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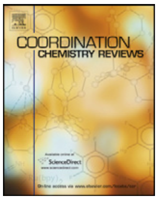

Review

Multicopper complexes and coordination polymers for mild oxidative functionalization of alkanes

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ABSTRACT

Alkanes (main components of natural gas and oil) are rather inert compounds and their functionalization under mild conditions, toward the synthesis of added value organic products, constitutes a challenge to modern chemistry. A promising approach concerns the development of bioinspired metal complex catalysts which, with an appropriate oxidizing agent and under tuned reaction conditions, are capable of

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Abbreviations: 1D, one-dimensional; 18-crown-6, 1,4,7,10,13,16-hexaoxacyclooctadecane; 2D, two-dimensional; 3D, three-dimensional; aq., aqueous; Bis–Tris, see H_5bts; bmpa, bis(2-pyridylmethyl)amine; *cis*-DMCH, *cis*-1,2-dimethylcyclohexane; CyOOH, cyclohexyl hydroperoxide; DFT, density functional theory; equiv., equivalents; ESR, electron spin resonance spectroscopy; GC, gas chromatography; H_2bdea, N-butyldiethanolamine; H_2dea, diethanolamine; H_2dipic, dipicolinic acid; H_2edea, N-ethyldiethanolamine; H_2mdea, *N*-methyldiethanolamine; H_2tpa, terephthalic acid; H_3bes, N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid; H_3tea, triethanolamine; H_4pma, pyromellitic acid; H_5bts, Bis–Tris (bis(2-hydroxyethyl)amino-tris(hydroxymethyl)methane); Hacra, acrylic acid; Hba, benzoic acid; Hbuta, butanoic acid; Hcba, 3-chlorobenzoic acid; Hdnba, Hdhba 3,5-dinitrobenzoic acid 3,5-dihydroxybenzoic acid; Hhepa, heptanoic acid; Hhexa, hexanoic acid; Hmacra, methacrylic acid; Hmba, 2-methoxybenzoic acid; Hmbuta, 2-methylbutanoic acid; Hmhba, 3-hydroxybenzoic acid; Hphba, 4-hydroxybenzoic acid; Hpta, 4-methylbenzoic acid; Hpz, pyrazole; HL^1, 4-methyl-2,6-bis(2-fluoroethyliminomethyl)phenol; HL^2, 4-methyl-2,6-bis(2-chloroethyliminomethyl)phenol; HL^3, 4-methyl-2,6-bis(2-bromoethyliminomethyl)phenol; H_4L^4, 2,7,13,18-tetramethyl-3,6,14,17-tetraazatricyclo-[17.3.1.1]-tetracosa-1(23),2,6,8(24),9,11,13,17,19,21-decaene-9,11,20,22-tetraol; H_4L^5, 2,7,13,18-tetramethyl-3,6,14,17-tetraazatricyclo-[17.13.1.1]-tetracosa-1(23),8(24),9,11,19,21-hexane-9,11,20,22-tetraol; H_2L^6, 3-(2-hydroxy-phenylhydrazo)pentane-2,4-dione; H_3L^7, 3-(phenylhydrazo-2-arsonic acid)pentane-2,4-dione; H_2L^8, 3-(2-carboxy-phenylhydrazo)pentane-2,4-dione; H_2L^9, 5,5-dimethyl-2-(2-hydroxy-phenylhydrazo)cyclohexane-1,3-dione; H_2L^{10}, 1-ethoxy-2-(2-hydroxy-phenylhydrazo)butane-1,3-dione; H_2L^{11}, 3-(2-hydroxy-4-nitrophenylhydrazo)-pentane-2,4-dione; HL^{12}, 4-isopropyl-2,6-bis[{4-hydroxy-3,5-bis(*tert*-butyl)phenyl}-iminomethyl]phenol; HL^{13}, 4-*tert*-butyl-2,6-bis[{4-hydroxy-3,5-bis(*tert*-butyl)phenyl}iminomethyl]phenol; HL^{14}, $\{Me_2N(CH_2)_3N{=}C(H)C_6H_3(OMe)(OH)\}$; HL^{15}, $\{Me_2N(CH_2)_3N{=}C(Me)C_6H_4(OH)\}$; L^{16}, 1,4,7-trimethyl-1,4,7-triazacyclononane; H_3L^{17}, N,N,N′,N′-tetrakis(2-hydroxyethyl)ethylenediamine; MCH, methylcyclohexane; pMMO, particulate methane monooxygenase; poba, 4-oxybenzoate(2−); py_2SSpy_2, bis{2-[N,N-bis(2-pyridylethyl)-amino]-1,1-dimethylethyl}disulfide; r.t., room temperature (20–25 °C); sMMO, soluble methane monooxygenase; TBHP, *tert*-butyl hydroperoxide; TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl; TFA, trifluoroacetic acid; TOF, catalyst turnover frequency (moles of products per mol of catalyst per hour); TON, catalyst turnover number (moles of products per mol of catalyst); tpzms, 2,2,2-tris(1-pyrazolyl)ethyl methanesulfonate; *trans*-DMCH, *trans*-1,2-dimethylcyclohexane; UV–vis, ultraviolet–visible spectroscopy.

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converting alkanes into valuable functionalized products. In view of the well recognized biological function of copper, which is present in the active sites of many oxidation enzymes including the multicopper particulate methane monooxygenase (pMMO), the current contribution summarizes recent advances in the oxidative functionalization of alkanes catalyzed by multicopper systems. The main types of polynuclear copper complexes and coordination polymers applied in homogeneous alkane transformations are classified, and the critical analysis of the most efficient catalytic systems in two different reactions is presented. These reactions include the mild oxidation of alkanes (typically cyclohexane as a model substrate) by hydrogen peroxide into alkyl hydroperoxides, alcohols, and ketones, as well as the hydrocarboxylation of gaseous and liquid C_n ($n = 2–9$) alkanes, by carbon monoxide, water, and potassium peroxodisulfate into the corresponding C_{n+1} carboxylic acids. The important effects of various reaction parameters are highlighted and the preferable requirements for a prospective homogeneous Cu-based catalyst in oxidative transformations of alkanes are identified. Emphasis is given on the use of hydrosoluble copper catalysts with an N,O-environment, acid co-catalysts, H_2O/MeCN mixed solvent, under mild reaction conditions.

1. Introduction

As the main components of natural gas and oil, alkanes are abundant and relatively cheap potential carbon raw materials for the synthesis of added value organic chemicals. However, the high inertness of saturated hydrocarbons under mild conditions impedes their broad synthetic use. Therefore, they are mainly utilized as fossil fuels or converted, via different power-consuming processes (cracking, dehydrogenation or reforming), into olefins that are common and more reactive species in large-tonnage organic synthesis [1–4].

Hence, the search for mild, efficient, and direct routes for oxidative functionalization of alkanes to industrially valuable products constitutes a subject of high relevance in various areas including homogeneous catalysis, bioinorganic, and green chemistry. A promising approach consists on the design and development of new bioinspired catalysts [1,2,5] which, with an appropriate oxidizing agent, are capable of converting alkane substrates into different oxidation products (alkyl hydroperoxides, alcohols, ketones, aldehydes, or carboxylic acids), under mild conditions and in aqueous medium.

Among various metals with a recognized biological function, copper is cheap and widespread in nature, being present in the active sites of many oxidation enzymes often as di-, tri- or polynuclear Cu centers that can selectively catalyze a number of oxidation reactions [5,6]. In this regard, particulate methane monooxygenase (pMMO) that bears an active site composed of a multicopper cluster with N,O-environment appears to be a unique copper enzyme capable of catalyzing the hydroxylation of alkanes and other substrates [7]. Although numerous examples of bioinspired multicopper complexes with intricate polydentate ligands have been designed as synthetic models of pMMO and other enzymes [5–7], their application in homogeneous catalysis with respect to alkanes is very scant, being mainly limited to functionalization of activated C—H bonds. A few reviews on pMMO models are available [7a,8].

Only a couple of reports [9,10] on the use of multicopper compounds in alkane oxidation were available before 2005 [9,10], when we started to develop [11] a versatile aqueous medium self-assembly method for the generation of diverse multicopper(II) complexes and coordination polymers upon combination in water of a copper salt with cheap and commercially available ligands such as aminopolyalcohols and benzenecarboxylates [11–15]. Such copper compounds disclosed a high catalytic activity for the oxidative functionalization of different C_1–C_9 alkanes under mild conditions. These transformations include the mild oxidation of alkanes (typically cycloalkanes) by hydrogen peroxide to the corresponding alkyl hydroperoxides, alcohols, and ketones [11–14,16–18], as well as the hydrocarboxylation of gaseous and liquid C_n ($n = 2–9$) alkanes, by CO and H_2O and in the presence of peroxodisulfate oxidant, to give C_{n+1} carboxylic acids [4,19–26]. Meanwhile, the types of multicopper catalytic systems used in alkane oxidation have also been extended to novel Cu(II) complexes and coordination polymers bearing azo derivatives of β-diketones [27–29], Schiff bases [30–33], pyrazole and various carboxylate ligands [34–37].

Given the fact that the research on oxidative functionalization of alkanes catalyzed by multicopper systems has not yet been reviewed in spite of its high potential for further developments, the main objective of the present contribution is to summarize recent advances in this area. Hence, herein we classify and describe the main types of multicopper compounds applied in homogeneous oxidative functionalization of alkanes (Section 2), and provide a critical analysis of the most efficient and selective catalytic systems for the oxidation (Section 3) and hydrocarboxylation (Section 4) of such hydrocarbons.

