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Metal-Free and Copper-Promoted Single-Pot Hydrocarboxylation of Cycloalkanes to Carboxylic Acids in Aqueous Medium

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Abstract: A simple and effective method for the transformation, under mild conditions and in aqueous medium, of various cycloalkanes (cyclopentane, cyclohexane, methylcyclohexane, *cis*- and *trans*-1,2-dimethylcyclohexane, cycloheptane, cyclooctane and adamantane) into the corresponding cycloalkanecarboxylic acids bearing one more carbon atom, is achieved. This method is characterized by a single-pot, low-temperature hydrocarboxylation reaction of the cycloalkane with carbon monoxide, water and potassium peroxodisulfate in water/acetonitrile medium, proceeding either in the absence or in the presence of a metal promoter. The influence of various reaction parameters, such as type and amount of metal promoter, solvent composition, temperature, time, carbon monoxide pressure, oxidant and cycloalkane, is investigated, leading to an optimization of the cyclohexane and cyclopentane carboxylations. The highest efficiency is observed in the systems promoted by a tetracopper(II) triethanolaminate-derived complex, which also shows different bond and stereoselectivity parameters (compared to the metal-free systems) in the carboxylations of methylcyclohexane and stereoisomeric 1,2-dimethylcyclohexanes. A free radical mechanism is proposed for the carboxylation of cyclohexane as a model substrate, involving the formation of an acyl radical, its oxidation and consequent hydroxylation by water. Relevant features of the present hydrocarboxylation method, besides the operation in aqueous medium, include the exceptional metal-free and acid-solvent-free reaction conditions, a rare hydroxylating role of water, substrate versatility, low temperatures (*ca.* 50 °C) and a rather high efficiency (up to 72% carboxylic acid yields based on cycloalkane).

Keywords: alkanes; carboxylation; carboxylic acids; C–C bond formation; metal-free transformations; water

Introduction

The development of new, efficient and sustainable processes for the mild oxidative functionalization of alkanes continues to be a challenging problem of modern chemistry, as evidenced by the increasing number of research publications in this field.[1,2] Alkanes are known as the most abundant carbon raw materials but are inert for selective transformations under mild conditions. Hence, in most of the cases,[1,2] such transformations are only undertaken in the presence of metal catalysts (typically comprising precious metals) and often require also the use of strongly acidic media (concentrated sulfuric[3] and trifluoroacetic[4,5] acids, or a superacid[6]). In view of environmental and economical concerns, there is a strong current interest in the search for metal-free,[7] acid-solvent-free and/or aqueous medium alternatives[8] of alkane functionalization, topics of significance in areas of green and organic chemistries and catalysis that still remain poorly explored with respect to alkanes.

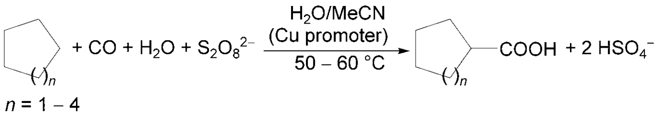
Among the variety of alkane functionalization reactions,[1–7] their direct carboxylation by CO to give carboxylic acids in a single-pot is particularly attractive,[4,5] since aliphatic carboxylic acids are important commodity chemicals with an increasing demand.[9] Their common synthetic procedures are characterized by one or several of the following drawbacks: (i) use of olefins and/or aldehydes as starting materials that are considerably more expensive than alkanes and require prior production, (ii) involvement of multi-stage transformations, (iii) requirement of harsh reaction conditions (high temperatures and pressures), (iv) use of costly metal catalysts, and (v) low conversions, poor selectivity and need of a complex work-up.[9] These limitations have stimulated an intensive research[5,10] focusing on the improvement and optimization of the alkane carboxylation method initially developed by Fujiwara,[4] which consisted in reacting an alkane with CO and $K_2S_2O_8$, at 80 °C, in absolute trifluoroacetic acid (TFA) and in the presence of a metal catalyst. Although remarkable improvements in the reaction efficiency have been achieved (i.e., yields and catalyst turnover numbers up to 93% and 2.0×10^4, respectively[10]), the principal limitation of using costly, corrosive and consumable TFA solvent constitutes a major problem of those carboxylation systems.

Within our general interest on the metal-catalyzed oxidative functionalization of alkanes,[10–12] namely on their selective oxidation to the corresponding alcohols and ketones,[11,12] and the single-pot carboxylation to carboxylic acids,[10] we have preliminary reported[13] a novel, efficient and cleaner reaction for the synthesis of various carboxylic acids from alkanes. In contrast to the carboxylation of alkanes in TFA,[4,5,10] this hydrocarboxylation reaction proceeds in aqueous medium (water being also a main source of the hydroxy group for the carboxylic acid product), at lower temperatures and even without any metal catalyst and any acid additive.[13]

Hence, in the present work we focus on the aqueous medium carboxylation of a diversity of cycloalkanes to the corresponding cycloalkanecarboxylic acids, aiming at (i) the exploration of the generality and versatility of the method, and (ii) the detailed investigation and optimization of cyclohexane and cyclopentane carboxylations, as models, by investigating their dependence on a variety of experimental conditions. The current study provides a very rare example of efficient alkane functionalization that proceeds under mild conditions, in aqueous medium and without requiring a metal catalyst (metal-free system).

Results and Discussion

The carboxylation reactions of cycloalkanes were studied in stainless steel autoclaves by allowing to react, at low temperatures (typically 50–60 °C) and in neutral H_2O/MeCN medium, a cycloalkane with carbon monoxide, potassium peroxodisulfate and water, either in the absence (metal-free) or in the presence (metal-promoted) of a metal promoter (Scheme 1). The effects of various reaction parameters, such as the (i) presence and type of a metal promoter, (ii) type of substrate, (iii) solvent composition, (iv) temperature, (v) time, (vi) CO pressure, and (vii) relative amounts of substrate and oxidant, were studied, aiming at the optimization of the cycloalkane carboxylation processes. In most of the cases, cyclohexane was chosen as a model substrate in view of leading to only one acid product, cyclohexanecarboxylic acid, and also due to the industrial significance of this acid, mainly as an intermediate in the toluene-based caprolactam process.[9c] Nevertheless, other carboxylic acids that can be obtained according to the procedures described in this work also possess valuable applications as intermediates in organic synthesis, in the manufacture of lubricants, flavours and fragrances.[9] The obtained results on cycloalkane carboxylations are summarized in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7 and Table 8 and discussed below. In Table 3, Table 4, Table 5, Table 6, Table 7 and Table 8, carboxylic acid (main product) concerns either $C_6H_{11}COOH$ or C_5H_9COOH, whereas ketone and alcohol (minor products) refer to either $C_6H_{10}O$ and $C_6H_{11}OH$, or C_5H_8O and C_5H_9OH.



