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Cobalt-Catalyzed Alkoxycarbonylation of Epoxides to β-Hydroxyesters

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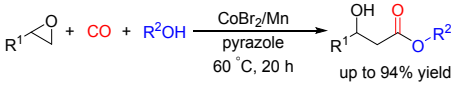
Supporting Information Placeholder



Cheap, air-stable Co(II) salts as pre-catalyst

ABSTRACT: Herein, we developed a new and practical catalytic system for the carbonylative synthesis of β-hydroxyesters. By using simple, cheap and air-stable cobalt(II) bromide as the catalyst, combined with pyrazole and catalytic amount of manganese, active cobalt complex can be generated in-situ and catalyze various epoxides to give the corresponding β-hydroxyesters in moderate to excellent yields. Mechanism studies indicate that pyrazole plays a crucial role in this reaction. Moreover, with the addition of catalytic amount of manganese, the active cobalt catalyst can be regenerated, which provide a possibility for reusing of the cobalt catalyst.

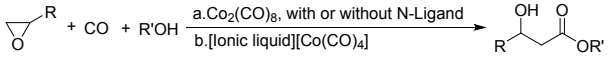
INTRODUCTION

Transition metal-catalyzed carbonylative transformation is one of the most powerful methodologies for the synthesize of various carbonyl-containing compounds in both academic and industrial.[1] Since the first report on homogenous carbonylation reaction around 70 years ago, many transition-metal complexes, especially noble metals, became the catalysts of choice.[2] However, noble metals are relatively low abundance and high costs. The associated toxicity issues for humans and environment are problematic as well.[3] Driven by economic and environmental considerations, researchers now are focusing on developing new, cheap, and efficient catalyst systems for carbonylation reactions.[4]

β-Hydroxyesters are important intermediates and building blocks for pharmaceuticals, fine chemicals, and polymeric materials.[5,6] For example, poly(β-hydroxyalkanoates) have a wide range of applications in medical materials and plastic because of its biocompatibility and biodegradability.[6] Today, there are many methodologies have been developed for the synthesis of β-hydroxyesters.[7] Among them, transition-metal-catalyzed alkoxycarbonylation of epoxide provides an efficient and atom-economic choice (Scheme 1). In this regard, various cobalt catalysts have been studied and exhibited excellent catalytic performance,[5g,8-10] including dicobalt octacarbonyl,[8a-8c] carbonyl cobalt complexes with N-donor ligands[8d-8g] (e.g. imidazole, 3-hydroxypyridine, and pyrazole), ionic liquid-based tetracarbonylcobaltate complexes[9] (e.g. [BuPy][$Co(CO)_4$], [bmin][$Co(CO)_4$]) and Coates's catalyst.[10] In general, the true catalytically active species in these catalysts is $Co(CO)_4^-$, which is formed from $Co_2(CO)_8$ or its cobalt tetracarbonyl salts. However, from the physical properties point of view, $Co_2(CO)_8$ is toxic, moderately air sensitive, and unstable at ambient temperature. It is also pyrophoric and easy to decompose.[11] Hence it is important to develop a cheaper, efficient and practical catalyst system, replacing of cobalt carbonyl, for the synthesis of β-hydroxyesters from epoxides. For example, Hamasaki and co-workers found that cobalt oxide supported gold nanoparticles under syngas can generate a cobalt carbonyl-like active species for the alkoxycarbonylation of epoxides.[12] Inspired by the successful usage of cobalt (II) halogen salts with reducing metal for Co-catalyzed cross-coupling reactions,[13] we are interested in developing a new catalytic system for the alkoxycarbonylation by the in situ formation of the active cobalt species using a stable cobalt(II) salt as the catalyst precursor.

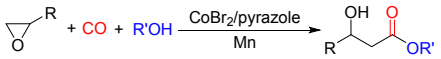
Scheme 1. Alkoxycarbonylation of epoxides.

Previous work: cobalt carbonyl and its derivatives as catalyst.[8-10]



	$Co_2(CO)_8$	$CoBr_2$
The price in Sigma-Aldrich:	2325 €/mol	319 €/mol
air:	senstive	stable
at ambient temperature:	unstable	stable
	pyrophoric	not-pyrophoric
	toxic	no-toxic

This work: Co(II)-catalyzed alkoxycarbonylation.