The scope of the present contribution does not cover the mononuclear copper complexes, the heterogeneous systems based on encapsulated or supported multicopper complexes, and the catalytic transformations of substrates that are not alkanes although containing aliphatic groups (e.g., alkylarenes).

2. Multicopper catalytic systems in homogeneous oxidative functionalization of alkanes

From both environmental and economical viewpoints, water is the ideal green solvent for many mild catalytic transformations including the oxidative functionalization of alkanes [38,39]. In contrast to organic solvents, water is also very stable toward oxidation. Moreover, the performance of catalytic reactions in aqueous medium typically requires the use of aqua-soluble catalysts that often mimic the functions of enzymes. Although a considerable number of bioinspired multicopper complexes have been developed as potential models of pMMO and related copper-based enzymes [5,6,7a], those catalysts were often not soluble in water and exhibited modest activities. In addition, they were hardly tested for alkane oxidation reactions. However, a series of multinuclear copper(II) complexes that typically possess a N,O-environment and exhibit aqueous solubility have recently been reported and applied as catalysts or catalyst precursors in such alkane reactions [11–14,16–25]. Although some parent complexes are not aqua-soluble, they can be catalyst precursors of active hydrosoluble species upon treatment with an acid promoter and/or oxidant [26–29,34–36,40,41]. Hence, multicopper catalysts or catalyst precursors are grouped on the basis of their nuclearity and briefly described in the following sections.

2.1. Dicopper complexes

Various types of dicopper complexes (**1**–**21**) have been applied in the oxidative transformations of alkanes (Table 1). Although

Table 1
Dicopper complexes as catalysts or catalyst precursors.

Compound number	Formula	Cu coord. number and environment	X-ray structure	Alkane substrates[a]	Ref.
1	$[Cu_2(\mu\text{-}H_2tea)_2(ba)_2]\cdot2H_2O$	6, $\{CuNO_5\}$	+	C_6H_{12}	[11,12]
2	$[Cu_2(\mu\text{-}H_2tea)_2(pta)_2]\cdot2H_2O$	6, $\{CuNO_5\}$	–	C_6H_{12}	[12]
3	$[Cu_2(\mu\text{-}H_2tea)_2(cba)_2]\cdot2H_2O$	6, $\{CuNO_5\}$	+	C_6H_{12}	[12]
4	$[Cu_2(\mu\text{-}Hedea)_2(NCS)_2]$	5, $\{CuN_2O_3\}$	+	Cyclic and linear C_5–C_8[b]	[24]
5	$[Cu_2(\mu\text{-}Hbdea)_2(N_3)_2]$	5, $\{CuN_2O_3\}$	+	C_6H_{12}	[16]
6	$[Cu_2(\mu\text{-}Hbdea)_2(pta)_2]\cdot2H_2O$	5, $\{CuNO_4\}$	+	C_6H_{12}	[16]
7	$[Cu_2Co_2Fe_2(\mu\text{-}dea)_6(NCS)_4(MeOH)_2]\cdot3.2H_2O$	5, $\{CuN_2O_3\}$	+	C_6H_{12}, C_5H_{10}	[41]
8	$[Cu_2(\mu\text{-}Cl)_2(Cl)_2(tpzms)_2]$	5, $\{CuN_2Cl_3\}$	+	C_6H_{12}	[42]
9	$[Cu_2(\mu\text{-}L^6)_2(H_2O)_2]$	5, $\{CuNO_4\}$	+	C_6H_{12}	[27]
10	$[Cu_2(\mu\text{-}L^6)_2(CH_3OH)_2]$	5, $\{CuNO_4\}$	+	C_6H_{12}	[28,29]
11	$[Cu_2(\mu\text{-}HL^7)_2(H_2O)_2]$	5, $\{CuNO_4\}$	+	C_6H_{12}	[29]
12	$[Cu_2(\mu\text{-}L^9)_2(H_2O)_2]$	5, $\{CuNO_4\}$	+	C_6H_{12}	[28]
13	$[Cu_2(\mu\text{-}L^{11})_2(H_2O)_2]$	5, $\{CuNO_4\}$	–	C_6H_{12}	[28]
14	$[Cu_2(L^4)]$	4, $\{CuN_2O_2\}$	–	C_6H_{12}	[30]
15	$[Cu_2(L^5)]$	4, $\{CuN_2O_2\}$	–	C_6H_{12}	[30]
16	$[Cu_2(L^{12})(\mu\text{-}Cl)(Cl)_2]\cdot5H_2O$	4, $\{CuNOCl_2\}$	–	C_6H_{12}	[31]
17	$[Cu_2(L^{13})(\mu\text{-}Cl)(Cl)_2]\cdot4H_2O$	4, $\{CuNOCl_2\}$	–	C_6H_{12}	[31]
18	$[Cu_2(L^{14})_2(NCS)_2]$	5, $\{CuO_2N_3\}$	+	C_6H_{12}, C_7H_{14}	[32]
19	$[Cu_2(L^{15})_2(NCS)_2]$	5, $\{CuO_2N_3\}$	+	C_6H_{12}, C_7H_{14}	[32]
20	$[K(18\text{-}crown\text{-}6]_2[Cu_2(\mu\text{-}Cl)_6]$	4, $\{CuCl_4\}$	+	C_6H_{12}	[9]
21	$[Cu_2(py_2SSpy_2)](ClO_4)_2$	4, $\{CuN_3S\}$	+	C_6H_{12}	[10]

[a] Unless stated otherwise, the substrates were used in oxidation reactions.

[b] Substrates used in hydrocarboxylation reactions.

they differ in the Cu coordination number and environment, most of them bear N,O-ligands (complexes **1**–**19**) such as aminopolyalcohols (**1**–**7**), a methanesulfonate scorpionate (**8**), functionalized azo derivatives of β-diketones (**9**–**13**), and Schiff bases (**14**–**19**). In addition, the compounds **20** and **21** show the $\{CuCl_4\}$ and $\{CuN_3S\}$ coordination environments, respectively (Table 1). With a single exception, the Cu(I) derivative **21**, all these complexes are copper(II) species and have been used in the cyclohexane oxidation as a model reaction. The range of substrates for compounds **4**, **7**, **18**, and **19** comprises other alkanes (Table 1).

The structural formulae and crystal structures of $[Cu_2(\mu\text{-}Hbdea)_2(N_3)_2]$ (**5**) and $[Cu_2(\mu\text{-}L^6)_2(H_2O)_2]$ (**9**) are shown in Figs. 1 and 2 as typical examples [16,27] within the two groups of related dicopper(II) complexes bearing either various aminopolyalcoholates (**1**–**6**) or azo derivatives of β-diketones (**9**–**13**). These compounds have been easily self-assembled by treatment of copper(II) nitrate with H_2bdea and NaN_3 in alkaline aqueous solution

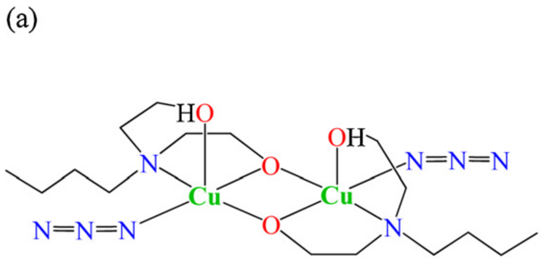


Fig. 1. Structural formula (a) and X-ray crystal structure (b) of **5**. In drawing (b), H atoms are omitted for clarity. Color codes: Cu, green balls; O, red; N, blue; C, cyan. Adapted from [16].

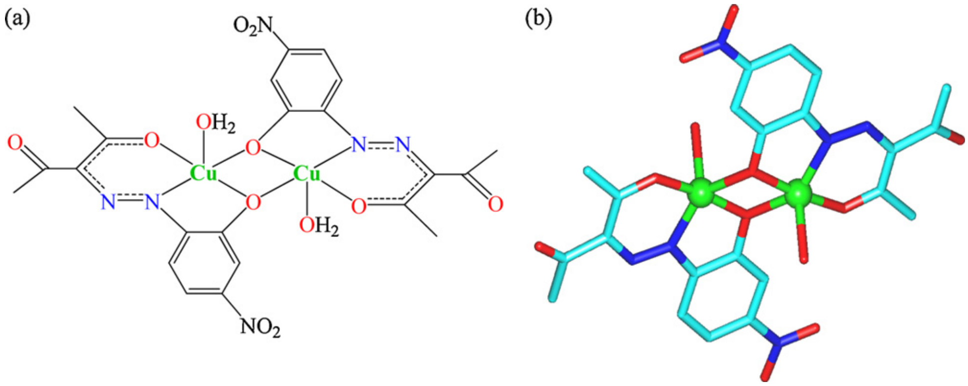


Fig. 2. Structural formula (a) and X-ray crystal structure (b) of **9** [27]. In drawing (b), H atoms are omitted for clarity. Color codes: Cu, green balls; O, red; N, blue; C, cyan.

Table 2
Tricopper complexes as catalysts or catalyst precursors.

