Supplementary Material (ESI) for Chemical Communications

Electronic Supplementary Information (ESI)

Alkanes to Carboxylic Acids in Aqueous Medium: Metal-free and Metal-promoted Highly Efficient and Mild Conversions

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ESI contains Full Experimental Details including general methods, experiments with ^{18}O-labeled water and full computational details; Supporting Discussion regarding the reaction mechanism; Supporting References; Supporting Figures S1–S5 with effects of different reaction parameters (Figs. S1, S2) on the yields of carboxylic acids, the ESI-MS^{-} spectra (Fig. S3) of the reaction mixtures (including experiments with ^{18}O-labeled water), as well as graphical material from DFT calculations with equlibrium structures of the transition states (Fig. S4), and energy profile for the carboxylation of ethane (Fig. S5); Supplementary Tables with comparison of different systems for carboxylation of alkanes in aqueous medium (Table S1), full version (including all experimental conditions) of Table 1 (Table S2), with results on carboxylation of cyclohexane promoted by various copper(II) compounds (Table S3), and with total energies and enthalpies of the structures from theoretical calculations (Table S4).

1. **Full Experimental Details**

General methods. All chemicals were obtained from commercial sources and used as received. Compound **1** was prepared according to the known[12] method. GC analyses were performed on a Fisons Instruments GC 8000 series gas chromatograph with a DB WAX (J&W) capillary column (P/N 122-7032; 30 m × 0.25 mm × 0.25 μm; helium was the carrier gas) and the Jasco-Borwin v.1.50 software. In some cases, carboxylation products were also identified by GC-MS, ^{1}H and ^{13}C-{^{1}H} NMR techniques using a Trio 2000 Fisons spectrometer with a coupled Carlo Erba (Auto/HRGC/MS) gas chromatograph, and a Varian UNITY 300 NMR spectrometer, respectively.

Alkane Carboxylations. In a typical experiment the reaction mixtures were prepared as follows: to 2.0–32.0 μmol (typically 8.0 μmol) of metal promoter (optional) contained in a 13.0 mL stainless steel autoclave, equipped with a Teflon-coated magnetic stirring bar, were added 1.00–2.00 mmol (typically 1.50 mmol) of $K_2S_2O_8$, 2.0–3.0 mL of H_2O, 2.0–4.0 mL of MeCN (typical total solvent volume of 6.0 mL) and 1.00–1.50 mmol (typically 1.00 mmol) of alkane (if liquid). Then the autoclave was closed and flushed with N_2 three times for removing the air and pressurized with 1−10 atm of alkane (if gaseous) and 0–40 atm (typically 20 atm) of CO. The reaction mixture was stirred for 1−20 h (typically 6 h) at 25–60 °C (typically 50 or 60°C) using a magnetic stirrer and an oil bath, whereupon it was cooled in an ice bath, degassed, opened and transferred to a Schlenk flask. Diethyl ether (9.0–11.0 mL) and 90 μL of cycloheptanone (GC internal standard) were added. The obtained mixture was stirred and the organic layer was typically analyzed by GC.

Additional experiments were performed under typical reaction conditions in the presence of the carbon-centered radical trap $CBrCl_3$ (used in an equimolar amount relatively to the alkane), revealing the full suppression of carboxylic acid formation, either in the presence or in the absence of the metal promoter.

Blank tests indicate that the metal-free carboxylation reactions proceed with similar efficacy in a Teflon reactor, thus confirming that reactions are not promoted by the reactor metal wall.

Experiments with ^{18}O-labeled water. Additional experiments (cyclohexane carboxylation) have been performed using $H_2{}^{18}O$ (97% ^{18}O, Cambridge Isotope Laboratories, Inc.) as solvent in order to check the involvement of water in the formation of the COOH group of the carboxylic acid product. The experiments were carried out similarly as described in Methods Summary (in a 13.0 mL stainless steel autoclave), reacting 1.00 mmol of $K_2S_2O_8$, 1.0 g of $H_2{}^{18}O$, 2.0 mL of MeCN, 1.00 mmol of cyclohexane, 20 atm of CO and 2.0 μmol of metal promoter **1** (or in the absence of **1** in a separate batch) for 5 h at 50ºC. After the completion the reaction and addition of 3.0 mL of Et_2O, the reaction mixture (organic phase) was analyzed by gas chromatography (using a Fisons