Scheme 1. Hydrocarboxylation of cycloalkanes to the corresponding cycloalkanecarboxylic acids in H_2O/MeCN medium.

Metal-Free *vs.* Metal-Promoted Carboxylation of Cyclohexane

In contrast to the alkane carboxylations in TFA[4,5,10] and to most of the processes for carboxylic acid syntheses,[9] the carboxylation of cycloalkanes by CO in the $H_2O/MeCN/K_2S_2O_8$ system proceeds even in the absence of any metal catalyst, leading to the formation of, for example, cyclohexanecarboxylic acid ($C_6H_{11}COOH$) in *ca.* 18% yield based on cyclohexane (Table 2, entry 2). A crucial role in this unusual metal-free and mild transformation of an inert alkane is played by the active radical sulfate $SO_4^{-\bullet}$ (known as an efficient single electron-transfer oxidant),[14] generated upon thermolysis of peroxodisulfate. It should be noted that the metal-free carboxylations also proceed with the same efficiency in a Teflon reactor, thus confirming that reactions are not promoted by the metal wall of the reactor.

Bearing in mind that various metal-free oxidation reactions can proceed more efficiently in the presence of a metal promoter,[7,13] we have screened a series of Cu, Fe, Cr, V, Mn, Zn, Co and Mo containing salts, oxides and coordination compounds (known catalysts for the oxidative functionalization of alkanes[10,11f,12]) for a potential promoting effect in the aqueous medium carboxylation of cyclohexane (Table 1). Although the majority of the selected metal compounds promote the carboxylation (see below), some Mo, V, Cr, Zn and Co species exhibit an inhibiting effect, leading to inferior yields of $C_6H_{11}COOH$ in comparison with the metal-free system (Table 1, entries 2–6). This observation would be somehow unexpected taking into consideration that for example,

Table 1. Influence of different metal compounds on the carboxylation of cyclohexane in H_2O/MeCN medium.[a]

Entry	Metal promoter	Promoter amount [μmol]	Yield of products [%][b]		
			$C_6H_{11}COOH$	$C_6H_{10}O$	$C_6H_{11}OH$
1	Metal-free	–	12.3	0.7	0.1
2	MoO_3	32.0	0	0.1	0
3	$H_4[PMo_{11}VO_{40}]\cdot 34\,H_2O$	8.0	3.0	5.0	3.4
4	$Cr(OH)_3\cdot 2.5\,H_2O$	16.0	6.4	0.3	0
5	$Zn(NO_3)_2$	16.0	8.3	0.6	0
6	$Co(acac)_3$[c]	16.0	9.3	0.5	0
7	MnO_2	32.0	14.4	0.6	0.1
8	$Ca[V\{ON(CH_2COO)_2\}_2]$[d]	10.0	14.7	1.0	1.0
9	$Fe(OH)_3\cdot 0.5\,H_2O$	16.0	15.8	1.0	0.1
10	$Cu(NO_3)_2\cdot 2.5\,H_2O$	32.0	31.6	3.6	0.1
11	$[Cu(H_2tea)(N_3)]$[e]	16.0	32.5	2.5	0.4
12	$K_2Cr_2O_7$	32.0	33.1	8.4	0.7
13	$[Cu_2(H_2tea)_2(tpa)]_n\cdot 2n\,H_2O$[e,f]	8.0	38.8	1.9	0.3
14	Compound **1**	4.0	72.3	3.8	0.8

[a] *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).

[b] Product yield [%] (moles of product/100 mol of cyclohexane).

[c] acac = acetylacetonate.

[d] H_2O (2.0 mL)/MeCN (2.0 mL).

[e] H_2tea = monodeprotonated form of triethanolamine.

[f] H_2tpa = terephthalic acid.

$H_4[PMo_{11}VO_{40}]\cdot 34\,H_2O$ and $Cr(OH)_3\cdot 2.5\,H_2O$[11f] are catalysts for the carboxylation of gaseous alkanes in TFA[10b] and for the peroxidative oxidation of cycloalkanes in MeCN/H_2O,[11f] respectively. However, it reflects the dependence of the catalytic activity on the composition of the system and on the experimental conditions.

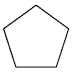
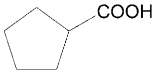
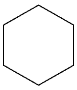
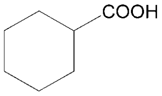
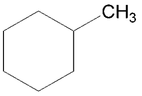
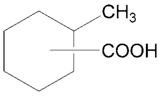
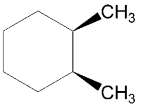
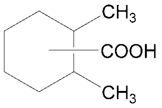
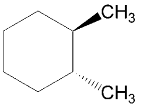
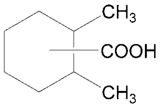
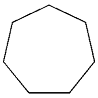
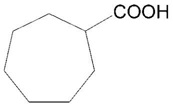
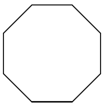
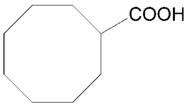
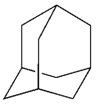
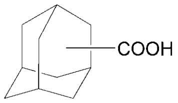
Among those metal compounds that exhibit a promoting effect (Table 1, entries 7–14), various derivatives of copper and potassium dichromate revealed the highest activity, leading to yields of $C_6H_{11}COOH$ (main product) in the 72–32% range. The formation of cyclohexanone and cyclohexanol as by-products due to the partial oxidation of cyclohexane is also detected (up to *ca.* 5 and 9% overall yields when promoted by Cu and Cr compounds, respectively). Since the most pronounced promoting behaviour is exhibited (Table 1, entry 14) by the hydrosoluble tetracopper(II) triethanolaminate derivative **1** – $[O\subset Cu_4\{N(CH_2CH_2O)_3\}_4(BOH)_4][BF_4]_2$ – (Scheme 2),[12a] it has been used in all further studies as the preferable metal promoter.