Compound number	Formula	Cu coord. number and environment	X-ray structure	Alkane substrates[a]	Ref.
22	$[Cu_3(\mu\text{-}H_2tea)_2(\mu\text{-}poba)_2(H_2O)]\cdot 4H_2O$	5, $\{CuNO_4\}\{CuO_5\}$	+	C_6H_{12}, CH_4, C_2H_6	[11,12]
23	$[Cu_3(\mu_3\text{-}BO)(\mu\text{-}H_3bts)_3][BF_4]\cdot 2H_2O$	6, $\{CuNO_5\}$	+	Linear C_2–C_8, cyclic C_5–C_8[b]	[23]
24	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(CH_3COO)_2(Hpz)]$	4, $\{CuN_2O_2\}$ $\{CuN_3O\}$	+	C_6H_{12}, C_5H_{10}	[35]
25	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(EtCOO)_2(H_2O)]$	4, $\{CuN_2O_2\}$	+	C_6H_{12}, C_5H_{10}	[34]
26	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(buta)_2(H_2O)]$	4, $\{CuN_2O_2\}$	–	C_6H_{12}, C_5H_{10}	[35]
27	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(mbuta)_2(EtOH)_2]$	5, $\{CuN_2O_3\}$ 4, $\{CuN_2O_2\}$	–	C_6H_{12}	[35]
28	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(hexa)_2(EtOH)]$	4, $\{CuN_2O_2\}$	–	C_6H_{12}	[35]
29	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(hepa)_2(EtOH)]$	4, $\{CuN_2O_2\}$	–	C_6H_{12}	[35]
30	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(\mu\text{-}buta)_2(MeOH)(H_2O)]_2$	5, $\{CuN_2O_3\}$ 4, $\{CuN_2O_2\}$	+	C_6H_{12}, C_5H_{10}	[35,43]
31	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(\mu\text{-}acra)_2(H_2O)_2(Hpz)]_2$	5, $\{CuN_2O_3\}$ $\{CuN_3O_2\}$	+	C_6H_{12}, C_5H_{10}	[36]

[a] Unless stated otherwise, the substrates were used in oxidation reactions.
[b] Substrates used in hydrocarboxylation reactions.

(**5**) [16], or by reacting the same Cu(II) salt with H_2L^6 in aqueous-ethanol solution in the presence of HCl (**9**) [27]. Both complexes **5** and **9** exhibit two five-coordinate copper atoms with distorted square-pyramidal geometries, displaying N,O_2-tridentate μ-Hbdea or μ-L^6 ligands, together with the azide or aqua moieties, respectively [16,27]. Owing to the bridging μ-Hbdea or μ-L^6, the Cu atoms are arranged into the $\{Cu_2(\mu\text{-}O)_2\}$ cores with Cu···Cu separations of 2.9574(5) Å in **5** and of 3.0503(7) Å in **9** [16,27].

Another remarkable case of a highly efficient catalyst in cycloalkane oxidation is provided by the heterometallic species $[Cu_2Co_2Fe_2(\mu\text{-}dea)_6(NCS)_4(MeOH)_2]\cdot 3.2H_2O$ (**7**) (Fig. 3) that has been generated from Cu powder, $Co(NCS)_2$, $FeCl_3$, and diethanolamine [41]. This complex is an unprecedented hexanuclear heterotrimetallic Cu(II)/Co(III)/Fe(III) derivative that has also been the first inorganic coordination compound containing these three transition metals [41]. The molecular structure of **7** is centrosymmetric with the inversion center situated at the mid-point of the $\{Fe_2(\mu\text{-}O)_2\}$ unit, which is sequentially bound via the μ-O atoms of diethanolaminate ligands to two Co atoms, and then to two "side" Cu atoms. The Cu···Co [~2.83 Å] and Co···Fe [~2.99 Å] separations are shorter than the Fe···Fe distance [~3.22 Å], and somewhat comparable to those reported for the closest metal centers in pMMO [~2.6 Å] and sMMO [~2.5 Å] [41]. Interestingly, a metal synergic effect on the catalytic activity has been reported for this heterotrimetallic complex [41].

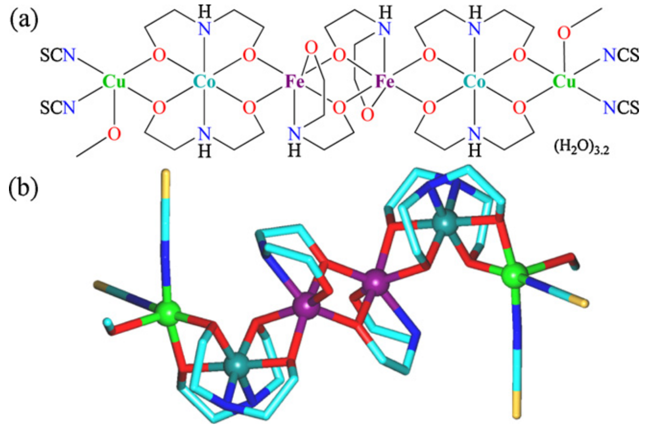


Fig. 3. Structural formula (a) and X-ray crystal structure (b) of **7**. In drawing (b), crystallization solvent molecules and H atoms are omitted for clarity. Color codes: Cu, green balls; Fe, purple balls; Co, turquoise balls; O, red; N, blue; C, cyan; S, yellow. Adapted from [41].

2.2. *Tricopper complexes*

Based on the type of main ligands, two groups of catalytically active tricopper(II) complexes can be identified (Table 2). The first one consists of $[Cu_3(\mu\text{-}H_2tea)_2(\mu\text{-}poba)_2(H_2O)]\cdot 4H_2O$ (**22**) and $[Cu_3(\mu_3\text{-}BO)(\mu\text{-}H_3bts)_3][BF_4]\cdot 2H_2O$ (**23**), derived from triethanolamine (H_3tea) and Bis–Tris (H_5bts) aminopolyalcohols, respectively [11,23]. The second group comprises a series of closely related complexes, **24**–**31**, derived from pyrazol and various carboxylic acids [34–36,43].

The compounds **22** and **23** are particularly curious on account of their unusual structural features, solubility in water, and good substrate versatility in the oxidative functionalization of alkanes, viz. the oxidation of cyclohexane, methane, and ethane (**22**), as well as the hydrocarboxylation of linear and cyclic alkanes (**23**). In fact, compound **22** was the first example of a trinuclear complex derived from triethanolamine, although this amine is commonly used for the generation of multinuclear assemblies. The molecular structure of **22** [11] consists of three five-coordinate Cu(II) atoms that are clustered by means of two μ-O atoms of H_2tea and two μ-COO groups of 4-oxybenzoate(2−), generating a non-planar $\{Cu_3(\mu\text{-}O)_2(\mu\text{-}COO)_2\}$ core with the Cu···Cu separations of 3.1138(4) Å (Fig. 4). Within that core, the "central" Cu atom is an inversion center and has a labile site occupied by one H_2O ligand. In contrast to the $\{CuO_5\}$ coordination environment of the "central" Cu atom, the "side" copper atoms possess a $\{CuNO_4\}$ environment [11].

The tricopper(II) complex $[Cu_3(\mu_3\text{-}BO)(\mu\text{-}H_3bts)_3][BF_4]\cdot 2H_2O$ (**23**) has been easily generated [23] by aqueous medium self-assembly from $Cu(NO_3)_2$, $NaBF_4$, NaOH, and Bis–Tris biobuffer (Fig. 5). Its molecular structure bears a $[Cu_3(\mu_3\text{-}BO)(H_3L)_3]^+$ cluster cation that consists of three symmetry equivalent Cu atoms [23]. These six-coordinate Cu centers are interconnected by the μ-O atoms from three pentadentate H_3bts ligands acting in a N,O_4-coordination mode. In addition, a μ_3-BO moiety simultaneously binds to other μ-O atoms from H_3bts furnishing the novel diamondoid $\{Cu_3B(\mu\text{-}O_6)\}$ core (Fig. 5b). In this core, the Cu and B atoms are located on the vertices of an almost regular tetrahedron with the Cu···Cu and Cu···B separations of 3.423(1) and 3.312(3) Å, respectively. Interestingly, **23** can be alternatively described as a tricopper derivative bearing a new boron-capped polyaminoalcoholate moiety $[OB(H_3bts)_3]^{5-}$ binding with a $\{N_3O_{12}\}$ donor set [23].

The structural formula and crystal structure of the complex $[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(EtCOO)_2(H_2O)]$ (**25**) are given in Fig. 6 as a representative example within the series of trinuclear

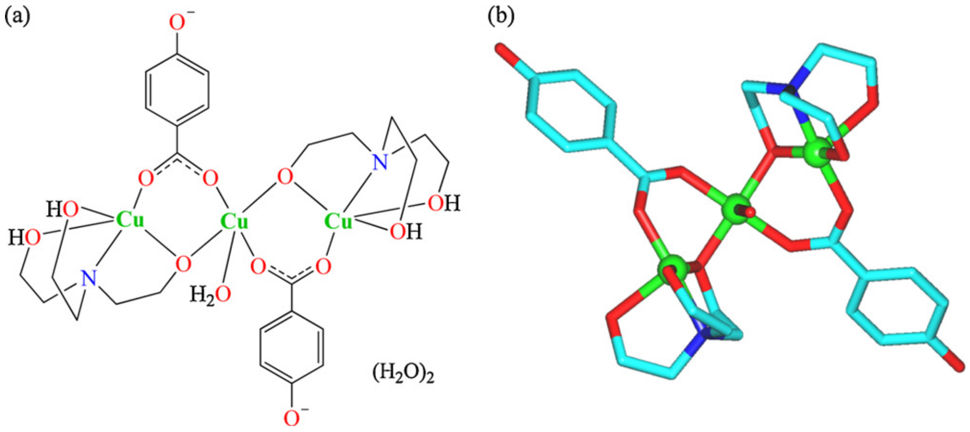


Fig. 4. Structural formula (a) and X-ray crystal structure (b) of **22** [11]. In drawing (b), crystallization H_2O molecules and H atoms are omitted for clarity. Color codes: Cu, green balls; O, red; N, blue, C, cyan.