Instruments GC 8000 series gas chromatograph) and ESI-MS$^-$ spectrometry (using a 500-MS LC Ion Trap instrument; Varian Inc, Alto Palo, CA, USA). The ESI–MS$^-$ spectra were run using (if necessary) further diluted MeCN/Et_2O solutions (with ca. 10^{-3} M of cyclohexanecarboxylic acid product) of the reaction mixtures. The ESI–MS$^-$ spectra (Fig. S3) reveal the formation of $C_6H_{11}CO^{18}OH$ as the main product [the relative peak intensities of $C_6H_{11}CO^{18}O^-$ ($m/z = 128.9$) and $C_6H_{11}COO^-$ ($m/z = 126.9$) are 4:1 or 3:2 for the experiments with cyclohexane in the presence or in the absence of the copper promoter **1**, respectively].

Computational details. Calculations were performed for reactions of ethane at the B3LYP level using the Gaussian-98 program.[S1] For the non-metal atoms, the 6-311+G** basis sets were applied. For the copper atoms, a relativistic Stuttgart pseudopotential and the appropriate basis set (8s7p6d)/[6s5p3d] were used.[S2] Solvent effects were treated using the CPCM model with water as solvent. Model aqua-copper-complexes were considered instead of the tetranuclear Cu^{II} complex for simplicity and because $Cu(NO_3)_2$ also shows a promoting effect.

The Hessian matrix was calculated analytically for the optimized structures in order to prove the location of correct minima (no "imaginary" frequencies) or saddle points (only one negative eigenvalue). Thermodynamic parameters were calculated at 60°C and pressure of 10 atm, i.e at typical experimental conditions. The solvent effects have been estimated at the single-point calculations on the basis of the gas-phase equilibrium geometries. The enthalpies in solution (H_s) were calculated by addition of the solvation energy ΔG_{solv} to gas-phase enthalpies (H_g).

The solvent effects cannot be treated accurately if the total number of the charged species with the same charges is different before and after reaction. In order to preserve this number, one chloride ion atom was added to the complexes $[Cu(H_2O)_4]^{n+}$. First, the full geometry optimization of $[Cu(H_2O)_4]^{n+}$ has been carried out, then the Cl^- ion, as a counterion, was placed along the axis orthogonal to the $\{Cu(O)_4\}$ plane at the distance of 4 Å from the Cu atom, and the gas-phase and CPCM single-point calculations have been performed on the basis of the equilibrium geometries of $[Cu(H_2O)_4]^{n+}$. Zero point energies and translation, rotation and vibrational contributions to the total energies were taken from the equilibrium geometries of the $[Cu(H_2O)_4]^{n+}$ species.

The geometry optimization of the reduced species $[Cu(H_2O)_4]^+$ led to elimination of two water molecules from the coordination sphere of the metal.

2. Supporting Discussion

Other less favourable mechanisms involving the hydroxyl radical. Alternatively, but with an higher barrier of activation, $SO_4^{\bullet -}$ could react with water [$H_2O + SO_4^{\bullet -} \rightarrow HO^{\bullet} + HSO_4^-$] giving the $HO^{\bullet}$ radical ($\Delta H_s^{\neq} = 17.9$ kcal/mol) which on reaction with the acyl radical $RCO^{\bullet}$ would yield the carboxylic acid. $RCO^•$ could also directly react with water giving RCOOH and $H^•$ ($\Delta H_s^{\neq}$ = 16.8 kcal/mol), but this is also less favourable than the oxidation by $S_2O_8^{2-}$ or M^n. In accord, the selectivity observed when using linear alkanes (see text) also suggests that the reactions do not proceed via the highly reactive $HO^•$ radical.[S3] In fact, the linear derivative (i.e. butyric acid) has been detected in a significant amount (ca. 4–5% yield) only in the case of propane carboxylation (Table 1, entry 2). For all the other *n*-alkanes, the yields of the linear carboxylic acids have not exceeded 1%.

The carboxylation reaction does not proceed in the presence of O_2 as the oxidant, but when O_2 is used together with persulfate, a significant yield drop (ca. 10 times) of carboxylic acid is observed. Therefore, O_2 acts also as a radical trap, reacting with the alkyl radical to give the peroxo radical $ROO^•$, thus leading to higher yields (ca. tenfold increase) of alcohol and ketone, what is in accord with the previously reported[S4,S5] radical mechanism for the oxidation of alkanes (RH) via the formation of $R^•$ radicals. Nevertheless, in our systems the overall formation of the alcohols and ketones (e.g. cyclohexanol and cyclohexanone in the case of cyclohexane) does not exceed 1–3% of the total yield based on alkane, and is detected preferably at lower CO pressures, when the carboxylation is less favourable.