Substrate Versatility and Selectivity in the Metal-Free and Copper-Promoted Carboxylation of Cycloalkanes

The metal-free and copper-promoted carboxylations in aqueous medium are extendable to a variety of cycloalkanes as shown in Table 2 for C_5–C_8 cycloalkanes, methyl-substituted derivatives, and adamantane. Hence, apart from the most reactive cyclohexane (entry 2, 72% yield), other cyclic hydrocarbons such as cyclopentane (entry 1), methylcyclohexane (entry 3) and cycloheptane (entry 6) undergo rather efficient carboxylations, leading to 21–22% yields (based on cycloalkane) of carboxylic acids, when promoted by **1**. The carboxylations of these cycloalkanes are less favourable in the absence of the metal-promoter, resulting in carboxylic acids yields of *ca.* 5–8%. These yields are modest in comparison with those obtained in the presence of the metal promoter **1**, but in reality they are remarkable when one takes into consideration the inertness of alkanes, the fact that the systems are metal-free, and the reaction conditions are very mild, namely low temperatures, short times and use of aqueous medium without any added acid.

Although the promoter **1** has generally an important effect, it does not affect significantly the carboxylation of cyclooctane and adamantane (entries 7 and 8), resulting in carboxylic acid yields of 9.6 and 7.3% (copper-promoted) *vs.* 6.7 and 6.9% (metal-free), respectively. The absence of an evident promoting effect in the carboxylation of adamantane can be associated to the similarity of the bond selectivity parameter (2°:3°) in both metal-free (1:13) and copper-promoted (1:14) systems, which points out the similarly preferable carboxylation at tertiary carbon atoms with formation of 1-adamantanecarboxylic acid as the major product (entry 8). This acid was also the main product in the *N*-hydroxophthalimide-catalyzed car-

Table 2. Substrate versatility of the metal-free and copper-promoted direct carboxylation of cycloalkanes to carboxylic acids.[a]

Entry	Cycloalkane	Carboxylic acid product	Total yield [%][b] (Selectivity) Metal-free	Copper-promoted[c]
1			8.2[d]	22.2[d,e]
2			17.5[f]	72.3
3			4.9[g] (1°:2°:3° = 1:8:7)	21.4[g] (1°:2°:3° = 1:10:42)
4			2.5 (*trans/cis* = 1.02)	14.4[h] (*trans/cis* = 0.62)
5			4.9 (*trans/cis* = 0.86)	13.0 (*trans/cis* = 0.43)
6			7.5	20.8[g]
7			6.7[g,i]	9.6
8			6.9[g] (2°:3° = 1:13)	7.3[g] (2°:3° = 1:14)

[a] Selected results (for more essays, see Table 2, Table 3, Table 4, Table 5, Table 6, Table 7 and Table 8); *typical (unless stated otherwise) reaction conditions:* cycloalkane (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).

[b] Total yield [%] (moles of all carboxylic acids/100 moles of cycloalkane) determined by GC analysis; whenever applicable, selectivity parameters are indicated in brackets: 1°:2°:3° stand for bond selectivity meaning the relative normalized reactivities of hydrogen atoms at primary, secondary and tertiary carbon atoms of cycloalkanes; the stereoselectivity *trans/cis* parameter is the ratio of the formed acid isomers with mutual *trans* or *cis* orientation of the methyl groups.

[c] In the presence of compound **1** (4.0 μmol).

[d] C_5H_{10} (1.50 mmol).

[e] *p*(CO) = 40 atm (10.64 mmol).

[f] *p*(CO) = 5 atm (1.33 mmol).

[g] H_2O (2.0 mL)/MeCN (4.0 mL).

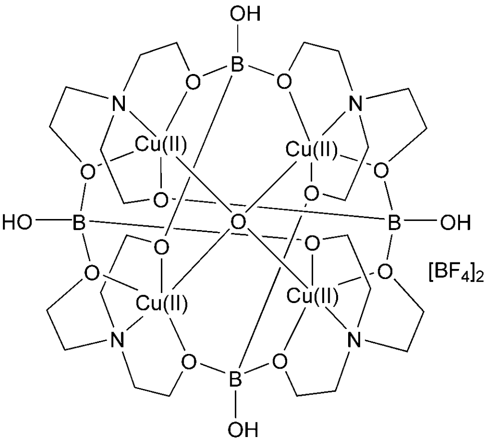
[h] Promoter **1** (8.0 μmol).

[i] 60 °C.

boxylation of adamantane in $CH_3COOH/(CH_2Cl)_2$ medium.[15]

In contrast, a different product pattern is observed when carboxylating methylcyclohexane. Thus, rather distinct bond selectivity parameters (1°:2°:3°) of 1:8:7 and 1:10:42 are obtained in the metal-free and copper-promoted carboxylations of methylcyclohexane, respectively (Table 2, entry 4). In the presence of compound **1** the reactivity of a tertiary carbon atom is dominant, leading to 1-methylcyclohexanecarboxylic acid as the main product, while in the metal-free carboxylation secondary and tertiary carbon atoms react similarly.

In order to reveal whether the presence of a metal promoter affects the stereoselectivity parameters,[1,16] we have studied the carboxylations of *cis*- and *trans*-1,2-dimethylcyclohexane (Table 2, entries 4 and 5). These reactions proceed significantly better in the presence of **1** resulting in 14.4 and 13.0% overall yields (1,2-dimethylcyclohexanecarboxylic acids being the main products) when using *cis*- and *trans*-cycloalkane, respectively, whereas in the metal-free systems the corresponding yields are only 2.5 and 4.9%. Al-



Scheme 2. Molecular formula of **1**.

though the metal-free carboxylation of both tested cycloalkane isomers proceeds non-stereoselectively (the *trans/cis* product ratios tend to approach unity), the presence of **1** leads to only a partial retention of the configuration (*trans/cis* = 0.62) upon carboxylation of the *cis*-isomer, while a substantial inversion of configuration (*trans/cis* = 0.43) is observed when carboxylating the *trans*-isomer of 1,2-dimethylcyclohexane.

Hence, the above features of bond and stereoselectivities allow us to conclude that the presence of compound **1** does not only promote the carboxylations of cycloalkanes, but also affects their mechanistic pathways and product distribution patterns. Nevertheless, in spite of providing inferior product yields, the metal-free systems are rather attractive from environmental and cost perspectives. Besides, the side reactions of cycloalkane oxidation to the corresponding alcohols and ketones are, in some cases, less extensive in the metal-free systems, leading to a superior selectivity towards the formation of carboxylic acids.