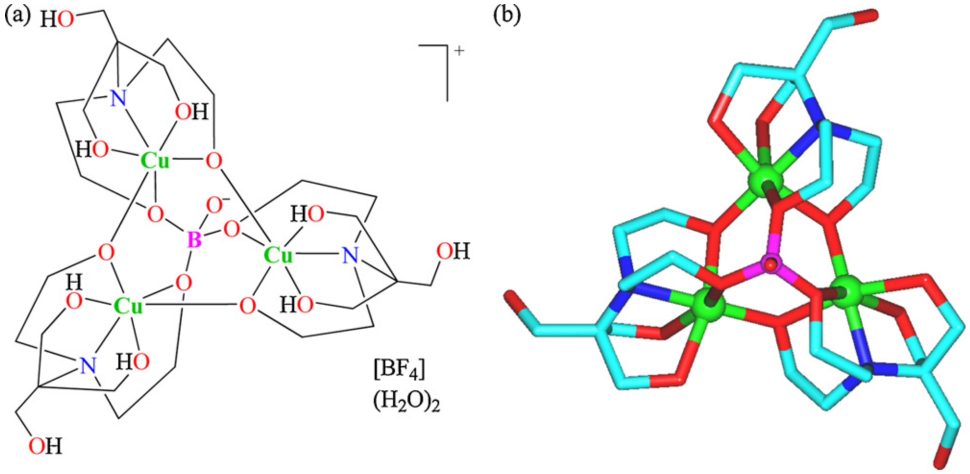


Fig. 5. Structural formula (a) and X-ray crystal structure (b) of **23**. In drawing (b), tetrafluoroborate anions, crystallization H_2O molecules, and H atoms are omitted for clarity. Color codes: Cu, green balls; B, magenta; O, red; N, blue; C, cyan.
Adapted from [23].

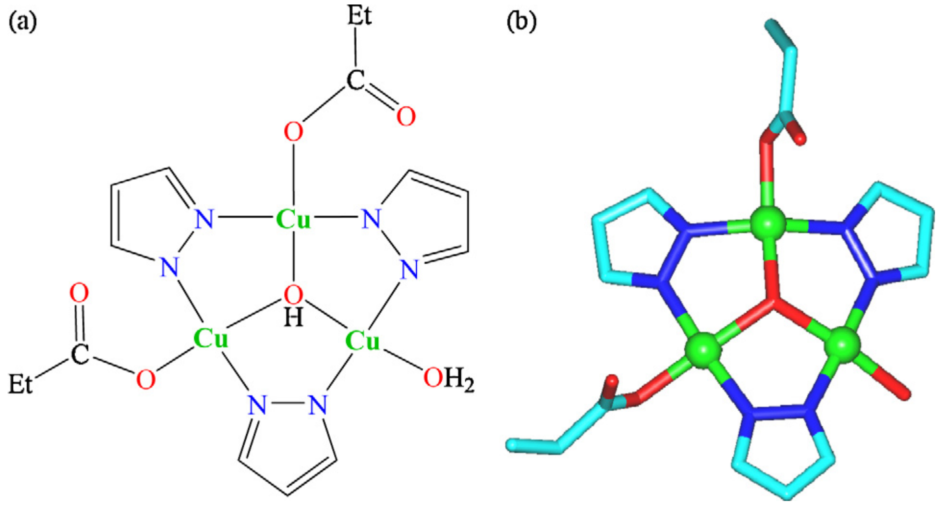


Fig. 6. Structural formula (a) and X-ray crystal structure (b) of **25**. In drawing (b), H atoms are omitted for clarity. Color codes: Cu, green balls; O, red; N, blue; C, cyan.
Adapted from [34].

triangular copper(II) clusters **24**–**31**, which bear similar $\{Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3\}^{2+}$ skeletons stabilized by different carboxylate ligands (CH_3COO **24**, EtCOO **25**, buta **26**/**30**, mbuta **27**, hexa **28**, hepa **29**, acra **31**) and additional solvent (H_2O, EtOH) or Hpz moieties (Table 2) [34–36]. The tricopper(II) complex **25** has been formed upon addition of pyrazole to an aqueous solution of $Cu(EtCOO)_2{\cdot}H_2O$, followed by crystallization at 18–22 °C [34]. Interestingly, different crystallization temperatures can slightly affect the composition

Table 3
Tetracopper complexes as catalysts or catalyst precursors.

Compound number	Formula	Cu coord. number and environment	X-ray structure	Alkane substrates[a]	Ref.
32	$[Cu_4(\mu_4\text{-}O)(\mu_3\text{-tea})_4(\mu_3\text{-}BOH)_4][BF_4]_2$	5, $\{CuNO_4\}$	+	C_6H_{12}, CH_4, C_2H_6, MCH, DMCH, $n\text{-}C_7H_{16}$, $n\text{-}C_8H_{20}$; linear C_2–C_8,[b] cyclic C_5–C_8[b]	[4,11,12,17–20,22]
33	$[Li(H_2O)_4][Cu_4(\mu\text{-Hbes})_4(\mu\text{-ba})]\cdot H_2O$	5, $\{CuNO_4\}$	+	Linear C_2–C_9[b] Cyclic C_5–C_8[b]	[25]
34	$[Cu_4(\mu_4\text{-}O)(\mu\text{-}L^1)_2(\mu\text{-}CH_3COO)_4]$	5, $\{CuNO_4\}$	–	C_6H_{12}	[33]
35	$[Cu_4(\mu_4\text{-}O)(\mu\text{-}L^2)_2(\mu\text{-}CH_3COO)_4]$	5, $\{CuNO_4\}$	+	C_6H_{12}	[33]
36	$[Cu_4(\mu_4\text{-}O)(\mu\text{-}L^3)_2(\mu\text{-}CH_3COO)_4]$	5, $\{CuNO_4\}$	–	C_6H_{12}	[33]
37	$[Cu_4(\mu\text{-}Cl)_6(Cl)_2(18\text{-crown-}6)(H_2O)_2]$	6, $\{CuO_4Cl_2\}$ 5, $\{CuCl_5\}$	+	C_6H_{12}	[9]
38	$\{[Cu(bmpa)Cl_2][Cu(bmpa)(H_2O)Cl][Cu(bmpa)Cl][CuCl_4]\}$	5, $\{CuN_3Cl(Cl/O)\}$ 4, $\{CuN_3Cl\}$	+	C_6H_{12}	[44]

[a] Unless stated otherwise, the substrates were used in oxidation reactions.
[b] Substrates used in hydrocarboxylation reactions.

of the final products [34]. The compound **25** is formed of three four-coordinate Cu atoms with distorted square-planar $\{CuN_2O_2\}$ coordination geometries filled by two μ-pz, one μ_3-OH, and one terminal carboxylate or aqua ligand (Fig. 6b) [34]. In the resulting nonplanar triangular cluster the Cu···Cu separations are in the ~3.31–3.39 Å range. Interestingly, the trinuclear units in **30** and **31** are dimerized by means of bridging modes of carboxylate groups in μ-buta and μ-acra, thus furnishing discrete hexamers [36,43]. All the compounds **24**–**31** are valuable catalyst precursors for cycloalkane oxidation [34–36].

2.3. Tetracopper complexes

The catalytically active tetracopper(II) complexes can also be divided into several groups based on the type of main ligands, which include aminopolyalcoholates (**32**, **33**), Schiff bases (**34**–**36**), crown-ether (**37**) and pyridyl-amine (**38**) derivatives (Table 3). In compounds **32**–**36**, the copper atoms are five-coordinate with a $\{CuNO_4\}$ environment [11,25,33], while other types of environments are observed in **37** and **38** [9,44].

The most notable example of a tetracopper catalyst concerns the triethanolaminate copper(II) complex $[Cu_4(\mu_4\text{-}O)(\mu_3\text{-tea})_4(\mu_3\text{-}BOH)_4][BF_4]_2$ (**32**) owing to its high solubility and stability in aqueous medium, facile self-assembly synthesis from simple and rather cheap chemicals [11], recyclability [12], high efficiency, and substrate versatility in both oxidation [11,12,17,18] and hydrocarboxylation [4,19,20,22] of a broad spectrum of alkanes and other substrates [18,38]. This catalyst can be easily self-assembled in water from a mixture containing $Cu(NO_3)_2$, H_3tea, $NaBF_4$, and NaOH [11]. The intricate cage-like structure of **32** (Fig. 7) is composed of four copper(II) centers located in the corners of an almost regular tetragon [Cu···Cu separations of 3.066(3)–3.196(3) Å], which are clustered through the triethanolaminate μ_3-O atoms and μ_3-BOH groups, being further stabilized by the "central" μ_4-O oxo atom [11]. The structure of **32** is somehow related to that of $[Cu_3(\mu_3\text{-}BO)(\mu\text{-}H_3bts)_3][BF_4]\cdot 2H_2O$ (**23**) due to the presence of stabilizing $\{\mu_3\text{-}BOH\}^{2+}$ or $\{\mu_3\text{-}BO\}^{+}$ groups, generated in situ from the tetrafluoroborate anion in alkali medium. However, compounds **23** and **32** bear the distinct boron-driven $\{Cu_3B(\mu\text{-}O)_6\}$ and $\{Cu_4B_4(\mu_4\text{-}O)(\mu\text{-}O)_{12}\}$ cores, respectively.