As in the TFA containing systems,[10] the carboxylation in H_2O/MeCN medium does not appear to proceed via formation of free CO_2 or free alcohols, since CO_2 does not promote the carboxylation of alkanes, and the alcohols are not converted into carboxylic acids in the presence of CO in our systems.

3. Supporting References

(S1) M. J. Frisch *et. al.*, Gaussian 98, revision A.9, Gaussian, Inc.: Pittsburgh PA, 1998.

(S2) M. Dolg, U. Wedig, H. Stoll, H. Preuss, *J. Chem. Phys.* 1987, **86**, 866.

(S3) M. Costas, K. Chen, L. Que, Jr. *Coord. Chem. Rev.* 2000, **200–202**, 517.

(S4) G. B. Shul'pin, *J. Mol. Cat. A. Chem.* 2002, **189**, 39.

(S5) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* 1997, **97**, 2879.

(S6) A. M. Kirillov, M. N. Kopylovich, M. V. Kirillova, E. Y. Karabach, M. Haukka, M. F. C. G. da Silva, A. J. L. Pombeiro, *Adv. Synth. Catal.* 2006, **348**, 159.

4. Supporting Figures

Full experimental conditions for Fig. 1. General reaction conditions: $p(C_3H_8)$ = 5 atm (1.33 mmol) or cyclohexane (1.00 mmol), compound **1** (8.0 µmol, optional), in an autoclave (13.0 mL-capacity), 6 h. Reaction conditions in (a): p(CO) = 30 or 20 atm for C_3H_8 or C_6H_{12} carboxylation, respectively; $K_2S_2O_8$ = 1.5 mmol; total H_2O/MeCN mixed solvent volume (6 mL); 60 or 50°C for C_3H_8 or C_6H_{12} carboxylation, respectively. Reaction conditions in (b): p(CO) = 20 atm; $K_2S_2O_8$ = 1.5 or 1.0 mmol for C_3H_8 or C_6H_{12} carboxylation, respectively; H_2O (3.0 mL)/MeCN (3.0 mL); 30–100°C.

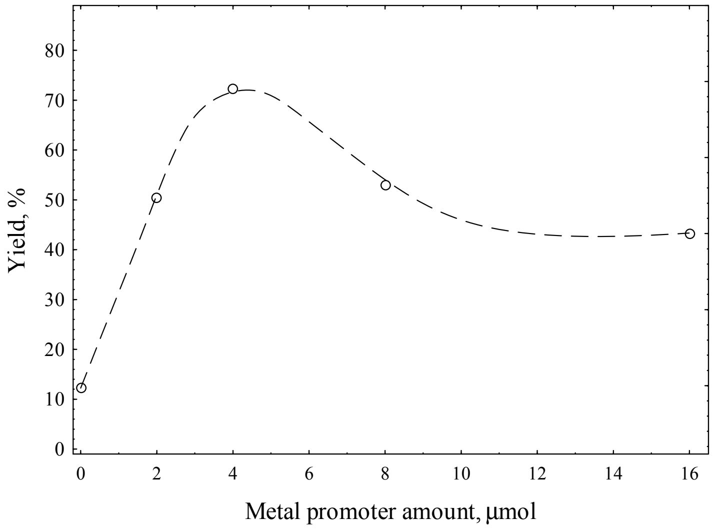


Figure S1. Effect of the amount of metal promoter **1** on the yield of cyclohexanecarboxylic acid. Reaction conditions: cyclohexane (1.00 mmol), p(CO) = 20 atm (5.32 mmol), $K_2S_2O_8$ (1.50 mmol), H_2O (3.0 mL)/MeCN (3.0 mL), 50 °C, 6 h in an autoclave (13.0 mL capacity).