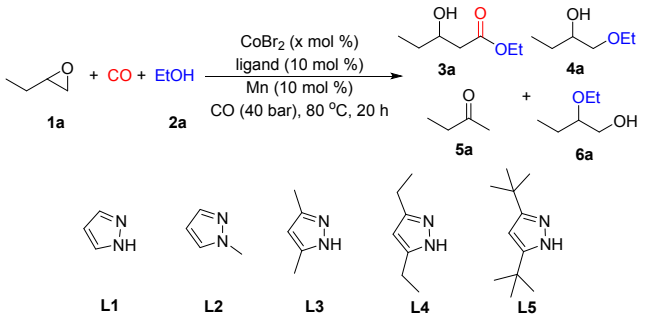


Herein, we describe a simple, efficient and practical catalytic system for the alkoxycarbonylation of epoxides to synthesize various β-hydroxyesters. This method employs cheap and stable cobalt(II) halogen as the catalyst precursor.[14] Combined with pyrazole and manganese powder, cobalt halogen could generate the active cobalt catalyst in the presence of CO gas.

RESULTS AND DISCUSSION

To begin the study, we choose 1,2-epoxybutane (**1a**) as the model substrate for reaction conditions optimization (Table 1, also see Table S1-4). As shown in Table 1, 31% of the desired ethyl β-hydroxypentanoate (**3a**) was obtained in the presence of $CoBr_2$ (5 mol%), and manganese powder (325 mesh) (10 mol%) in ethanol at 80 °C under 40 bar of CO gas (Table 1, entry 1). N-donating ligands have been broadly used and shown good performance in cobalt-catalyzed alkoxycarbonylation of epoxides.[9] Thus, we subsequently examined the effects of N-containing ligands. 3-Hydroxypyridine, a good ligand for alkoxycarbonylation of epoxides,[9b,c] is not effective in this catalytic system (Table 1, entry 2). Similarly, other ligands such as imidazole and pyridine also showed poor results (Table 1, entries 3-9). However, a significant increase in the selectivity, as well as the yield, was observed when pyrazole (**L1**) was used in this reaction, giving 73% yield of **3a** (Table 1, entry 10). Further investigation demonstrates the N-H in pyrazole is important because N-methyl pyrazole leads to a rather lower yield of ethyl β-hydroxypentanoate (Table 1, entry 11). Replacement of the pyrazole by 3,5-disubstituted pyrazole results in poor yields (Table 1, entries 12-14). When decreasing the $CoBr_2$ loading to 2.5 mol%, the yield of **3a** increased to 78% (Table 1, entry 15), but further lower the loading of $CoBr_2$ resulted lower yield (Table 1, entry 16). Finally, when using 10 mol % pyrazole and 15 mol % Mn powder (325 mesh) at 60 °C, almost no side-product was observed in this reaction and affording 98% yield of the desired ethyl β-hydroxypentanoate (**3a**). Moreover, we also tested different cobalt sources, only $CoCl_2$ show similar results (93% conversion; 90% yield, see Table S4 of Supporting Information).

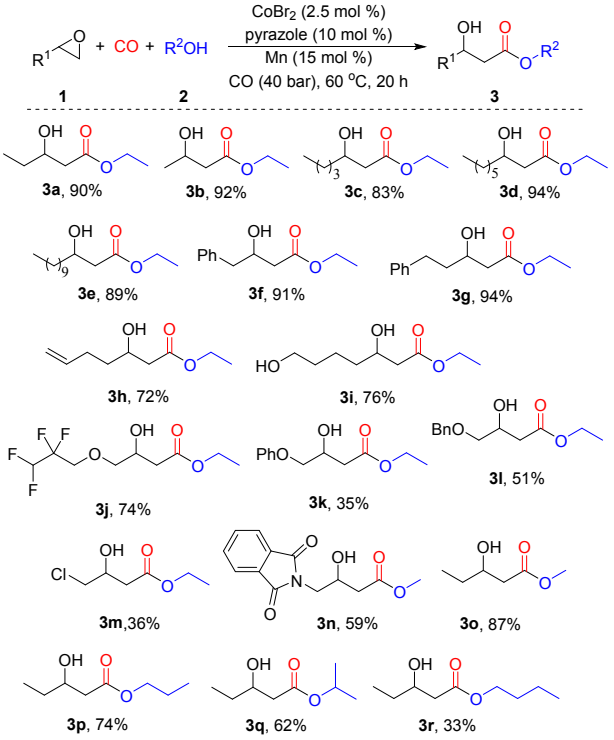
Table 1. Optimization of the Reaction Conditions.[a]