The compound $[Li(H_2O)_4][Cu_4(\mu\text{-Hbes})_4(\mu\text{-ba})]\cdot H_2O$ (**33**) represents another interesting example of a hydrosoluble tetracopper(II) catalyst capable of hydrocarboxylating various alkanes (Fig. 8) [25]. This complex has also been obtained by aqueous medium self-assembly, but applying a different aminopolyalcohol as a main ligand, namely H_3bes $[(HOCH_2CH_2)_2N(CH_2CH_2SO_3H)]$ that is a well-known biobuffer. In **33**, the $[Cu_4(\mu\text{-Hbes})_4(\mu\text{-ba})]^-$ cluster anion is composed of two pairs of Cu atoms, four μ-O bridging Hbes ligands (acting in different N,O_2- and N,O_3-coordination modes) and one μ-COO benzoate ligand (Fig. 8). All four Cu atoms act as square pyramids fused via common vertexes into the $\{Cu_4(\mu\text{-}O)_4(\mu\text{-}COO)\}$ cluster cores, wherein the metal centers are almost

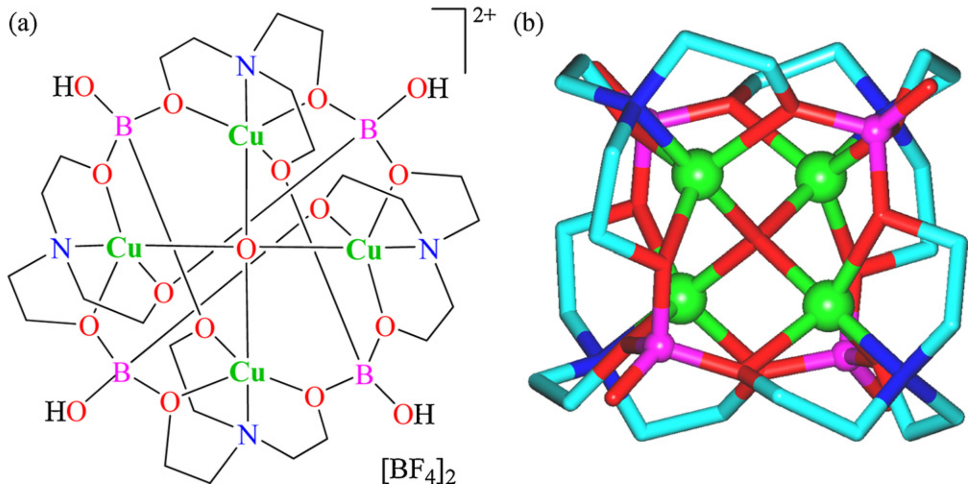


Fig. 7. Structural formula (a) and X-ray crystal structure (b) of **32**. In drawing (b), counter anions and H atoms are omitted for clarity. Color codes: Cu, green balls; B, magenta balls; O, red; N, blue; C, cyan.

Adapted from [11,17].

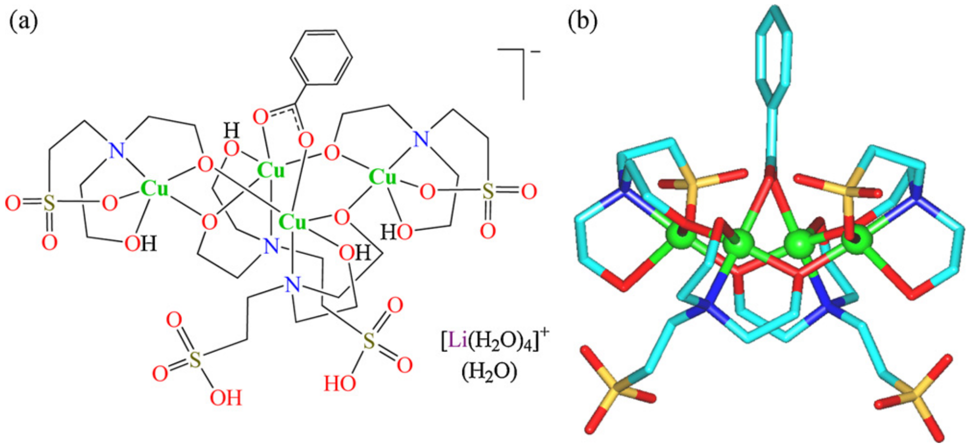


Fig. 8. Structural formula (a) and X-ray crystal structure (b) of **33**. In drawing (b), $[Li(H_2O)_4]^+$ cations, crystallization H_2O molecules, and H atoms are omitted for clarity. Color codes: Cu, green; O, red; N, blue; C, cyan; S, yellow.

Adapted from [25].

coplanar, with the Cu···Cu separations of 3.058(1) and 5.930(1) Å between the "central" and "side" Cu atoms, respectively [25].

A different type of the tetracopper(II) core supported by two Schiff base (μ-L^{1-3}) and four μ-acetate ligands, and one μ_4-oxo moiety is disclosed in compounds **34**–**36** with general formulae of $[Cu_4(\mu_4\text{-}O)(\mu\text{-}L^{1-3})_2(\mu\text{-}CH_3COO)_4]$ (L^1 **34**, L^2 **35**, L^3 **36**) [33]. These compounds, as well as $[Cu_4(\mu\text{-}Cl)_6(Cl)_2(18\text{-crown-}6)(H_2O)_2]$ (**37**) that bears a $[Cu_4(\mu\text{-}Cl)_6(Cl)_2]$ core supported by 18-crown-6 [9], and the Cu-bmpa derivative $\{[Cu(bmpa)Cl_2][Cu(bmpa)(H_2O)Cl][Cu(bmpa)Cl][CuCl_4]\}$ (**38**) with four mononuclear units [44], have been applied in the oxidation of cyclohexane.

2.4. Coordination polymers

Although coordination polymers are mainly designed for use in heterogeneous catalysis [45], those that possess some solubility in aqueous and/or organic medium can also be applied as precursors of catalytically active species in homogeneous catalytic reactions, particularly including those that mimic enzymatic processes [25]. In this regard, the aqueous solubility of some copper(II) coordination polymers and their ability to dissociate into ionic species with labile and coordinatively unsaturated Cu centers can open up the use of these compounds as bioinspired catalyst precursors in homogeneous aqueous medium reactions.

The coordination polymers **39**–**57** (Table 4) can be divided into several groups based on the type and nuclearity of Cu-containing building blocks. Hence, the first group includes the polymers **39**–**41**, **48**, and **49** composed of dimeric $[Cu_2(\mu\text{-aminopolyalcoholate})_2]^{2+}$ units (similar to those in **1**–**6**) that are extended into 1D (**39**, **41**), 2D (**40**), and 3D (**48**, **49**) coordination networks by means of different linkers based on aromatic carboxylates or $[Fe(CN)_6]^{4-}$ moieties [11,13,16,40]. Although all these compounds are catalyst precursors in the mild oxidation of cyclohexane by H_2O_2, one should highlight the polymer $[Cu_2(\mu_3\text{-}H_2tea)_2(\mu_4\text{-}pma)\{Na_2(\mu\text{-}H_2O)_2(H_2O)_2\}]_n\cdot 10nH_2O$ (**40**) constructed from dicopper(II) triethanolaminate and aqua-sodium building blocks, and μ_4-pyromellitate linkers (Fig. 9) [13]. Apart from forming a grid-like 2D network, this compound is one of the unique examples of Cu containing coordination polymers that feature a high solubility in water ($S_{25\,^\circ C} \approx 110\ mg\,mL^{-1}$).

The second group contains the coordination polymers **43**–**47** that bear tetracopper(II) $[Cu_4(\mu\text{-}Hbes)_4(\mu\text{-benzenecarboxylate})]^-$ building blocks similar to that of the discrete complex **33** (Fig. 8), but assembled into 1D (**43**) or 3D (**44**–**47**) coordination networks through bridging and charge-balancing $\{Na\}^+$, $\{Na(H_2O)_2\}^+$, $\{Na(H_2O)_4\}^+$, or $\{Li(H_2O)_2\}^+$ moieties [21,25]. The 3D networks of **46** and **47** feature an unprecedented topology [25]. Apart from representing very rare examples of coordination compounds derived from H_3bes, **43**–**47** are also soluble in water and were applied as efficient and versatile catalyst precursors for the mild (60 °C)

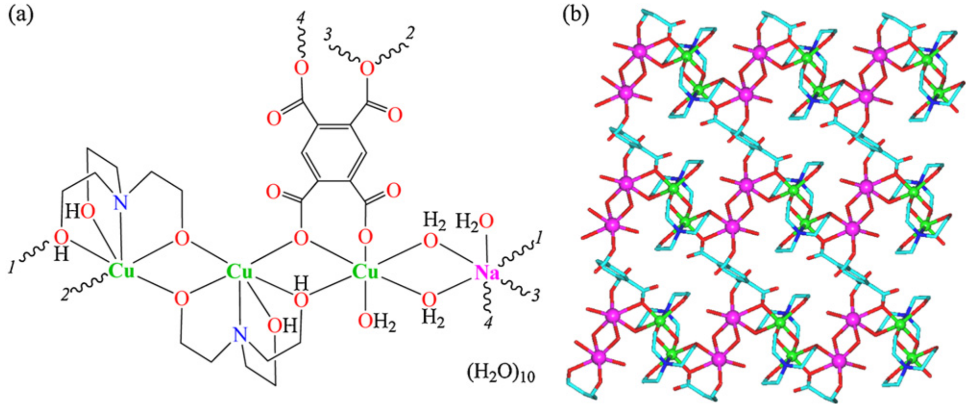


Fig. 9. Structural formula (a) and X-ray crystal structure (b) of **40**. In scheme (a) numbers correspond to extensions of polymeric motifs. In drawing (b), crystallization H_2O molecules and H atoms are omitted for clarity. Color codes: Cu, green balls; Na, magenta balls; O, red; N, blue; C, cyan.

Adapted from [13].

Table 4
Coordination polymers as catalysts or catalyst precursors.