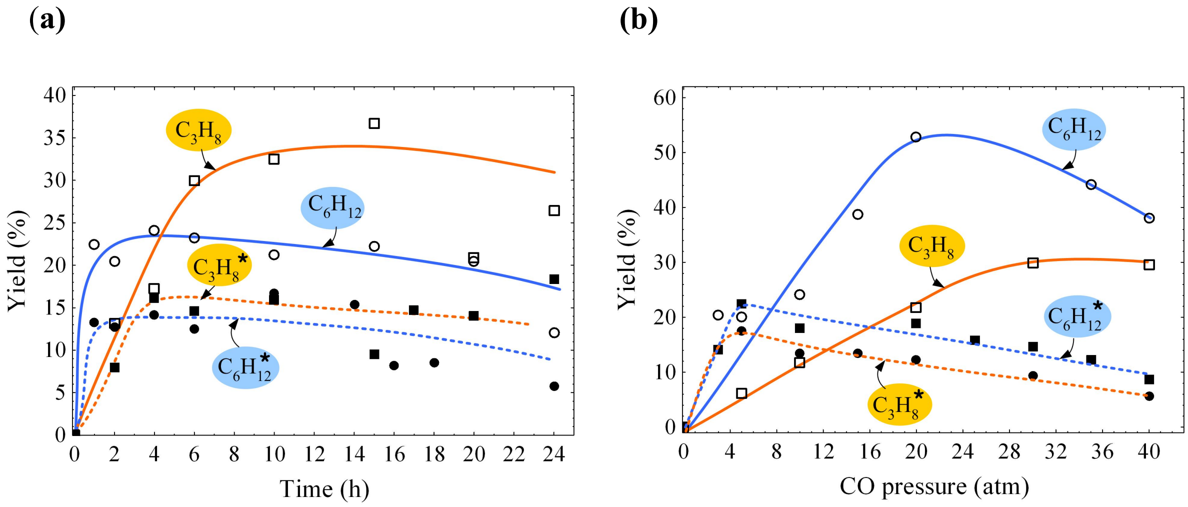


Figure S2. Effects of time (a) and CO pressure (b) on the total yields (% relatively to alkane) of carboxylic acids. Orange and blue curves correspond to carboxylation of propane and cyclohexane, respectively, promoted by **1** or metal-free (curves with asterisks). General reaction conditions: $p(C_3H_8)$ = 5 atm (1.33 mmol) or cyclohexane (1.00 mmol), compound **1** (8.0 μmol, optional), in an autoclave (13.0 mL-capacity), 6 h. Reaction conditions in (a): p(CO) = 30 or 20 atm for C_3H_8 or C_6H_{12} carboxylation, respectively; $K_2S_2O_8$ = 1.5 or 1.0 mmol for C_3H_8 or C_6H_{12} carboxylation, respectively; H_2O (3.0 mL)/MeCN (3.0 mL); 50 or 80°C for C_3H_8 or C_6H_{12} carboxylation, respectively; 0–20 h. Reaction conditions in (b): $p(C_3H_8)$ = 5 atm; p(CO) = 0–40 atm; $K_2S_2O_8$ = 1.5 mmol; H_2O (3.0 mL)/MeCN (3.0 mL); 60 or 50°C for C_3H_8 or C_6H_{12} carboxylation, respectively; 6 h.