Effect of Solvent Composition

A significant advantage of the present carboxylation method with respect to prior work[4,5,6c,10,15,17,18] consists in the efficient application of the easily available, cheap, simple and recyclable water/acetonitrile medium, avoiding the use of an acid solvent, such as absolute trifluoroacetic acid. The solvent composition is a very important reaction parameter in the carboxylation of cycloalkanes (Table 3), which does not proceed in either only water (entries 8, 13) or only acetonitrile (entries 1, 9), or in the absence of both of them (i.e., only in cycloalkane). Acetonitrile dissolves the organic species, whereas water is needed not only to solubilize the peroxodisulfate oxidant (leading to a liquid biphasic medium), but also to provide the main source of the hydroxy group for the carboxylic acid product. For the first time, such an unprecedented carboxylating role of water has been proved by us in the reaction of cyclohexane with CO in $H_2{}^{18}O$/MeCN medium.[13a] This reaction resulted in the formation of the ^{18}O-labelled cyclohexanecarboxylic acid, $C_6H_{11}CO^{18}OH$, as the main product detected by ESI-MS^-.[13a]

Table 3. Effect of solvent composition on the copper-promoted and metal-free (yield values in brackets for the latter case) carboxylation of cyclohexane and cyclopentane.[a]

Entry	Cycloalkane	H_2O/MeCN [mL/mL]	Yield of products [%][b]		
			Carboxylic acid	Ketone	Alcohol
1	C_6H_{12}	0/6	0 (0)	0 (0)	0 (0)
2	C_6H_{12}	2/2	37.7 (8.2)	2.7 (0)	1.0 (0)
3	C_6H_{12}	2/4	36.8 (3.0)	1.8 (0)	0.2 (0)
4	C_6H_{12}	3/3	52.9 (5.6)	2.5 (0)	0.6 (0)
5	C_6H_{12}	3/4	46.3	3.1	0.7
6	C_6H_{12}	4/4	36.8	3.3	0.8
7	C_6H_{12}	4/2	7.7 (8.0)	3.4 (0)	0.7 (0)
8	C_6H_{12}	6/0	0 (0)	0 (0)	0 (0)
9	C_5H_{10}	0/6	0	0	0
10	C_5H_{10}	2/4	15.4	3.4	0.9
11	C_5H_{10}	3/3	19.6 (8.2)	4.8 (0)	1.7 (0.6)
12	C_5H_{10}	4/2	8.7	3.9	1.6
13	C_5H_{10}	6/0	0	0	0

[a] *Reaction conditions:* C_6H_{12} (1.00 mmol) or C_5H_{10} (1.50 mmol), compound **1** (8.0 μmol), $p(CO) = 20$ atm, $K_2S_2O_8$ (1.50 mmol), 50 °C, 6 h in an autoclave (13.0 mL capacity).

[b] Product yield [%] (moles of product/100 mol of cycloalkane); carboxylic acid concerns either cyclohexanecarboxylic acid ($C_6H_{11}COOH$) or cyclopentanecarboxylic acid (C_5H_9COOH), derived from cyclohexane or cyclopentane, respectively; ketone and alcohol refer to either cyclohexanone ($C_6H_{10}O$) and cyclohexanol ($C_6H_{11}OH$), or to cyclopentanone (C_5H_8O) and cyclopentanol (C_5H_9OH), derived from cyclohexane or cyclopentane, respectively.

The optimization of both the volumetric H_2O/MeCN ratio and the total amount of solvent in the hydrocarboxylation of cyclohexane and cyclopentane (Table 3) shows that, for the copper-promoted transformations, the highest yields of the corresponding carboxylic acids (*ca.* 53 and 20% of $C_6H_{11}COOH$ and C_5H_9COOH, respectively) are reached at the H_2O (3 mL)/MeCN (3 mL) composition (entries 4, 11). However, for the metal-free carboxylation of cyclohexane the yields are slightly higher (i.e., 5.6 *vs.* 8.2%) at the H_2O (2 mL)/MeCN (2 mL) and H_2O (4 mL)/MeCN (4 mL) compositions (entries 2, 4, 7). No significant effect of solvent composition on the formation of cyclohexanone and cyclohexanol by-products (*ca.* 2–4% overall yield) is revealed.

The H_2O/MeCN solvent appears to be a unique reaction medium (apart from TFA) for the efficient carboxylation of various alkanes. In fact, in the course of the search for an alternative to TFA reaction medium, we have tested,[10] apart from water and acetonitrile, a great variety of other solvents such as methanol, ethanol, dichlorometane, chloroform, formic acid, concentrated sulfuric and nitric acids, peroxymonosulfuric acid, acetic, trichloroacetic and tribromoacetic acids, trifluorotoluene and 1,1,2-trichlorotrifluoroethane, but all appeared to be unsuitable for the carboxylation of alkanes.

Although some direct alkane transformations to carboxylic acids in water have been reported,[17,18] including (i) the metal-free[17a] and Rh-catalyzed[17b] carbonylations of methane and ethane in the $H_2O/CO/K_2S_2O_8$ (or O_2) systems, and (ii) the V-catalyzed carboxylations of methane in the H_2O/CO/air system,[18] these processes are characterized by very low alkane conversions to carboxylic acids (their yields based on alkanes do not exceed 0.4%), the common use of higher temperature in addition to modest selectivities and applicability only to particular alkanes. Hence, our method in mixed H_2O/MeCN solvent allows one to obtain two orders of magnitude higher yields of products, under milder temperatures (50–60 °C *vs.* 95–115 °C), shorter reaction times (1 h *vs.* 10–352 h) and, even for the metal-free system, is also applicable to a variety of cycloalkanes.

Effect of Temperature and Time

The reaction temperature has also an important effect (Table 4), and the carboxylation of, for example, cyclohexane proceeds even at 25 °C. However, at this temperature the process is rather slow requiring 40 h to achieve *ca.* 12% yield of cyclohexanecarboxylic acid (entry 1). The reaction is faster and more efficient upon slightly increasing the temperature. Hence, for the copper-promoted carboxylation of cyclohexane under the reaction conditions of Table 4, the increase of temperature from 30 to 50 °C leads to a yield growth from *ca.* 3 to 38% (entries 2–4). Further augmentation of the temperature in the 60–100 °C interval leads to a gradual yield drop (entries 5–7), associated with the thermal decomposition of peroxodisulfate.[13a,14] A similar temperature profile is observed in the carboxylation of cyclopentane (entries 8–10), where the maximum acid product yield of *ca.* 20% is achieved at 50 °C. The optimum temperature of 60 °C is slightly higher in the metal-free carboxylation of cyclohexane (entries 3–6). No significant influence of the temperature (in the 50–100 °C range) on the yields of the cyclohexanone and cyclohexanol by-products is observed.