entry	*x*	*ligand*	*conv. (%)*[b]	*select. (%)*[c]	*yield (%)*[b]
1	5	-	41	75.6	31
2	5	3-HP	23	-	-
3	5	imidazole	7	-	-
4	5	I*t*Bu·HCl	<1	-	N.R.
5	5	pyridine	29	-	-
6	5	pyrazine	53	41.5	22
7	5	TPA	53	52.8	28
8	5	DMAE	15	-	-
9	5	pyrrole	53	-	-
10	5	L1	90	81	73
11	5	L2	43	79	34
12	5	L3	<1	-	-
13	5	L4	10	80	8
14	5	L5	32	81.2	26
15	2.5	L1	85	91.7	78
16	1	L1	75	76	57
17[d]	2.5	L1	92	93.4	86
18[d,e]	2.5	L1	91	95.6	87
19[d,e,f]	2.5	L1	>99	98	98

Note: [a]Reaction conditions: 1,2-epoxybutane (2 mmol), $CoBr_2$ (x mol %), ligand (10 mol %), Mn powder (325 mesh) (10 mol %), alcohol (2 mL), CO (40 bar), 80 °C, 20 h. [b]GC yield of **3a** by using hexadecane as an internal standard. [c]The selectivity of **3a** was determined by GC. [d]Co: Pyrazole = 1:4. [e]15 mol% of Mn. [f]60 °C 3-HP = 3-hydroxypyridine, I*t*Bu·HCl = 1,3-di-*tert*-butylimidazolium chloride, TPA = triphenylamine, DMAE = 2-dimethylaminoethanol.

Scheme 2. Cobalt-catalyzed carbonylation of epoxides.



Having identified the optimal reaction conditions, we tested a variety of epoxides to probe the versatility of this catalytic system (Scheme 2). The reaction was more facile for epoxides with alkyl substitutions at 3-positions, which were transformed into the desired products **3a-e** in high yields (83-94%). According to previous studies, terminal epoxides bearing an aromatic group gave lower yields.[8b] Fortunately, 3-phenyl and 3-benzyl substituted epoxides give the desired β-hydroxyester **3f** and **3g** in excellent yields (91% and 94%) with this catalytic system. Epoxide with pendent alkene was also proved to be suitable for this method to produce **3h** in good yield (72%). Interestingly, 4-(oxiran-2-yl) butyl acetate (**1i**) gave the ethyl 3, 7-dihydroxyheptanoate (**3i**) in 76% yield after alkoxycarbonylation and alcoholysis. However, glycidol ether-functionalized epoxides affording the desired β-

hydroxyester in lower yields (**3k** and **3l**), except 2-((2,2,3,3-tetrafluoropropoxy) methyl) oxirane (**3j**). This phenomenon is mainly due to the low activity of glycidol ethers. Similarly, epichlorohydrin with a heteroatom at 3-position is also obtained desired product **3m** in low yield, whereas 3-phthalimidohexyl-1, 2-epoxybutane including an N-heteroatom give the desired *β*-hydroxyester in moderate yield (**3n**). Moreover, other alcohols, such as methanol, 1-propanol, and isopropyl alcohol all can gave the desired products in moderate to good yields (**3o-r**), whereas low yield was obtained with 1-butanol (**3r**).

To check the reusability of this cobalt and pyrazole system, four sequential experiments were performed (Table 2). After four cycles, the conversion, as well as the yield, could be maintained in good level.