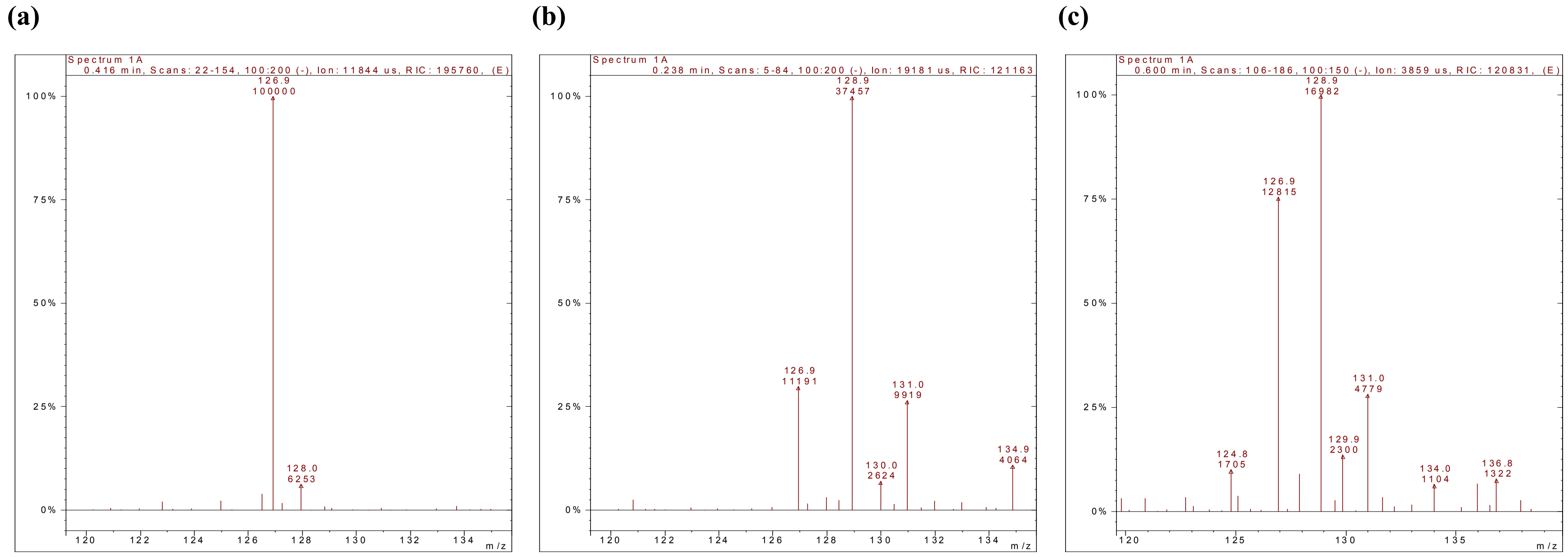


Figure S3. Fragments of the ESI-MS$^-$ spectra (relative intensity vs. *m/z* plots) of the final reaction mixtures in the carboxylation of cyclohexane. (a) Standard experiment with unlabeled water and in the presence of the metal promoter **1**. (b) With ^{18}O-labeled water in the presence of metal promoter **1**. (c) With ^{18}O-labeled water in the absence of metal promoter **1**. The most intense signals correspond to $C_6H_{11}COO^-$ ($m/z = 126.9$) (in a) or $C_6H_{11}CO^{18}O^-$ ($m/z = 128.9$) (in b, c). For details, see Full Experimental Details section.

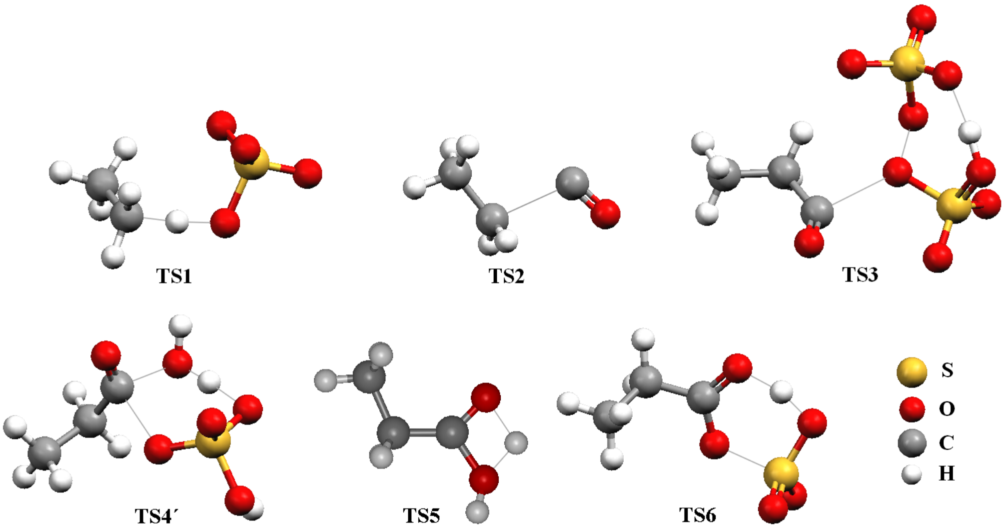


Figure S4. Equilibrium structures of the transition states for ethane carboxylation.