Table 4. Effect of reaction temperature on the copper-promoted and metal-free (yield values in brackets for the latter case) carboxylation of cyclohexane and cyclopentane.[a]

Entry	Cycloalkane	Temperature [°C]	Yield of products [%][b]		
			Carboxylic acid	Ketone	Alcohol
1	C_6H_{12}	25[c]	12.4	0.6	0.3
2	C_6H_{12}	30	2.7	0.4	0.1
3	C_6H_{12}	40	28.5 (4.3)	1.0 (0)	0.4 (0)
4	C_6H_{12}	50	37.7 (8.2)	2.7 (0)	1.0 (0)
5	C_6H_{12}	60	33.9 (17.5)	2.8 (0)	1.1 (0)
6	C_6H_{12}	80	23.2 (11.9)	2.7 (0)	0.9 (0)
7	C_6H_{12}	100	11.0	2.5	0.4
8	C_5H_{10}	40	5.4	1.1	1.7
9	C_5H_{10}	50	19.6 (8.2)	4.8 (0)	1.7 (0.6)
10	C_5H_{10}	60	17.4	4.6	1.5

[a] *Reaction conditions (unless stated otherwise):* C_6H_{12} (1.00 mmol) or C_5H_{10} (1.50 mmol), compound **1** (8.0 μmol), $p(CO) =$ 20 atm, $K_2S_2O_8$ (1.00 or 1.50 mmol for C_6H_{12} or C_5H_{10}, respectively), H_2O (2.0 mL)/MeCN (2.0 mL) or H_2O (3.0 mL)/MeCN (3.0 mL) for C_6H_{12} or C_5H_{10}, respectively; 6 h in an autoclave (13.0 mL capacity).

[b] Same as footnote [b] of Table 3.

[c] 40 h reaction time.

Table 5. Effect of reaction time on the copper-promoted and metal-free (yield values in brackets for the latter case) carboxylation of cyclohexane and cyclopentane.[a]

Entry	Cycloalkane	Time [h]	Yield of products [%][b]		
			Carboxylic acid	Ketone	Alcohol
1	C_6H_{12}	1	22.4 (13.3)	2.5 (0)	0.6 (0)
2	C_6H_{12}	2	23.0 (13.7)	2.4 (0)	0.5 (0)
3	C_6H_{12}	4	24.1 (14.2)	3.0 (0)	0.7 (0)
4	C_6H_{12}	6	23.2 (12.5)	2.7 (0)	0.9 (0)
5	C_6H_{12}	10	21.2 (16.7)	2.5 (0)	0.9 (0)
6	C_6H_{12}	15	22.2 (15.4)	2.9 (0)	0.9 (0)
7	C_5H_{10}	2	10.3	2.9	1.6
8	C_5H_{10}	4	19.9	4.4	1.5
9	C_5H_{10}	6	19.6	4.8	1.7
10	C_5H_{10}	8.5	21.6	3.9	1.4
11	C_5H_{10}	15	21.1	4.5	1.4

[a] *Reaction conditions:* C_6H_{12} (1.00 mmol) or C_5H_{10} (1.50 mmol), compound **1** (8.0 μmol), $p(CO) = 20$ atm, $K_2S_2O_8$ (1.00 or 1.50 mmol for C_6H_{12} and C_5H_{10}, respectively), H_2O (2.0 mL)/MeCN (2.0 mL) or H_2O (3.0 mL)/MeCN (3.0 mL) for C_6H_{12} and C_5H_{10}, respectively; 80 or 50 °C for C_6H_{12} or C_5H_{10}, respectively; in an autoclave (13.0 mL capacity).

[b] Same as footnote [b] of Table 3.

The carboxylation of cycloalkanes in the H_2O/CH_3CN medium is rather fast, as is typical for reactions proceeding *via* free radicals. High yields that are close to the maximum values can be achieved after 1 h reaction time at 80 °C (Table 5, entry 1 *vs.* entries 2–6), both in the copper-promoted and metal-free carboxylations of, for example, cyclohexane. However, at the optimum temperature of 50 °C, the reactions are slower requiring *ca.* 4–6 h to achieve the best conversions, as shown for the carboxylation of cyclopentane (Table 5, entries 7–11). From the selectivity viewpoint, it is worthwhile to mention that even at prolonged reaction times the metal-free carboxylation of cyclohexane proceeds with practically no formation of cyclohexanone and cyclohexanol by-products. Moreover, neither linear nor cyclic dicarboxylic acids, eventually formed as a result of ring opening or carboxylation at two positions, have been detected in the carboxylation of cyclohexane, in the present work.

Effect of the Copper Promoter Amount

Although the carboxylation of cycloalkanes proceeds even in the absence of any metal promoter (Table 1 and Table 2), the copper(II) complex **1** exhibits a noticeable promoting effect that depends on its relative amount (Table 6). Hence, even a very small quantity of **1** (i.e., 2 μmol corresponding to a C_6H_{12}/**1** molar ratio of 500) is sufficient to reach a rather high yield of $C_6H_{11}COOH$ (50.4%) with a turnover number (TON) of 191 (upon deducting the carboxylic acid

Table 6. Effect of the promoter **1** amount on the carboxylation of cyclohexane and cyclopentane.[a]

Entry	Cycloalkane	Promoter **1** [μmol]	Yield of products [%][b]			TON[c]
			Carboxylic acid	Ketone	Alcohol	
1	C_6H_{12}	–	12.3	0.7	0.1	–
2	C_6H_{12}	2.0	50.4	1.7	0.2	191
3	C_6H_{12}	4.0	72.3	3.8	0.8	150
4	C_6H_{12}	8.0	52.9	2.5	0.6	51
5	C_6H_{12}	16.0	48.5	2.7	0.5	23
6	C_5H_{10}	–	8.2	0	0.6	–
7	C_5H_{10}	2.0	20.5	5.3	1.3	92
8	C_5H_{10}	4.0	20.6	4.5	1.4	47
9	C_5H_{10}	8.0	19.6	4.8	1.7	21
10	C_5H_{10}	16.0	12.0	4.8	1.3	4

[a] *Reaction conditions:* C_6H_{12} (1.00 mmol) or C_5H_{10} (1.50 mmol), $p(CO) = 20$ atm, $K_2S_2O_8$ (1.00 or 1.50 mmol for C_6H_{12} and C_5H_{10}, respectively), H_2O (3.0 mL)/MeCN (3.0 mL), 50 °C, 6 h in an autoclave (13.0 mL capacity).