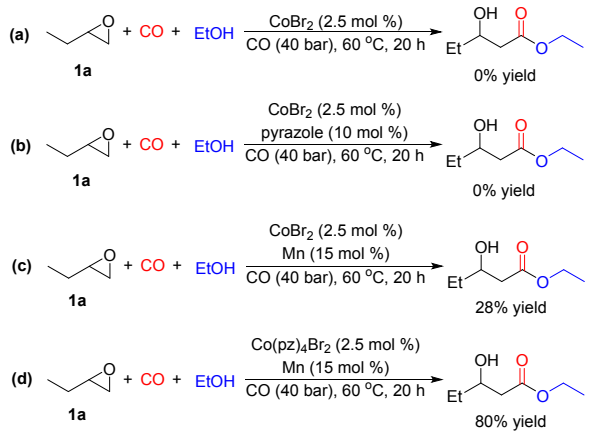
Table 2. Optimization of the Reaction Conditions.[a]

Cycle[c]	*Conversion (%)*[b]	*Selectivitiy (%)*[b]	*Yield (%)*[b]
1	93	96.7	90
2	93	95.6	89
3	89	91	81
4	87	90	78

Note: [a]1,2-Epoxybutane (2 mmol), $CoBr_2$ (2.5 mol %), pyrazole (10 mol %), and manganese powder (15 mol %) in EtOH (4 mL) under 40 bar CO at 60 °C. [b]Determined by GC using hexadecane as the interstandard. [c]After each cycle, another 2 mmol 1,2-epoxybutane and 15 mol% manganese powder was added.

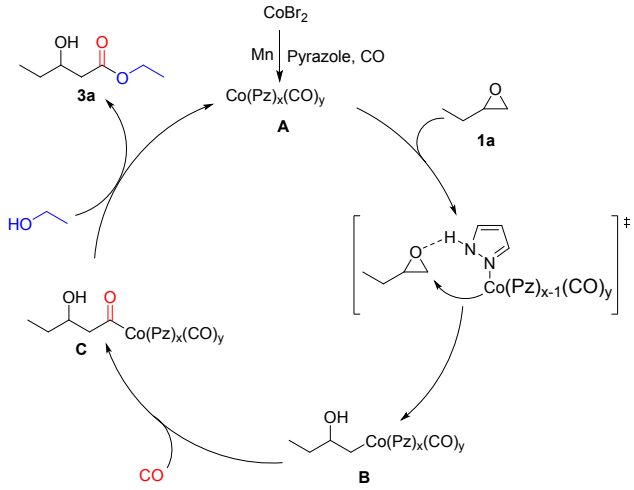
For having a deeper insight into the reaction mechanism, we conducted some control studies. Firstly, the reaction did not occur in the absence of manganese, with or without pyrazole (Scheme 3, a and b). In the absence of pyrazole, the desired *β*-hydroxyester could be obtained in 28% yield (Scheme 3, c).We also synthesize the cobalt complex $Co(pz)_4Br_2$[15] and used it for the reaction, the desired product **3a** was in 80% yield(Scheme 3, d).

Scheme 3. Control experiments.



Referring to the published works,[13] low-valent cobalt was generated with manganese powder as the reductant, and then combined with CO and catalyzed the alkoxycarbonylation. Pyrazole in this catalyst system plays a role in stabilizing cobalt complex and activating epoxides. That is also the reason the yield of **3a** was a significant improvement when added 10 mol % of pyrazole (see Table 1, entry 19). In addition, when using N-methyl pyrazole as the ligand, the result is similar to that obtained without ligand (see Table 1, entry 1 vs 11). With in-suit NMR analyses, all the peaks appear as broad single bands, most caused by the paramagnetism of cobalt,[9a,b] which is most likely a Co^0 complex in this case. That's why the hypothetical cobalt complex is not stable without CO gas, and brown solid will be generated from the purple clear solution after taken out from CO atmosphere. This also lead to challenge to determine it by ESI and IR, it also difficult to isolate and purify the active cobalt complex. Based on our results and literatures,[16] a plausible reaction mechanism was proposed (Scheme 4).

Scheme 4. Proposed reaction mechanism.



CONCLUSIONS

In summary, we have successfully developed a new catalyst system for the alkoxycarbonylation of epoxides. Using inexpensive, air-stable cobalt bromide, combined with pyrazole and catalytic amount of manganese powder, terminal epoxides bearing alkyl, alkenyl, alkyl-aryl, glycidyl and heteroatom groups were transformed into the corresponding *β*-hydroxyesters in moderate to excellent yields. Meanwhile, we found the active cobalt catalyst complex could be regenerated by adding additional amount of manganese, which provides a possibility for reuse of cobalt catalyst. Mechanism study indicates that pyrazole plays a crucial role in this reaction.