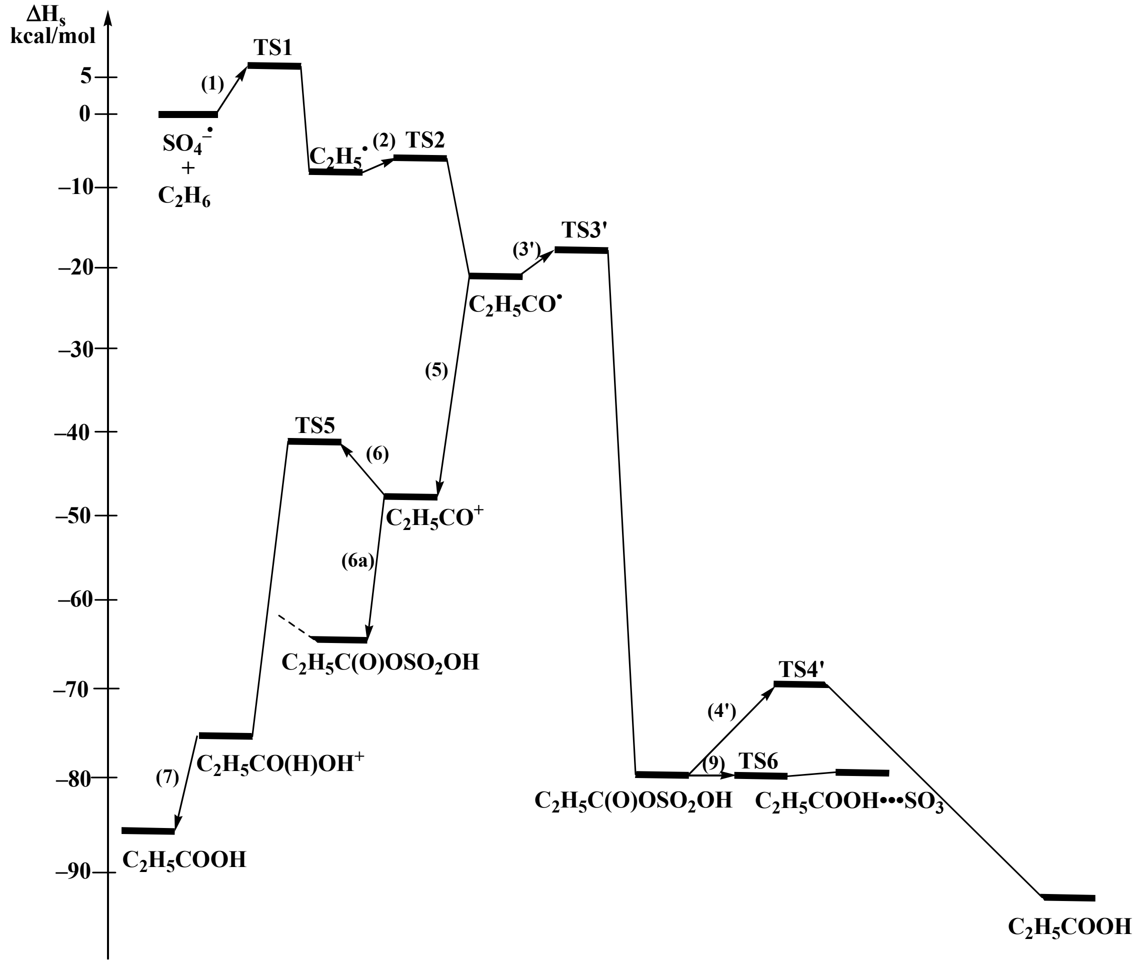


Figure S5. Energy profile for the carboxylation of ethane to propionic acid.

5. Supporting Tables

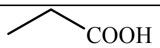
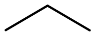
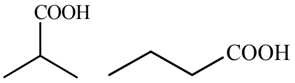
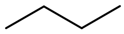
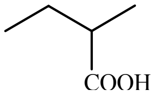
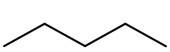
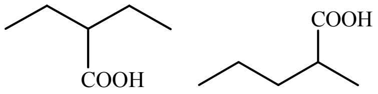
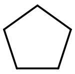
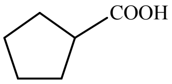
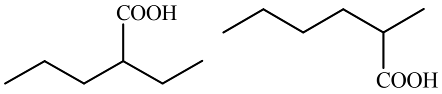
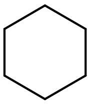
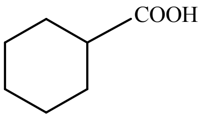
Table S1. Comparison of different systems for carboxylation (carbonylation) of alkanes with CO to carboxylic acids in aqueous medium (for comparative purposes all product yields were recalculated relative to alkane).