Compound number	Formula	Cu coord. number and environment	Network[a]	Alkane substrates[b]	Ref.
39	$[Cu_2(\mu\text{-}H_2tea)_2(\mu_2\text{-}tpa)]_n\cdot 2nH_2O$	6, $\{CuNO_5\}$	1D	C_6H_{12}	[11,12]
40	$[Cu_2(\mu_3\text{-}H_2tea)_2(\mu_4\text{-}pma)\{Na_2(\mu\text{-}H_2O)_2(H_2O)_2\}]_n\cdot 10nH_2O$	6, $\{CuNO_5\}$	2D	C_6H_{12}	[13,14]
41	$[Cu_2(\mu\text{-}Hbdea)_2(\mu_2\text{-}tpa)]_n\cdot 2nH_2O$	5, $\{CuNO_4\}$	1D	C_6H_{12}	[16]
42	$[\{Cu(H_3tea)\}_2(\mu_4\text{-}pma)]_n$	6, $\{CuNO_5\}$	1D	C_6H_{12}	[14]
43	$[Cu_4(\mu_3\text{-}Hbes)_2(\mu\text{-}Hbes)_2(\mu\text{-}phba)\{Na(H_2O)_4\}]_n$	5, $\{CuNO_4\}$	1D	C_3H_8, $n\text{-}C_4H_{10}$[c]	[21]
44	$[Cu_4(\mu_3\text{-}Hbes)_4(\mu\text{-}ba)(Na)]_n$	5, $\{CuNO_4\}$	3D	C_3H_8, $n\text{-}C_4H_{10}$[c]	[21]
45	$[Cu_4(\mu_3\text{-}Hbes)_4(\mu\text{-}mba)\{Na(H_2O)_2\}]_n\cdot nH_2O$	5, $\{CuNO_4\}$	3D	C_3H_8, $n\text{-}C_4H_{10}$[c]	[21]
46	$[Cu_4(\mu_3\text{-}Hbes)_4(\mu\text{-}mhba)\{Li(H_2O)_2\}]_n\cdot 3nH_2O$	5, $\{CuNO_4\}$	3D	Linear C_2–C_9[c] Cyclic C_5–C_8[c]	[25]
47	$[Cu_4(\mu_3\text{-}Hbes)_4(\mu\text{-}dhba)\{Li(H_2O)_2\}]_n\cdot 3nH_2O$	5, $\{CuNO_4\}$	3D	Linear C_2–C_9[c] Cyclic C_5–C_8[c]	[25]
48	$[Cu_6(\mu\text{-}H_2tea)_6\{Fe(\mu\text{-}CN)_6\}]_n(NO_3)_{2n}\cdot 6nH_2O$	6, $\{CuN_2O_4\}$	3D	C_6H_{12}	[40]
49	$[Cu_6(\mu\text{-}Hmdea)_6\{Fe(\mu\text{-}CN)_6\}]_n(NO_3)_{2n}\cdot 7nH_2O$	5, $\{CuN_2O_3\}$	3D	C_6H_{12}	[40]
50	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(\mu\text{-}HCOO)(HCOO)(Hpz)_2]_n$	5, $\{CuN_3O_2\}$, $\{CuN_2O_3\}$ 4, $\{CuN_3O\}$	1D	C_6H_{12}, C_5H_{10}	[35,43]
51	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(\mu\text{-}EtCOO)_2(EtOH)]_n$	5, $\{CuN_2O_3\}$ 4, $\{CuN_2O_2\}$	1D	C_6H_{12}, C_5H_{10}	[34,35,43]
52	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(\mu\text{-}acra)_2(MeOH)]_n$	5, $\{CuN_2O_3\}$ 4, $\{CuN_2O_2\}$	1D	C_6H_{12}, C_5H_{10}	[36]
53	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(\mu\text{-}macra)_2]_n$	5, $\{CuN_2O_3\}$ 4, $\{CuN_2O_2\}$	1D	C_6H_{12}, C_5H_{10}	[36]
54	$[Cu(\mu\text{-}L^8)]_n$	5, $\{CuNO_4\}$	1D	C_6H_{12}	[29]
55	$[Cu_2(\mu_3\text{-}L^{10})_2]_n$	5, $\{CuNO_4\}$	1D	C_6H_{12}	[28]
56	$[Cu(\mu_4\text{-}dipic)_2\{Na_2(\mu\text{-}H_2O)_4\}]_n\ 2nH_2O$	6, $\{CuN_2O_4\}$	2D	C_6H_{12}, C_5H_{10}	[37]
57	$[Cu_2Mg_2(\mu\text{-}Htea)_2(\mu_6\text{-}pma)(H_2O)_6]_n\cdot 6nH_2O$	5, $\{CuNO_4\}$	2D	Linear C_5–C_9[c] Cyclic C_5–C_8[c]	[26]

[a] All compounds **39**–**57** have been structurally characterized.
[b] Unless stated otherwise, the substrates were used in oxidation reactions.
[c] Substrates were used in hydrocarboxylation reactions.

single-pot hydrocarboxylation, by CO and H_2O, of various gaseous, liquid linear, and cyclic C_n alkanes into the corresponding C_{n+1} carboxylic acids, in H_2O/MeCN medium and in the presence of potassium peroxodisulfate [21,25].

The third group consists of the coordination polymers **50**–**53** that are constructed from triangular tricopper(II) cluster nodes $\{Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3\}^{2+}$ [34–36,43]. In contrast to analogous discrete trinuclear complexes **24**–**31**, the carboxylate ligands in **50**–**53** act in a μ-bridging mode, thus giving rise to the linkage of adjacent tricopper units into 1D coordination chains. The compounds **50**–**53** are catalyst precursors in the oxidation of cyclohexane and cyclopentane [34–36].

Miscellaneous examples of catalytically active coordination polymers also include the compounds $[Cu(\mu\text{-}L^8)]_n$ (**54**) and $[Cu_2(\mu_3\text{-}L^{10})_2]_n$ (**55**) composed of repeating mono- and dicopper(II) units bearing functionalized azo derivatives of β-diketones [28,29]. These polymers are related to their discrete dicopper(II) complexes **10**–**13** (Table 1). A different example concerns the polymer $[\{Cu(H_3tea)\}_2(\mu_4\text{-}pma)]_n$ (**42**) constructed from cationic monocopper $\{Cu(H_3tea)\}^{2+}$ units that are assembled by μ_4-pma(4−) linkers into a 1D network [14]. In the somewhat related compound $[Cu_2Mg_2(\mu\text{-}Htea)_2(\mu_6\text{-}pma)(H_2O)_6]_n\cdot 6nH_2O$ (**57**), two $\{Cu(\mu\text{-}Htea)\}^+$ fragments are clustered with a $\{Mg(H_2O)_2\}^{2+}$ moiety and μ_6-pma(4−) spacer, forming an unprecedented heterometallic $\{Cu_2Mg(\mu\text{-}O)_2(\mu\text{-}COO)_2\}^-$ core [26]. Such cores are further assembled by $\{Mg(H_2O)_4\}^{2+}$ linkers and μ_6-pma ligands into interdigitated 2D metal-organic layers [26]. The water-soluble 2D Cu/Na coordination polymer $[Cu(\mu_4\text{-}dipic)_2\{Na_2(\mu\text{-}H_2O)_4\}]_n\cdot 2nH_2O$ (**56**) that bears anionic monocopper $\{Cu(dipic)_2\}^{2-}$ units represents another interesting example [37]. It has been self-assembled from water solution containing Cu(II) nitrate, dipicolinic acid, and sodium hydroxide. The molecular structure of **56** (Fig. 10) features six-coordinate copper atoms with a distorted octahedral $\{CuN_2O_4\}$ environment formed by two nearly planar N,O_2-dipicolinate ligands. The $\{Cu(dipic)_2\}^{2-}$ blocks are simultaneously linked to four aqua-sodium moieties, resulting in the nonplanar 2D metal-organic layers. Being derived from the biologically relevant dipicolinate ligand, **56** acts as a promising bioinspired catalyst precursor for the mild oxidation of cycloalkanes by H_2O_2 without requiring the presence of an acid promoter [37].

3. Oxidation of alkanes

3.1. *Oxidation of cyclohexane as a model substrate*

Cyclohexane has extensively been tested as a recognized model substrate in the development of mild and selective catalytic oxidation [1,2,11–14,16–21,46], particularly in view of the importance of the products, since cyclohexanol and cyclohexanone are intermediates in nylon-6,6′ and polyamide-6 productions [3,46]. However, the industrial processes for the oxidation of cyclohexane show a number of limitations. For example, the Dupont process appears to operate with only 4% conversion, 85% selectivity, at ~150 °C using air as oxidant (~12 atm) and cobalt(III) naphthenate as a homogeneous catalyst [3,12]. Therefore, a significant body of research has been directed toward the development of more efficient cyclohexane oxidation protocols, namely by implementing selective oxidation under mild conditions with H_2O_2 and searching for effective transition metal based catalytic systems. In fact,

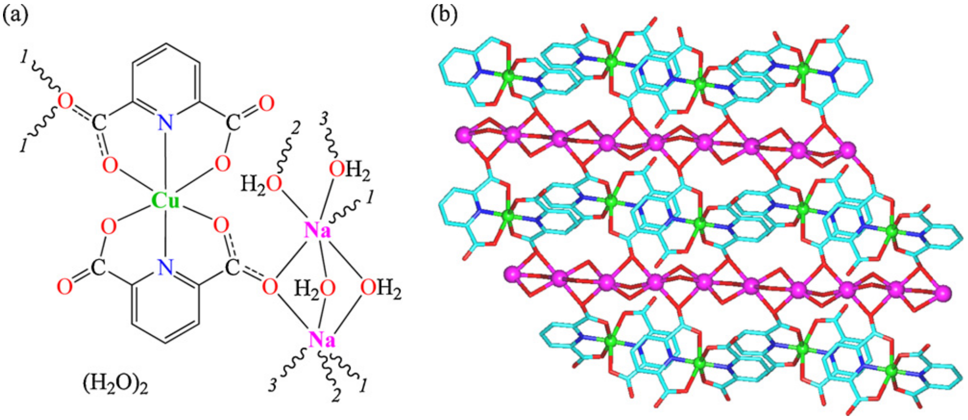
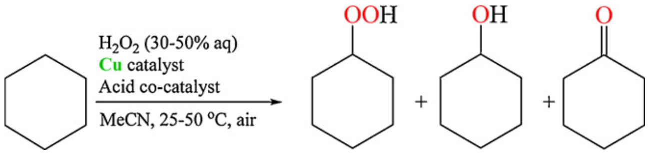


Fig. 10. Structural formula (a) and X-ray crystal structure (b) of **56**. In scheme (a) numbers correspond to extensions of polymeric motifs. In drawing (b), crystallization H_2O molecules and H atoms are omitted for clarity. Color codes: Cu, green balls; Na, magenta balls; O, red; N, blue; C, cyan.
Adapted from [37].