EXPERIMENTAL SECTION

General Information. ^1H NMR spectra were recorded on 300 or 400 MHz spectrophotometers. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$: δ = 7.26 ppm). ^{13}C NMR was recorded at 75 MHz or 100 MHz: chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$: δ = 77.16 ppm). Electron impact (EI) mass spectra were recorded on AMD 402 mass spectrometer (70 eV).High resolution mass spectra (HR-MS) were recorded on Agilent 6210. The data were given as mass units per charge (m/z).Gas chromatography analysis was performed on an Agilent HP-5890 instrument with a FID

detector and HP-5 capillary column (polydimethylsiloxane with 5 % phenyl groups, 30 m, 0.32 mm i.d., 0.25 μm film thickness) using argon as carrier gas. All of the reagents were purchased from Sigma-Aldrich, Alfa-Aesar, Acros, TCI, and used without further purification.

General Procedures. A 4 mL screw-cap vial was charged with $CoBr_2$ (10.9 mg, 2.5 mol%), Mn powder (~ 325 mesh) (16.5 mg, 15 mol%), pyrazole (13.6 mg, 10 mol%) and an oven-dried stirring bar. The vial was closed by Teflon septum and phenolic cap and connected with atmosphere with a needle. After flashed the vials with argon and vacuum three times, Absolute ethanol (2 mL) and 1, 2-epoxybutane (2 mmol) were injected by syringe. The vial was fixed in an alloy plate and put into Paar 4560 series autoclave (500 mL) under argon atmosphere. At room temperature, the autoclave is flushed with carbon monoxide for three times and 40 bar of carbon monoxide was charged. The autoclave was reacted at 60°C for 20 hours. Afterwards, the pressure was carefully released. After removal of solvent under reduced pressure, pure product was obtained by column chromatography.

Analytic data. *Ethyl 3-hydroxypentanoate* (***3a***).[9a] 264.4 mg, 90% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.1 Hz, 2H), 3.97 – 3.82 (m, 1H), 3.09 (s, 1H), 2.48 (dd, *J* = 16.3, 3.4 Hz, 1H), 2.36 (dd, *J* = 16.3, 8.9 Hz, 1H), 1.59 – 1.39 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.2, 69.4, 60.7, 41.0, 29.5, 14.2, 9.9. GC-MS (EI, 70 eV): m/z (%) = 145(5), 128(10), 117(100), 101(25), 89(40), 71(70). HRMS (ESI-TOF) calcd for $C_7H_{14}O_3$ [M + Na]$^+$: 169.0835, Found: 169.0838.

Ethyl 3-hydroxybutanoate (***3b***).[9a] 243.9 mg, 92% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 – 3.98 (m, 3H), 3.03 (s, 1H), 2.60 – 2.22 (m, 2H), 1.25 (d, *J* = 7.1 Hz, 2H), 1.25 – 1.15 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.9, 64.3, 60.7, 42.9, 22.5, 14.2. GC-MS (EI, 70 eV): m/z (%) = 131(2), 117(70), 87(75), 71(65), 60(55), 43(100).

Ethyl 3-hydroxyheptanoate (***3c***).[9a] 290.3 mg, 83% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.99 – 3.92 (m, 1H), 3.00 (s, 1H), 2.45 (dd, *J* = 16.3, 3.3 Hz, 1H), 2.35 (dd, *J* = 16.3, 8.9 Hz, 1H), 1.56 – 1.26 (m, 6H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.1, 68.1, 60.7, 41.5, 36.3, 27.7, 22.6, 14.2, 14.1. GC-MS (EI, 70 eV): m/z (%) = 174(1), 156(5), 127(10), 117(100), 88(35), 71(55). HRMS (ESI-TOF) calcd for $C_9H_{18}O_3$ [M + Na]$^+$: 197.1148, Found: 197.1151.

Ethyl 3-hydroxynonanoate (***3d***).[17a] 380.9 mg, 94% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.1 Hz, 2H), 4.04 – 3.88 (m, 1H), 2.92 (s, 1H), 2.47 (dd, *J* = 16.3, 3.4 Hz, 1H), 2.36 (dd, *J* = 16.3, 8.8 Hz, 1H), 1.58 – 1.10 (m, 13H), 0.92 – 0.76 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.2, 68.1, 60.7, 41.4, 36.6, 31.9, 29.3, 25.5, 22.7, 14.2, 14.1. GC-MS (EI, 70 eV): m/z (%) = 201(1), 184(2), 155(3), 139(10), 117(100), 97(10), 89(25), 71(35). HRMS (ESI-TOF) calcd for $C_{11}H_{22}O_3$ [M + Na]$^+$: 225.1461, Found: 225.1467.