[b] Same as footnote [b] of Table 3.

[c] Turnover number has been estimated as the difference between the numbers of moles of carboxylic acid product in the presence and in the absence of **1**, divided by the number of moles of **1**.

amount formed under metal-free conditions) in the carboxylation of cyclohexane (Table 6, entry 2). However, the maximum yield of cyclohexanecarboxylic acid (72.3%) is obtained when using 4 μmol of **1** (C_6H_{12}/**1**=250), featuring the also high TON value of 150 (entry 3). A further enhancement of the copper promoter amount leads to a yield drop (entries 4 and 5). The carboxylation of cyclopentane is found to be less sensitive to the amount of **1**, leading to almost similar yields of C_5H_9COOH (*ca.* 20–21%) in the presence of 2–8 μmol of **1** (corresponding to the C_5H_{10}/**1** molar ratios of 750–188), although the TON values vary from 92 to 21 (entries 7–9). The yield of cyclopentanecarboxylic acid also decreases at a higher amount of **1** (16 μmol), thus pointing out the occurrence of an inhibiting effect as in the case of cyclohexane carboxylation. It should be noted that apart from the high activity of **1**, the use of this compound as a preferable metal promoter is advantageous due to its hydrosolubility, high stability and facile aqueous medium self-assembly synthesis from rather cheap and readily available chemicals.[12]

In the systems promoted by **1**, TONs and yields of C_5H_9COOH and $C_6H_{11}COOH$ (Table 6) are comparable to or even higher than those reported for the V-catalyzed carboxylations of cyclopentane (TON=50, 33% yield) and cyclohexane (TON=73, 50% yield) in TFA[5c] which, however, were attained at longer reaction times (20 *vs.* 6 h) and higher temperatures (80 *vs.* 50 °C). Besides, aqueous medium carboxylations are more selective since typical by-products (alkyl trifluoroacetates, carbon dioxide) in the processes in TFA[10] are not formed.

Effect of CO Pressure

As a carboxylating agent, CO should be introduced into the system in some excess relative to the cycloalkane to achieve the best yields of carboxylic acids (Table 7). For the copper-promoted carboxylation of C_6H_{12}, an increase of the CO pressure in the 0–20 atm interval leads to a $C_6H_{11}COOH$ yield growth (entries 1–6) that reaches the maximum value of 53% at 20 atm of CO. A subsequent increase of the CO pressure results in a yield diminution. Interestingly, in the metal-free carboxylation of cyclohexane, the highest yield of carboxylic acid (17.5%) is achieved at the lower *p*(CO) of 5 atm (entry 3), which corresponds to the CO/C_6H_{12} molar ratio of 1.33. The carboxylation of C_5H_{10} promoted by **1** appears to be less sensitive to CO pressure in the 15–40 atm range, as attested by the rather close yields (i.e., *ca.* 17–22%) of cyclopentanecarboxylic acid (entries 14–17).

In contrast to the alkane carboxylations in TFA that can proceed even in the absence of CO (with TFA acting as a carbonylating agent[5,10]), the hydrocarboxylation reactions in the present work cannot

Table 7. Effect of CO pressure on the copper-promoted and metal-free (yield values in brackets for the latter case) carboxylation of cyclohexane and cyclopentane.[a]

Entry	Cycloalkane	*p*(CO)[b] [atm]	Yield of products [%][c]		
			Carboxylic acid	Ketone	Alcohol
1	C_6H_{12}	0	0 (0)	3.9 (0)	1.6 (0)
2	C_6H_{12}	3	20.4 (14.1)	8.7 (0)	3.1 (0)
3	C_6H_{12}	5	20.6 (17.5)	7.7 (0)	1.0 (0)
4	C_6H_{12}	10	24.2 (13.5)	7.5 (0)	1.8 (0)
5	C_6H_{12}	15	38.7 (13.4)	2.9 (0)	0.7 (0)
6	C_6H_{12}	20	52.9 (12.3)	2.5 (0)	0.6 (0)
7	C_6H_{12}	35	44.1	2.9	0.3
8	C_6H_{12}	40	38.1 (5.7)	2.0 (0)	0.1 (0)
9	C_6H_{12}	35[d]	54.3	3.0	0.5
10	C_6H_{12}	20 atm CO_2	0	9.4	4.9
11	C_5H_{10}	0	0	4.5	3.0
12	C_5H_{10}	5	7.2	4.5	2.5
13	C_5H_{10}	10	9.5	5.1	2.1
14	C_5H_{10}	15	19.8	4.6	1.9
15	C_5H_{10}	20	19.6	4.8	1.7
16	C_5H_{10}	30	17.2	3.4	0.8
17	C_5H_{10}	40	22.2	3.3	0.7

[a] *Reaction conditions (unless stated otherwise):* C_6H_{12} (1.00 mmol) or C_5H_{10} (1.50 mmol), compound **1** (8.0 μmol), $K_2S_2O_8$ (1.00 or 1.50 mmol for C_6H_{12} and C_5H_{10}, respectively), H_2O (3.0 mL)/MeCN (3.0 mL), 50 °C, 6 h in an autoclave (13.0 mL capacity).

[b] Measured at 25 °C (amount of CO gas corresponds to 0.266 $mmol \cdot atm^{-1}$.

[c] Same as footnote [b] of Table 3.

[d] 20 h reaction time.

occur to any extent in the absence of CO (Table 7, entries 1 and 11). Besides, the MeCN solvent is inert under the used reaction conditions and its conversion into acetic acid has not been detected. Hence, carbon monoxide is the only source of the carbonyl group in the acid product.

The attempted replacement of CO by CO_2 as an alternative carboxylating agent was not successful, although carbon dioxide appeared to promote the oxidation of cyclohexane leading to increased yields of the cyclohexanone and cyclohexanol by-products (Table 7, entry 10). Besides, the formation of these oxidation products is more favourable at low CO pressures in the copper-promoted reactions of cycloalkanes (entries 1–4 and 11–13), when the competition of carboxylation *vs.* oxidation is hampered by the low $p(CO)$.