Scheme 1. Oxidation of cyclohexane to cyclohexyl hydroperoxide (primary product), cyclohexanol and cyclohexanone (final products), under mild conditions.

the majority of multicopper complexes (**1**–**38**) and coordination polymers (**39**–**57**) have been primarily tested in the oxidation of cyclohexane (Tables 1–4).

Hence, in the presence of various multicopper catalysts or catalyst precursors, cyclohexane can be oxidized by aq. H_2O_2 into a mixture of cyclohexyl hydroperoxide (CyOOH, main primary product) with cyclohexanol and cyclohexanone, which are the major final products after the autodecomposition of CyOOH or its reduction with PPh_3, following a method developed by Shul'pin [47]. This oxidation of C_6H_{12} under mild conditions typically proceeds in aqueous acetonitrile medium, under atmospheric pressure, at r.t. or with a slight heating (50 °C), and in the presence (optional) of an acid co-catalyst (Scheme 1). Selected catalytic systems are summarized in Table 5.

Thus, various types of di-, tri-, tetra- and polymeric copper(II) compounds act as rather efficient catalysts or catalyst precursors in the oxidation of cyclohexane by H_2O_2, leading to total product yields in the 22–45% range, with the highest values achieved when using compounds **7** (45%), **32** (39%), and **22** (37%). Hereinafter, % yields are expressed as moles of products per 100 mol of substrate. However, these multicopper(II) systems typically require the presence of an acid co-catalyst (promoter) that drastically improves their activity. In our early studies, we have observed [11,12,41] that nitric acid is a simple and highly efficient co-catalyst in the cyclohexane oxidation catalyzed by aminopolyalcoholate derivatives **1**–**3**, **7**, **22**, **32**, **39**, and **41**, the activity of which depends on the relative amount of HNO_3. It has been found [11,12,16,41] that for certain systems even 5–10 equiv. of HNO_3 relative to catalyst is sufficient to attain high yields of the oxidation products. Since then, this acid has been employed as a reference co-catalyst when testing new multicopper (e.g., **5**, **6**, **9**–**13**, **24**–**31**, **34**–**36**, **39**–**42**, **48**–**55**) and other transition metal based catalysts in oxidation of alkanes [16,27–29,33–36,40].

The monocopper(II) complexes $[Cu(H_2tea)(N_3)]$ and $[Cu(Hbdea)_2]·2Hdnba$ derived from related aminopolyalcoholate ligands are usually less active (Table 5, entries 9 and 10) than various multicopper derivatives, e.g., **7**, **22**, **32**, **36**, and **52**. Besides, a simple copper salt like copper(II) nitrate exhibits poor activity in the cyclohexane oxidation (entry 11), thus pointing out the relevance of polydentate N,O-ligands that is probably associated with their involvement in various proton-transfer steps [11,12].

Apart from HNO_3, the promoting effects of other acid co-catalysts have also been investigated for compounds **5** [16], **32** [17], **48** [40], and **49** [40]. For example, Table 6 shows how the type of acid co-catalyst and its relative amount have an influence on the C_6H_{12} oxidation catalyzed by $[Cu_2(\mu\text{-}Hbdea)_2(N_3)_2]$ (**5**). This compound is almost inactive in the absence of any acid co-catalyst, while the addition of 5 equiv. of trifluoroacetic acid (TFA) leads to a drastic product yield growth up to 27% (entry 2), achieving the

Table 5
Selected multicopper catalytic systems for the oxidation of C_6H_{12} by H_2O_2 in the presence of HNO_3 co-catalyst, under mild conditions.[a]

Entry	Catalyst or catalyst precursor	Max. total yield (%)[b]	Ref.
1	$[Cu_2(\mu\text{-}Hbdea)_2(N_3)_2]$ (**5**)	22	[21]
2	$[Cu_2Co_2Fe_2(\mu\text{-}dea)_6(NCS)_4(MeOH)_2]·3.2H_2O$ (**7**)	45	[41]
3	$[Cu_3(\mu\text{-}H_2tea)_2(\mu\text{-}poba)_2(H_2O)]·4H_2O$ (**22**)	37	[12]
4	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(EtCOO)_2(H_2O)]$ (**25**)	28	[34]
5	$[Cu_4(\mu_4\text{-}O)(\mu_3\text{-}tea)_4(\mu_3\text{-}BOH)_4][BF_4]_2$ (**32**)	39	[12]
6	$[Cu_4(\mu_4\text{-}O)(\mu\text{-}L^3)_2(\mu\text{-}CH_3COO)_4]$ (**36**)	36	[33]
7	$[Cu_2(\mu_3\text{-}H_2tea)_2(\mu_4\text{-}pma)\{Na_2(\mu\text{-}H_2O)_2(H_2O)_2\}]_n·10nH_2O$ (**40**)	29	[14]
8	$[Cu_3(\mu_3\text{-}OH)(\mu\text{-}pz)_3(\mu\text{-}acra)_2(MeOH)]_n$ (**52**)	35	[36]
9[c]	$[Cu(H_2tea)(N_3)]$	28	[12]
10[c]	$[Cu(Hbdea)_2]·2Hdnba$	19	[16]
11[c]	$Cu(NO_3)_2$	5	[12]

[a] Typical reaction conditions: C_6H_{12} (0.6–1.0 mmol), aq. H_2O_2 (2–10 mmol), catalyst (10 μmol), $n(HNO_3)/n(catalyst) = 10:1$, MeCN solvent, 6 h, r.t.
[b] Moles of products (cyclohexanol + cyclohexanone)/100 mol of C_6H_{12}; typically determined by GC after the treatment with PPh_3.
[c] Given for comparative purposes.

Table 6
Effect of acid co-catalyst in the oxidation of C_6H_{12} by H_2O_2 in the presence of **5**, under mild conditions.[a]

Entry	Acid co-catalyst	n(acid)/n(catalyst **5**)	Total yield (%)[b]
1	–	–	1
2	TFA	5	27
3	TFA	10	38
4	TFA	15	34
5	TFA	30	23
6	HNO_3	10	22
7	HNO_3	30	28
8	HCl	10	26
9	HCl	30	27
10	H_2SO_4	10	16
11	H_2SO_4	30	18
12	CH_3COOH	20	4

Adapted from [16].

[a] Reaction conditions: C_6H_{12} (1 mmol), aq. H_2O_2 (7.5 mmol), catalyst **5** (10 μmol), co-catalyst (0.05–0.3 mmol), MeCN solvent, 6 h, r.t.

[b] Moles of products (cyclohexanol + cyclohexanone)/100 mol of C_6H_{12}; determined by GC after the treatment with PPh_3.

maximum of 38% at 10 equiv. of TFA (entry 3), beyond which the yield drops to 23% at the n(TFA)/n(**5**) molar ratio of 30 (Table 6, entries 1–5) [16]. Compared with TFA, nitric and hydrochloric acids have a weaker promoting effect, resulting in the maximum total yields of 28 and 27%, respectively. Sulfuric acid is the least active co-catalyst among the tested strong acids (18% yield), whereas acetic acid is barely efficient (4% yield). Hence, for the catalyst precursor **5** the promoting efficacy of various acid co-catalysts follows the trend TFA > $HNO_3 \geq$ HCl > $H_2SO_4 \gg CH_3COOH$ [16].

In the cyclohexane oxidation catalyzed by $[Cu_4(\mu_4\text{-}O)(\mu_3\text{-}tea)_4(\mu_3\text{-}BOH)_4][BF_4]_2$ (**32**), the nature of acid promoter (HCl, H_2SO_4, HNO_3, and TFA) is also a key factor that significantly affects the reaction rate [17]. Although all these acids exhibit a noticeable promoting effect, in the presence of HCl the reaction proceeds extremely rapidly, being one order faster than those promoted by the other acids, and allowing to achieve the remarkably high turnover frequencies (TOFs) of ca. 600 h^{-1} [17]. It has been proposed that the unusual promoting effect of HCl concerns the ability of chloride ions to stabilize the Cu(I) oxidation state upon generation of species with terminal or bridging chloride ligands [17]. A more pronounced promoting effect of hydrochloric over nitric acid has also been observed [40] in the cyclohexane oxidation catalyzed by the compounds **48** and **49**.