Ethyl 3-hydroxytridecanoate (***3e***). 460.6 mg, 89% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.1 Hz, 2H), 4.06 – 3.88 (m, 1H), 2.98 (s, 1H), 2.48 (dd, *J* = 16.4, 3.3 Hz, 1H), 2.37 (dd, *J* = 16.4, 8.8 Hz, 1H), 1.58 – 1.37 (m, 3H), 1.32 – 1.20 (m, 18H), 0.86 (t, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.2, 68.1, 60.7, 41.4, 36.6, 32.0, 29.7, 29.7, 29.7, 29.6, 29.4, 25.6, 22.8, 14.3, 14.2. GC-MS (EI, 70 eV): m/z (%) = 258(1), 240(2), 195(4), 169(6), 117(100), 89(20), 71(25). HRMS (ESI-TOF) calcd for $C_{15}H_{30}O_3$ [M + Na]$^+$: 281.2087, Found: 281.2093.

Ethyl 3-hydroxy-4-phenylbutanoate (***3f***).[9a] 381.6 mg, 91% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 7.21 – 7.13 (m, 3H), 4.26 – 4.15 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.88 (d, *J* = 3.8 Hz, 1H), 2.81 (dd, *J* = 13.6, 7.1 Hz, 1H), 2.70 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.46 (dd, *J* = 16.4, 3.8 Hz, 1H), 2.37 (dd, *J* = 16.4, 8.5 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.8, 137.8, 129.5, 128.6, 126.7, 69.1, 60.8, 43.0, 40.6, 14.2. GC-MS (EI, 70 eV): m/z (%) = 190(32), 145(20), 117(100), 91(74), 71(30). HRMS (ESI-TOF) calcd for $C_{12}H_{16}O_3$ [M + Na]$^+$: 231.0991, Found: 231.0996.

Ethyl 3-hydroxy-5-phenylpentanoate (***3g***).[17b] 418.1 mg, 94% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.23 – 7.14 (m, 3H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.07 – 3.95 (m, 1H), 3.13 (d, *J* = 3.8 Hz, 1H), 2.88 – 2.77 (m, 1H), 2.75 – 2.64 (m, 1H), 2.50 (dd, *J* = 16.5, 3.6 Hz, 1H), 2.43 (dd, *J* = 16.5, 8.5 Hz, 1H), 1.90 – 1.79 (m, 1H), 1.78 – 1.68 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.1, 141.8, 128.5, 128.5, 125.9, 67.3, 60.8, 41.4, 38.2, 31.8, 14.2. GC-MS (EI, 70 eV): m/z (%) = 220(1), 204(25), 159(10), 130(83), 117(32), 91(100). HRMS (ESI-TOF) calcd for $C_{13}H_{18}O_3$ [M + Na]$^+$: 245.1148, Found: 245.1151.

Ethyl 3-hydroxyhept-6-enoate (***3h***).[9a] 247.3 mg, 72% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 – 5.65 (m, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 4.93 (d, *J* = 10.2 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.03 – 3.93 (m, 1H), 3.05 (s, 1H), 2.46 (dd, *J* = 16.3, 3.7 Hz, 1H), 2.37 (dd, *J* = 16.3, 8.5 Hz, 1H), 2.25 – 1.98 (m, 2H), 1.75 – 1.38 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.9, 138.1, 115.0, 67.4, 60.7, 41.4, 35.6, 29.8, 14.2. GC-MS (EI, 70 eV): m/z (%) = 171(1), 154(25), 143(8), 130(33), 117(100), 109(40), 81(100), 71(99). HRMS (ESI-TOF) calcd for $C_9H_{16}O_3$ [M + Na]$^+$: 195.0977, Found: 195.1003.