Effect of Oxidant and Cycloalkane Amounts

The use of potassium peroxodisulfate (typically in the equimolar amount or in a slight excess relative to cycloalkane) is indispensable for the carboxylation reactions, since no products are observed in its absence (Table 8, entries 1, 7). Peroxodisulfate acts as both a radical initiator and an oxidizing agent, leading, under the conditions of Table 8, to the maximum carboxylic acid yields of *ca.* 53 and 20% in the copper-promoted carboxylation of cyclohexane and cyclopentane, respectively (entries 3, 9), obtained at $K_2S_2O_8/C_6H_{12}$ and $K_2S_2O_8/C_5H_{10}$ molar ratios of 1.5:1 and 1:1. The peroxodisulfate is rationally consumed with an oxidant efficiency (% product yield based on oxidant) up to, for example, 48% in the copper-promoted carboxylation of C_6H_{12} (conditions of entry 2, Table 2). Moreover, $K_2S_2O_8$ is almost quantitatively transformed during the reaction to give $KHSO_4$ which, upon cooling the reaction mixture, can be easily crystallized and separated by filtration, and potentially reconverted to peroxodisulfate *via* established electrochemical processes.[19] Other peroxodisulfate salts, for example, $(NH_4)_2S_2O_8$, can be also applied providing similar yields.

It should be noted that the carboxylations do not occur upon replacement of peroxodisulfate by other inorganic or organic oxidants such as, for example, H_2O_2, *t*-BuOOH or KIO_4. Besides, carboxylation does not proceed with O_2 as a sole oxidant (entry 6), but when dioxygen is used together with peroxodisulfate, a significant decrease in the yield of $C_6H_{11}COOH$ (*ca.* 53 to 7%, entry 3 *vs.* 5) is detected. This is indicative that O_2 acts as a radical scavenger, reacting with the cycloalkyl radical ($R^\bullet$) to give the peroxyl radical ($ROO^\bullet$), thus promoting the formation of oxygenated products, cyclohexanone and cyclohexanol, with an overall yield of *ca.* 12% (entry 5) *vs.* 3% in the carboxylation without added O_2.

Traces of dioxygen can be generated from peroxodisulfate[14c] or be present as adventitious air, thus explaining the formation (*via* the peroxyl radical) of cyclic alcohols and ketones as by-products. Alkyl hydroperoxide (ROOH) is a plausible intermediate, derived from $ROO^\bullet$, and its amount could be estimated from the variations in the alcohol and ketone yields, determined by GC analyses, before and after addition to the final reaction mixture of PPh_3, according to a method reported by Shul'pin.[2a] Nevertheless, in the present work, no variation in alchohol and ketone yields upon addition of PPh_3 was detected, suggesting

Table 8. Effects of cycloalkane and oxidant amounts on the copper-promoted carboxylation of cyclohexane and cyclopentane.[a]

Entry	Cycloalkane [mmol]	$K_2S_2O_8$ [mmol]	Yield of products [%][b] Carboxylic acid	Ketone	Alcohol
Cyclohexane carboxylation					
1	1.0	0	0	0	0
2	0.5	1.5	34.8	4.0	0
3	1.0	1.5	52.9	2.5	0.6
4	1.5	1.5	36.0	2.9	0.6
5	1.0	$1.5+O_2$ (10 atm)	7.0	10.1	1.7
6	1.0	$0+O_2$ (10 atm)	0	0.2	0
Cyclopentane carboxylation					
7	1.0	0	0	0	0
8	1.0	1.5	14.5	7.0	1.4
9	1.5	1.5	19.6	4.8	1.7
10	2.0	1.5	11.8	3.6	3.5
11	1.5	2.0	11.0	4.0	1.4

[a] *Reaction conditions:* Compound **1** (8.0 μmol), $p(CO)=20$ atm, H_2O (3.0 mL)/MeCN (3.0 mL), 50 °C, 6 h in an autoclave (13.0 mL capacity).

[b] Same as footnote [b] of Table 3.

that ROOH has already decomposed into the corresponding alcohol and ketone along the reaction course.

Reaction Mechanism

The accumulated background on alkane carboxylations, both in TFA[5,10] and H_2O/MeCN[13] media, is indicative of free radical reaction mechanisms. Based on the combination of literature and experimental data, tests with radical traps and ^{18}O-labelled H_2O,[13a] the simplified mechanistic pathway of Scheme 3 can be proposed for the hydrocarboxylation of cyclohexane, used as a model substrate. For both metal-free and copper-promoted carboxylations of cyclohexane, it involves the formation of a free cyclohexyl radical, which is generated by H atom abstraction from C_6H_{12} (reaction 1) by the sulfate radical $SO_4^{-\bullet}$. The latter is derived from the thermolytic and copper-promoted (when in the presence of **1**) decomposition of $K_2S_2O_8$.[10c,13a,17a]

This involvement of cyclohexyl radical is confirmed by performing the carboxylations (both metal-free and copper-promoted) in the presence of the carbon-centred radical trap $CBrCl_3$, what results in the full suppression of cylcohexanecarboxylic acid formation and the appearance of cyclohexyl bromide as the main product with yields of *ca.* 22% under the reaction conditions of entry 3 of Table 8. The radical pathway is also supported by the inhibiting effect of O_2, acting as a cyclohexyl trap to give the $C_6H_{11}COO^{\bullet}$ peroxyl radical.

