **5a**.[8a,d,k]

3.4.2. *p*-Chlorophenyl trifluoromethyl ketone (5b). From 89 mg (0.35 mmol) of **4b** was obtained 62 mg (85%) of **5b**.[12]

3.4.3. *p*-Methoxyphenyl trifluoromethyl ketone (5c). From 88 mg (0.35 mmol) of **4c** was obtained 60 mg (85%) of **5c**.[8a,h,k,12]

3.4.4. 1-Naphthyl trifluoromethyl ketone (5d). From 95 mg (0.35 mmol) of **4d** was obtained 67 mg (86%) of **5d**.[8a,h,k]

3.4.5. 2-Naphthyl trifluoromethyl ketone (5e). From 95 mg (0.35 mmol) of **4e** was obtained 70 mg (90%) of **5e**.[8k]

3.4.6. 1,1,1-Trifluoro-4-phenyl-2-butanone (5g). From 87 mg (0.35 mmol) of **4g** was obtained 67 mg (95%) of **5g**.[8j]

3.4.7. 1,1,1-Trifluoro-4-phenyl-3-butyn-2-one (5h). From 85 mg (0.35 mmol) of **4h** was obtained 56 mg (81%) of **5h**.[8d,j]

3.4.8. Cyclohexyl trifluoromethyl ketone (5i). From 79 mg (0.35 mmol) of **4i** was obtained 52 mg (82%) of **5i**.[8a,d]

3.4.9. 1,1,1-Trifluoro-2-dodecanone (5j). From 99 mg (0.35 mmol) of **4j** was obtained 71 mg (85%) of **5j**.[8h,12]

3.4.10. 1,1,1-Trifluoro-12-tridecen-2-one (5k). From 103 mg (0.35 mmol) of **4k** was obtained 66 mg (80%) of **5k**: oil; IR (NaCl) ν 1765 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.78 (1H, ddq, J=16.5, 10.2, 6.8 Hz), 4.96 (1H, ddd, J=16.5, 3.5, 1.7 Hz), 4.89 (1H, ddd, J=10.2, 3.5, 1.7 Hz), 2.68 (2H, t, J=7.1 Hz), 2.00 (2H, q, J=7.1 Hz), 1.64 (2H, q, J=7.1 Hz), 1.40–1.10 (12H, m); ^{13}C NMR (δ, $CDCl_3$) 191.6 (C, q, $^2J_{C-F}$=34 Hz), 139.1 (CH), 115.6 (CF_3, q, $^1J_{C-F}$=290 Hz), 114.1 (CH_2), 36.3 (CH_2), 33.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 22.3 (CH_2); ^{19}F NMR (δ, $CDCl_3$) −79.8 (s); MS (EI) *m/z* 250 (M^+, 10), 232 (2), 221 (5), 207 (7), 55 (100); HRMS 250.1544, $C_{13}H_{21}F_3O$ required 250.1545.

3.4.11. 1,1,1-Trifluoro-13-methoxyethoxymethoxy-2-tridecanone (5l). From 140 mg (0.35 mmol) of **4l** was obtained 99 mg (80%) of **5l**: oil; IR (NaCl) ν 1765 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.66 (2H, s), 3.64 (1H, dd, J=6.5, 4.3 Hz), 3.50 (3H, m), 3.34 (3H, s), 1.61 (2H, m, J=7.0 Hz), 1.53 (2H, m, J=7.1 Hz), 1.30–1.10 (12H, m); ^{13}C NMR (δ, $CDCl_3$) 191.6 (C, q, $^2J_{C-F}$=34 Hz), 115.5 (CF_3, q, $^1J_{C-F}$=290 Hz), 95.4 (CH_2), 71.7 (CH_2), 67.9 (CH_2), 66.6 (CH_2), 58.9 (CH_3), 36.3 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (2 CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.2 (CH_2), 22.3 (CH_2); ^{19}F NMR (δ, $CDCl_3$) −79.8 (s); MS (EI) *m/z* 356 (M^+, 1), 325 (5), 281 (50), 251 (54), 89 (95), 59 (100); HRMS 356.2183, $C_{17}H_{31}F_3O_4$ required 356.2174.

3.4.12. 1,1,1-Trifluoro-13-hydroxy-2-tridecanone (5m). From 100 mg (0.32 mmol) of **4m** was obtained 72 mg (85%) of **5m**: oil; IR (NaCl) ν 3440, 1760 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 3.61 (2H, t, J=6.6), 2.68 (2H, t, J=7.2 Hz), 1.64 (2H, m, J=7.4 Hz), 1.54 (2H, q, J=7.4 Hz), 1.40–1.10 (12H, m); ^{13}C NMR (δ, $CDCl_3$) 191.6 (C, q, $^2J_{C-F}$=34 Hz), 115.5 (CF_3, q, $^1J_{C-F}$=290 Hz), 63.0 (CH_2), 36.3 (CH_2), 32.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 26.3 (CH_2), 22.3 (CH_2); ^{19}F NMR (δ, $CDCl_3$) −79.6 (s); MS (EI) *m/z* 250 (M^+−18, 1), 138 (15), 110 (26), 82 (42), 69 (70), 55 (100); HRMS 250.1552, $C_{13}H_{21}OF_3$ 250.1545.

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