Ethyl 7-acetoxy-3-hydroxyheptanoate (***3i***).[17c] 292.7 mg, 63% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.1 Hz, 2H), 4.06 – 3.90 (m, 1H), 3.61 (t, *J* = 6.1 Hz, 2H), 3.28 (s, 1H), 2.48 (dd, *J* = 16.3, 3.8 Hz, 1H), 2.39 (dd, *J* = 16.3, 8.5 Hz, 1H), 2.18 (s, 1H), 1.65 – 1.36 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.1, 68.0, 62.6, 60.8, 41.5, 36.2, 32.4, 21.7, 14.3. GC-MS (EI, 70 eV): m/z (%) = 170(2), 142(5), 127(15), 117(100), 85(45), 71(50), 43(30). HRMS (ESI-TOF) calcd for $C_9H_{18}O_4$ [M + Na]$^+$: 213.1103, Found: 213.1111.

Ethyl 3-hydroxy-4-(2,2,3,3-tetrafluoropropoxy)butanoate (***3j***). 389.9 mg, 74% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 – 5.61 (m, 1H), 4.20 (dd, 1H), 4.18 – 4.12 (m, 2H), 3.89 (t, *J* = 12.6 Hz, 2H), 3.66 – 3.54 (m, 2H), 2.99 (s, 1H), 2.51 (d, *J* = 6.2 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.2, 115.1 (t, *J* = 26.9 Hz), 109.3 (tt, *J* = 249.4, 34.8 Hz), 75.6, 68.5 (t, *J* = 28.2 Hz), 67.2, 61.0, 37.8, 14.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ -121.73 – -126.92 (m), -139.50 (d, J = 53.1 Hz). GC-MS (EI, 70 eV): m/z (%) = 263(1), 244(5), 217(30), 199(8), 175(65), 145(15), 117(100), 89(36), 71(80). HRMS (ESI-TOF) calcd for $C_9H_{14}O_4F_4$ [M + Na]$^+$: 285.0726, Found: 285.0735.

Ethyl 3-hydroxy-4-phenoxybutanoate (***3k***).[9a] 156.4 mg, 35% yield($CoBr_2$ as catalyst); 312.8 mg, 70% yield($CoCl_2$ as catalyst), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.00 – 6.85 (m, 3H), 4.49 – 4.36 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.00 (d, *J* = 5.3 Hz, 2H), 3.16 (s, 1H), 2.76 – 2.68 (m, 1H), 2.67 – 2.59 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.2, 158.5, 129.6, 121.3, 114.7, 70.7, 66.9, 61.0, 38.2, 14.3. GC-MS (EI, 70 eV): m/z (%) = 224(12), 206(23), 179(10), 161(35), 131(100), 103(75), 94(86), 85(35), 77(57). HRMS (ESI-TOF) calcd for $C_{12}H_{16}O_4$ [M + Na]$^+$: 247.0941, Found: 247.0949.

Ethyl 4-(benzyloxy)-3-hydroxybutanoate (***3l***).[17d] 242.7 mg, 51% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 4.56 (s, 2H), 4.29 – 4.20 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.54 – 3.49 (m, 1H), 3.47 (dd, *J* = 9.2, 5.5 Hz, 1H), 3.06 (s, 1H), 2.54 (d, *J* = 6.3 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.2, 138.0, 128.5, 127.9, 127.8, 73.5, 73.2, 67.3, 60.8, 38.4, 14.2. GC-MS (EI, 70 eV): m/z (%) = 238.1(1), 163(2), 132(10), 117(20),

91(100), 71(20). HRMS (ESI-TOF) calcd for $C_{13}H_{18}O_4$ [M + Na]$^+$: 261.1097, Found: 261.1104.

Ethyl 4-chloro-3-hydroxybutanoate (***3m***).[9a] 224.1 mg, 67% yield($CoCl_2$ as catalyst), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 – 4.20 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.69 – 3.44 (m, 2H), 3.29 (s, 1H), 2.68 – 2.60 (m, 1H), 2.60 – 2.51 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.9, 68.0, 61.1, 48.2, 38.6, 14.2. GC-MS (EI, 70 eV): m/z (%) = 165(1), 139(3), 117(100), 85(40), 79(31), 71(70). HRMS (ESI-TOF) calcd for $C_6H_{11}O_3Cl$ [M + Na]$^+$: 189.0289, Found: 189.0284.