System	Alkane	Oxidant	Solvent	Catalyst/ promoter	Other Reaction Conditions	Product	Yield (relative to oxidant)[a]	Yield (relative to alkane)[b]
Sen system [ref. 7a]	CH_4 (700 psi = 48 atm = 189 mmol)	$K_2S_2O_8$ (0.74 mmol)	D_2O (4 mL)	–	CO (300 psi = 20 atm), 105–115 ºC, 10–16 h [c]	CH_3COOH	48.6%	ca. **0.19%**[d]
Sen system [ref. 7a]	C_2H_6 (550 psi = 37 atm = 146 mmol)	$K_2S_2O_8$ (0.74 mmol)	D_2O (4 mL)	–	CO (500 psi = 34 atm), 105–115 ºC, 10–16 h [c]	C_2H_5COOH	40.8%	ca. **0.21%**[d]
Sen system [ref. 7b]	CH_4 (1000 psi = 68 atm = 318 mmol)	O_2 (100 psi = 6.8 atm = 31.8 mmol)	D_2O (5 mL)	$RhCl_3$ (0.01 M)+HCl+KI	CO (200 psi = 13.5 atm), 95 ºC, 352 h)	CH_3COOH	4.3%[d]	**0.43%**[d]
Shul'pin system [ref 7c]	CH_4 (50 atm = 143 mmol)	Air (15 atm = 9.0 mmol O_2)	H_2O (30 mL)	$NaVO_3$ ($1.0 \cdot 10^{-4}$ M)	CO (15 atm), 100 ºC, 50 h	CH_3COOH	1.2%[d]	**0.08%**[d]
This work	C_2H_6 (10 atm = 2.66 mmol)	$K_2S_2O_8$ (2.0 mmol)	H_2O/MeCN (3 mL/3 mL)	–	CO (20 atm), 60 ºC, 6 h,	C_2H_5COOH	13.2%	**9.9%**
This work	C_3H_8 (3 atm = 0.78 mmol)	$K_2S_2O_8$ (1.5 mmol)	H_2O/MeCN (2 mL/4 mL)	Compound **1** (8 µmol)	CO (30 atm), 60 ºC, 6 h	C_3H_7COOH	19.8%	**38.0%**
This work	C_6H_{12} (1.0 mmol)	$K_2S_2O_8$ (1.5 mmol)	H_2O/MeCN (3 mL/3 mL)	Compound **1** (4 µmol)	CO (20 atm), 50 ºC, 6 h	$C_6H_{11}COOH$	48.2%	**72.3%**

[a] Product yield % (moles of carboxylic acid products / 100 moles of oxidant). [b] Product yield % (moles of carboxylic acid products / 100 moles of alkane). [c] The reactor capacity (ca. 100 mL), although not indicated in ref. 7a, was kindly provided by Prof. A. Sen (personal information). [d] Calculated by us for comparative purposes.

Comment: As it can be seen from Table S1, all previously reported systems[7] for alkanes carboxylations in aqueous medium exhibit very low conversions to carboxylic acids. Our method in mixed H_2O/MeCN solvent allows to obtain ***two orders of magnitude higher yields*** of carboxylic acids (relative to alkane), under milder temperatures (50–60 ºC vs. 95–115 ºC), shorter reaction times (6 h vs. 10–352 h), and even in the absence of any metal catalyst, being also applicable to a variety of alkanes.

Table S2. Full version (including all experimental details) of Table 1. Metal-free and metal-promoted direct carboxylation, in H_2O/MeCN medium, of C_n alkanes to C_{n+1} carboxylic acids.[a]

Run	Alkane	Carboxylic acid product	Total yield (%)	
			Metal-free	Metal-promoted (by **1**)
1			9.9[b]	9.4[c]
2			23.2[d,e]	38.0[c,f]
3			6.2	29.6[g]
4			17.6[f]	23.2[f]
5			8.2[g,h]	22.2[c,g,h]
6			9.0[f]	44.6[f]
7			12.3[g]	72.3[g,i]

[a] Selected results; typical (unless otherwise stated) reaction conditions: p(gaseous alkane) = 10, 3 or 1.5 atm (2.66, 0.78 or 0.40 mmol) for C_2H_6, C_3H_8 or n-C_4H_{10}, respectively, liquid alkane (1.00 mmol), p(CO) = 20 atm (5.32 mmol), $K_2S_2O_8$ (1.50 mmol), H_2O (3.0 mL)/MeCN (3.0 mL), in the presence (optional) of compound **1** (8.0 µmol), 60 °C, 6 h in an autoclave (13.0 mL capacity). [Product yield % (moles of carboxylic acid products / 100 moles of alkane) determined by GC analysis; % yields based on oxidant, if required, can be estimated as [(% yield based on alkane)×n(mmol alkane)/1.5], e.g. 8.2 and 48.2% for entry 7. Major product is indicated first; molar ratios between the two carboxylic acids for metal-free and metal-promoted (values in brackets) systems are: 6.5:1 (9.0:1), 3.2:1 (2.7:1) or 1.0:1 (1.1:1) for C_3H_8, n-C_5H_{12} or n-C_6H_{14} carboxylation, respectively; the formation of minor amounts (<1%) of linear carboxylic acids is not considered herein. [b] $K_2S_2O_8$ (2.00 mmol). [c] p(CO) = 30 atm. [d] 70 °C. [e] $p(C_3H_8)$ = 5 atm (1.33 mmol). [f] H_2O (2.0 mL)/MeCN (4.0 mL). [g] 50 °C. [h] C_5H_{10} (1.50 mmol). [i] Metal promoter (4.0 µmol).