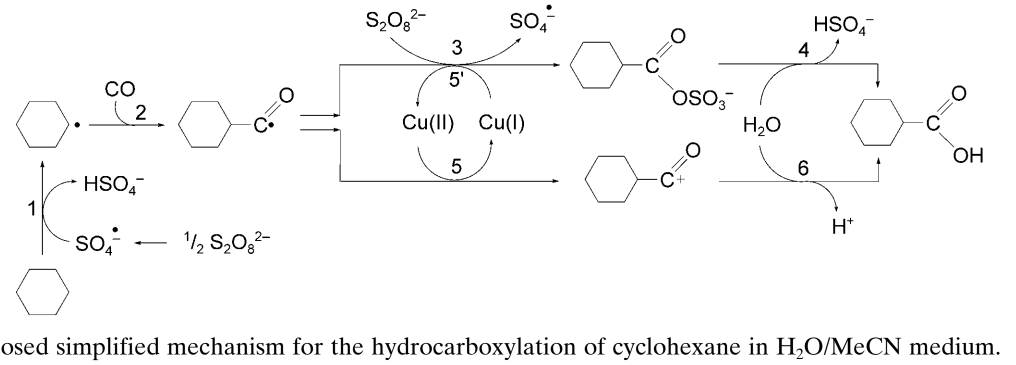
Subsequent carbonylation of the cyclohexyl radical by carbon monoxide results in the acyl radical $C_6H_{11}CO^{\bullet}$ (reaction 2) that upon oxidation by $S_2O_8^{2-}$ generates the acyl sulfate $C_6H_{11}C(O)OSO_3^-$ (reaction 3). This is hydrolyzed by water (reaction 4) furnishing the cyclohexanecarboxylic acid.[13a] In the copper-promoted process, an alternative route (reaction 5) can occur, where the tetracopper(II) complex **1** can behave as an oxidant of the acyl radical (reaction 5). This route involves the Cu(II)/Cu(I) redox couple and requires $K_2S_2O_8$ for regeneration (reaction 5′) of the Cu(II) form. The highest activity of copper(II) in comparison with the other tested metal compounds (Table 1) can be accounted for by its particular effectiveness[14a] in the oxidation of carbon-centred radicals. Hydrolysis of the thus formed acyl cation $C_6H_{11}CO^+$ ultimately leads to the $C_6H_{11}COOH$ product (reaction 6), *via* protonated cyclohexanecarboxylic acid $C_6H_{11}C(OH)_2^+$ which is deprotonated by water, as supported by theoretical calculations on the corresponding species derived from the ethyl radical.[13a]

The hydroxylating role of water is played in both metal-free (3 → 4) and copper-promoted (5 → 6) pathways, as confirmed[13a] by experiments with $H_2^{18}O$ leading to $C_6H_{11}CO^{18}OH$ as the main product. Less favourable routes include the formation of unlabelled $C_6H_{11}COOH$, proceeding through the mixed anhydride $C_6H_{11}C(O)OSO_3H$ that is obtained by protonation of the acyl sulfate by HSO_4^-, or by coupling of $C_6H_{11}CO^+$ with HSO_4^-. This anhydride would undergo intramolecular H-transfer with elimination of SO_3, thus furnishing the $C_6H_{11}COOH$ product.[13a] It should also be noted that our type of mechanism (Scheme 3) is different from that proposed by Ishii[15] for the *N*-hydroxyphthalimide-catalyzed carboxylation of polycyclic alkanes in the $CO/O_2/CH_3COOH/(CH_2Cl)_2$ system, where the HO oxygen of the carboxylic moiety (RCO*O*H) originates not from H_2O but from O_2 which, upon addition to an acyl radical ($RCO^{\bullet}$), forms the corresponding intermediate peroxyl $RC(O)OO^{\bullet}$ radical.

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

Conclusions

In the present study, we have extended to a variety of cycloalkane substrates our recently developed method[13] for the hydrocarboxylation of saturated hy-



Scheme 3. Proposed simplified mechanism for the hydrocarboxylation of cyclohexane in H_2O/MeCN medium.

drocarbons in aqueous medium. Hence, cyclopentane, cyclohexane, methylcyclohexane, *cis*- and *trans*-1,2-dimethylcyclohexanes, cycloheptane, cyclooctane and adamantane can be carboxylated by CO and water to the corresponding cycloalkanecarboxylic acids.

Important features of these single-pot transformations consist in (i) the use of the cheap and recyclable water/acetonitrile medium (thus avoiding an acid solvent such as absolute trifluoroacetic acid[4,5,10]), (ii) the uncommon and useful application of water not only as a solvent component but also as a relevant reagent (providing the main source of the OH group in the carboxylic acid product), (iii) the possibility to operate under metal-free conditions and very mild temperatures (typically *ca.* 50 °C), and (iv) the rather high efficiency and selectivity with yields (based on cycloalkane) of carboxylic acids up to 72% (*vs.* maximum yields of 0.4% in other alkane carbonylation/carboxylation systems[17,18] operating either in sole H_2O or MeCN). Considering the high inertness of C–H bonds in cycloalkanes, the soft reaction conditions (low temperatures, short reaction times, acid-solvent-free and metal-free systems) in combination with the rather high yields are very remarkable and, to the best of our knowledge, have never been reached in the area of alkane functionalization involving reactions of C–C bond formation.[7,8a]

Besides, the carboxylations of cyclohexane and cyclopentane (used as model substrates) have been optimized by studying the effects of a variety of experimental factors, namely metal promoters, their types and amounts, solvent composition, temperature, time, CO pressure, oxidant and cycloalkane. Furthermore, the difference in bond and stereoselectivity parameters, found in the metal-free and copper-promoted carboxylations of methylcyclohexane and stereoisomeric 1,2-dimethylcyclohexanes, corroborate the involvement of distinct mechanistic pathways. A free radical mechanism, supported by literature background,[5,10,13a] experimental data, and tests with radical traps and ^{18}O-labelled H_2O,[13a] has been discussed for the cyclohexane carboxylation, taken as a model reaction.

The work has also been extended to new cycloalkane substrates and their carboxylations with the recognized catalytic application of the hydrosoluble tetracopper(II) triethanolaminate-derived complex **1** in the field of alkane functionalization under mild conditions.[12,13] However, further exploration of alkane carboxylation catalysts should not be limited to compound **1**, and other water-soluble copper complexes[11a,d,20] will be screened.

Although higher yields are typically attained in the copper-promoted systems, this should not discourage further exploration of the uncommon and remarkable metal-free alkane carboxylations, which are rather attractive from environmental, cost and selectivity perspectives. Further development of cycloalkane carboxylations in aqueous medium, aiming at the recycling of reagents, and searching for other oxidants, promoters and more favourable reaction conditions, is currently in progress.

Experimental Section

General Methods

All chemicals were obtained from commercial sources and used as received. Compound **1**[12] and the other tested promoters[11f,12,21] were prepared according to published procedures. 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, ^1H and ^{13}C-{^1H} 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.

Cycloalkane Carboxylations

In a typical experiment the reaction mixtures were prepared as follows: to 0.0–32.0 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 was 6.0 mL) and 1.00–1.50 mmol (typically 1.00 mmol) of cycloalkane. Then the autoclave was closed and flushed with N_2 three times for removing the air and pressurized with 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 the contents 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 vigorously stirred for 10 min, and the organic layer was analyzed typically by GC.

Additional experiments were performed under typical reaction conditions in the presence of the carbon-centred 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.

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