Methyl 4-(1,3-dioxoisoindolin-2-yl)-3-hydroxybutanoate (***3n***).[8b] 279.6 mg, 59% yield, white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.74 – 7.65 (m, 2H), 4.42 – 4.29 (m, 1H), 3.86 (dd, *J* = 14.1, 7.0 Hz, 1H), 3.76 (dd, *J* = 14.0, 4.6 Hz, 1H), 3.68 (s, 3H), 3.30 (d, *J* = 5.1 Hz, 1H), 2.59 (dd, *J* = 16.4, 4.4 Hz, 1H), 2.50 (dd, *J* = 16.5, 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.2, 168.7, 134.2, 132.0, 123.5, 66.6, 52.0, 43.0, 39.0. GC-MS (EI, 70 eV): m/z (%) = 245(2), 229(3), 213(15), 186(20), 161(100), 133(15), 104(23), 76(15). HRMS (ESI-TOF) calcd for $C_{13}H_{13}NO_5$ [M + Na]$^+$: 286.0686, Found: 286.0689.

Methyl 3-hydroxypentanoate (***3o***).[8b] 229.4 mg, 87% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 – 3.85 (m, 1H), 3.68 (s, 3H), 2.90 (s, 1H), 2.49 (dd, *J* = 16.3, 3.4 Hz, 1H), 2.38 (dd, *J* = 16.3, 8.8 Hz, 1H), 1.58 – 1.41 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.6, 69.4, 51.8, 40.8, 29.5, 9.9. GC-MS (EI, 70 eV): m/z (%) = 131(2), 114(10), 103(100), 83(17), 71(65), 59(40), 43(60).

Propyl 3-hydroxypentanoate (***3p***). 236.7 mg, 74% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (t, *J* = 6.7 Hz, 2H), 3.94 – 3.85 (m, 1H), 2.96 (s, 1H), 2.52 – 2.44 (m, 1H), 2.42 – 2.33 (m, 1H), 1.68 – 1.58 (m, 2H), 1.56 – 1.41 (m, 2H), 0.96 – 0.92 (m, 3H), 0.92 – 0.88 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.3, 69.4, 66.3, 40.9, 29.5, 22.0, 10.4, 9.9. GC-MS (EI, 70 eV): m/z (%) = 161(1), 131(41), 101(54), 89(100), 83(25), 71(32), 59(30), 43(50). HRMS (ESI-TOF) calcd for $C_8H_{16}O_3$ [M + Na]$^+$: 183.0991, Found: 183.0994.

Isopropyl 3-hydroxypentanoate (***3q***). 196.3 mg, 62% yield, colorless. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 – 4.91 (m, 1H), 3.99 – 3.77 (m, 1H), 3.05 (s, 1H), 2.47 – 2.40 (m, 1H), 2.37 – 2.28 (m, 1H), 1.55 – 1.39 (m, 2H), 1.22 – 1.18 (m, 6H), 0.95 – 0.87 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.7, 69.4, 68.2, 41.3, 29.5, 21.8, 9.9. GC-MS (EI, 70 eV): m/z (%) = 161(1), 131(24), 117(5), 101(33), 89(100), 83(22), 71(25), 59(34), 43(50). HRMS (ESI-TOF) calcd for $C_8H_{16}O_3$ [M + Na]$^+$: 183.0991, Found: 183.0988.

Butyl 3-hydroxypentanoate (***3r***). 115.9 mg, 33% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 – 4.05 (m, 2H), 3.98 – 3.83 (m, 1H), 2.76 (s, 1H), 2.55 – 2.45 (m, 1H), 2.38 (dd, *J* = 16.4, 8.9 Hz, 1H), 1.67 – 1.56 (m, 2H), 1.56 – 1.42 (m, 2H), 1.41 – 1.29 (m, 2H), 0.99 – 0.94 (m, 3H), 0.93 – 0.88 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.3, 69.5, 64.7, 41.0, 30.7, 29.5, 19.2, 13.8, 9.9. GC-MS (EI, 70 eV): m/z (%) = 172(2), 156(5), 145(28), 101(85), 89(100), 83(70), 71(25), 57(90), 41(65). HRMS (ESI-TOF) calcd for $C_9H_{18}O_3$ [M + Na]$^+$: 197.1148, Found: 197.1154.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Optimization data, and NMR spectra of products. (PDF)

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Notes

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