Table S3. Carboxylation of cyclohexane to cyclohexanecarboxylic acid, in H_2O/MeCN medium, promoted by copper(II) compounds.[a]

Entry	Metal promoter	Metal promoter amount (μmol)	Yield (%)
1	$Cu(NO_3)_2 \cdot 2.5H_2O$	32	31.6
2	$[Cu(H_2tea)(N_3)]$[b]	16	32.5
3	$[Cu_2(H_2tea)_2\{C_6H_4(COO)_2\text{-}1,4\}]_n \cdot 2nH_2O$[b]	8.0	38.8
4	$[O\subset Cu_4\{N(CH_2CH_2O)_3\}_4(BOH)_4][BF_4]_2$ (**1**)	4.0	72.3

[a] Selected results; typical (unless otherwise stated) reaction conditions: cyclohexane (1.00 mmol), *p*(CO) = 20 atm (5.32 mmol), $K_2S_2O_8$ (1.50 mmol), H_2O (3.0 mL)/MeCN (3.0 mL), 50 °C, 6 h in an autoclave (13.0 mL capacity). Product yield % (moles of cyclohexanecarboxylic acid / 100 moles of cyclohexane). H_2tea = monodeprotonated form of triethanolamine.

[b] See refs. 11 and S6 for the syntheses of these compounds.

Table S4. Total energies for gas phase and for solution (E_g and E_s) and enthalpies (H) of the structures calculated at the B3LYP/6-311+G** level of theory (in Hartree).

Structure	E_g	E_s	H
$HS_2O_8^-$	–1398.911453	–1398.983700	–1398.854742
$SO_4^{-\bullet}$	–699.174833	–699.266116	–699.154177
HSO_4^-	–699.840384	–699.946412	–699.806624
H_2SO_4	–700.342619	–700.368983	–700.296325
C_2H_6	–79.857573	–79.854516	–79.777690
$C_2H_5^\bullet$	–79.186023	–79.186193	–79.120906
CO	–113.350544	–113.349498	–113.341594
$C_2H_5CO^\bullet$	–192.558831	–192.561275	–192.479502
$C_2H_5CO^+$	–192.305151	–192.398868	–192.224536
$C_2H_5C(O)OSO_2OH$	–892.367288	–892.376104	–892.248910
C_2H_5COOH	–268.483713	–268.500856	–268.385190
$C_2H_5CO(H)OH^+$	–268.805144	–268.917258	–268.693667
$C_2H_5COOH\cdots SO_3$	–892.373626	–892.376469	–892.254917
SO_3	–623.859515	–623.859028	–623.842190
$OH^\bullet$	–75.763068	–75.771250	–75.750707
H_2O	–76.459175	–76.469648	–76.433414
H_3O^+	–76.731723	–76.901184	–76.692790
$H^\bullet$	–0.502156	–0.499790 [a]	–0.499360
$\{[Cu(H_2O)_4]Cl\}^+$	–963.193436 [b]	–963.342604 [b]	
$[Cu(H_2O)_2](H_2O)_2Cl$	–963.463504 [b]	–963.545060 [b]	
$[Cu(H_2O)_4]^{2+}$	–502.596129	–502.939167	–502.479940
$[Cu(H_2O)_2](H_2O)_2^+$	–503.052478	–503.140830	–502.940458
TS1	–779.011071	–779.105302	–778.914931
TS2	–192.532472	–192.531920	–192.456921
TS3'	–1591.465185	–1591.539337	–1591.328272
TS4'	–968.801036	–968.656418	–968.828791
TS5	–268.725353	–268.855249	–268.620461
TS6	–892.362069	–892.370841	–892.248117

[a] For $H^\bullet$, the Bondi's atomic radius was used. [b] For details, see Computational details section.