Although not yet being fully established, the role of the acid co-catalyst can be associated with (i) its involvement in proton transfer steps, (ii) catalyst activation by unsaturation of the Cu(II) centers upon ligand protonation, (iii) acceleration of the oxidation reaction, (iv) enhancement of oxidative properties of the multicopper catalysts and H_2O_2 (acids can also be oxidants themselves), and (v) facilitation of the formation of peroxo complexes, (vi) preventing the decomposition of H_2O_2 to water and oxygen (i.e., suppressing eventual catalase activity in acidic medium), and (vii) increase of selectivity to cyclohexanone by dehydrogenation of cyclohexanol, a reaction typically catalyzed by strong mineral acids or heterogeneous copper systems [12,16,17]. In spite of the fact that acid co-catalysts are essential for the majority of multicopper systems, a few catalysts or catalyst precursors (e.g., compounds **14**, **15**, **16**, **17**, **38**, and **56**) are rather active even in the absence of any acid promoter [30,31,37,44].

The efficiencies of Cu-catalyzed oxidation of C_6H_{12} significantly depend on other parameters, besides the type and the amount of co-catalyst, namely the relative amounts of oxidant, substrate, catalyst, and solvent (MeCN/H_2O), reaction temperature and time. These effects have been studied in detail for a number of catalytic systems (e.g., compounds **1**–**3** [12], **5**–**7** [16,41], **22** [12], **25** [34], **32** [12,17], and **39**–**41** [12,16]) aiming at optimizing the oxidation of cyclohexane.

As an oxidant, hydrogen peroxide has a marked influence on the overall yields of products which are enhanced in many catalytic systems upon increasing the amount of H_2O_2 [11–14,16,17,34–37,40–42]. Hence, H_2O_2 is typically required in a twofold molar excess relatively to C_6H_{12} to reach good product yields, although often these tend to grow further when using higher amounts of hydrogen peroxide (e.g., up to tenfold molar excess). However, a high excess of H_2O_2 can also facilitate over-oxidation processes, thus decreasing the overall selectivity toward main products, i.e., cyclohexyl hydroperoxide, cyclohexanol, and cyclohexanone. In this regard, it should be mentioned that multicopper(II) aminopolyalcoholate catalysts **5**, **7**, **22**, and **32** exhibit a very high overall selectivity (presumably close to 100%) toward the formation of those main products, as supported by GC and GC–MS analyses of the reaction mixtures that showed no traces of any by-products [11,12,16,41]. Such a high selectivity is also explained by the fact that alcohols, once formed, typically do not undergo further oxidation by H_2O_2 in the presence of multicopper catalysts. In contrast, the same catalysts are rather efficient for the oxidation of alcohols to the corresponding ketones by TBHP [18].

Alkane oxidation by H_2O_2 was typically performed in air (Scheme 1) [11,12,14–17], since dioxygen also plays an important role, namely toward the generation of intermediate peroxyl radicals $ROO^\bullet$ from alkyl radicals $R^\bullet$ and O_2. Nevertheless, alkane oxidation with H_2O_2 can also proceed under an inert atmosphere (e.g., N_2), leading to slightly inferior product yields than those observed in the reactions in air. In fact, even under inert atmosphere, O_2 is present since it is generated from H_2O_2 via its partial decomposition (catalase activity) assisted by copper complexes.

Concerning the catalyst amount, the optimized conditions typically correspond to 1–3 mol.% of catalyst relatively to substrate, but some systems also show good activity at lower catalyst loadings [12,14,17,34,40]. Rather high turnover numbers (TONs) in the 300–470 range have been exhibited by various catalytic systems [12,17,40]. The reaction time and temperature are also parameters in cyclohexane oxidation which, in the majority of catalytic systems, were set to 6 h and 20–25 °C (r.t.), respectively, to attain the best yields. Nevertheless, some systems operate better at slightly higher temperatures (40–80 °C) and may require different reaction times. For instance, when using the highly active tetramer $[Cu_4(\mu_4\text{-}O)(\mu_3\text{-}tea)_4(\mu_3\text{-}BOH)_4][BF_4]_2$ (**32**) with HCl as a co-catalyst, the cyclohexane oxidation by H_2O_2 at 50 °C can be completed within 10 min [17].

As mentioned above, the mild oxidation of cyclohexane proceeds in aqueous acetonitrile medium, wherein water typically comes with aq. H_2O_2 and/or catalyst solution. The mixed MeCN/H_2O solvent is crucial to solubilize both substrate and catalyst. In fact, the mild cyclohexane oxidation does not proceed to a considerable extent only in water as a sole solvent (i.e., in the absence of acetonitrile). The choice of MeCN was governed by (i) the solubilization of cyclohexane, catalysts and products in this solvent, (ii) the miscibility with water, (iii) the high stability toward oxidation under the reaction conditions applied (in contrast to other solvents, e.g., methanol, ethanol, or acetone), (iv) the similarity of its boiling point with that of cyclohexane what would allow an easy recirculation of the cyclohexane and solvent mixture, (v) its coordination ability, and also in view of the best results previously obtained in this solvent [1a,12,46].

In spite of the relative inertness of acetonitrile, some studies [48] have shown that it can be oxidized with the participation of hydroxyl radicals affording formaldehyde, formic acid and/or CO_2 [48a], while peroxyimidic acid can be generated from MeCN in a basic medium [48b]. Nevertheless, under the mild (r.t., atmospheric pressure) and slightly acidic conditions of

Table 7
Catalyst recycling in the cyclohexane oxidation catalyzed by **32** and **40** [12,14].[a]

Entry	Catalyst	$n(HNO_3)/n(\text{catalyst})$	Cycle	Total yield (%)[b]
1	**32**	10	1	34
2	**32**	–	2	33
3	**32**	–	3	33
4	**32**	–	4	33
5	**32**	–	5	32
6	**40**	10	1	29
7	**40**	10	2	27
8	**40**	10	3	26

[a] Reaction conditions: C_6H_{12} (0.63 mmol), aq. H_2O_2 (6.30 mmol), **32** (25 μmol) or **40** (10 μmol), HNO_3 co-catalyst (optional), MeCN solvent, 6 h, r.t. The catalyst was recovered after each reaction cycle by full evaporation of the reaction mixture under vacuum, and the subsequent batch was initiated upon addition of new standard portions of other reagents and solvent.

[b] Moles of products (cyclohexanol + cyclohexanone)/100 mol of C_6H_{12}; typically determined by GC after the treatment with PPh_3.

Cu-catalyzed alkane oxygenations, the oxidation of acetonitrile is not appreciable [11,12,17]. Indeed, in the cyclohexane oxidation by the **32**/H_2O_2/acid co-catalyst system the ratio between the rate constants of acetonitrile and cyclohexane oxidation is very low (~0.006) [17].

Although water is usually present as a solvent component in oxidation with hydrogen peroxide, it typically plays an inhibiting role and should be avoided in high concentrations. However, we have found [17] an unprecedented promoting role of H_2O in the cyclohexane oxidation in acetonitrile by the **32**/HCl/H_2O_2 and **32**/TFA/H_2O_2 systems. For example, in the reaction catalyzed by the **32**/HCl, the increase of the total water concentration $[H_2O]_{total}$ from 1 to 4 M in the reaction mixture leads to a drastic acceleration of the cyclohexane oxidation, as attested by the growth of the initial rate W_0 from 15×10^{-6} to 110×10^{-6} M s^{-1}, respectively. Such a promoting feature of water can also be of potential practical importance, allowing the use of diluted aqueous solutions of H_2O_2 that are easily generated in situ [17]. Although not yet clearly established, the role of water in oxidation catalyzed by the hydrosoluble complex $[Cu_4(\mu_4\text{-}O)(\mu_3\text{-tea})_4(\mu_3\text{-BOH})_4][BF_4]_2$ (**32**) conceivably consists in the solubilization and activation of catalyst, formation and stabilization of intermediate aqua- and/or hydroxo Cu complexes, as well as in the facilitation of H-transfer steps, crucial in the generation of the hydroxyl radical that is the active oxidizing species [17]. To this end, it should be mentioned that a "water-assisted" mechanism has been theoretically proposed in the $[MeReO_3]/H_2O_2/H_2O\text{-}CH_3CN$ system [49a], whereas an unprecedented hydroxylating role of water has also been disclosed [19] in the hydrocarboxylation of alkanes to carboxylic acids in the presence of compound **32** (Section 4).

Although the efficient recycling of a homogeneous catalytic system is usually a difficult task from the technical point of view, one should highlight the possibility of recycling the catalysts **32** [12] and **40** [14] in the mild oxidation of cyclohexane by H_2O_2 (Table 7). These catalysts can be reused maintaining almost full activity even after five (**32**) or three (**40**) reaction cycles, as attested by the close product yields before and after multiple recycling (i.e., 34 vs. 32% for **32**; 29 vs. 26% for **40**). An important distinctive feature of **32** also consists in the fact that once activated by HNO_3 this catalyst is highly efficient even without further additions of the acid co-catalyst [12]. Besides, catalyst **32** is very stable and can be isolated, after the cyclohexane oxidation, in a pure crystalline form [12]. Many multicopper compounds (catalyst precursors) do not remain intact in the course of alkane transformations, and can undergo various transformations upon treatment with oxidant and/or acid co-catalyst, thus preventing their reuse. To overcome such a limitation, the heterogenization of the most active catalyst precursors on different supports appears to be a particularly promising research direction that needs to be explored.

Moreover, the activity of various multicopper catalysts (based on mass and averaged over the reaction time) is comparable or even higher [11,14,41] than those of particular (pMMO) or soluble (sMMO) methane monooxygenases [7d,41], although in different conditions. For example, the oxidation of cyclohexane catalyzed by the **7**/HNO_3 system [41] leads to 214 nmol of cyclohexanol and cyclohexanone per min and mg of catalyst vs. 17 nmol of EtOH and 84 nmol of MeOH per min and mg of pMMO or sMMO, respectively, for the enzymatic hydroxylations of methane or ethane, which are particularly favorable substrates for these enzymes. Even lower activities of ~40 and 73 nmol of alcohols per min and mg of protein are exhibited by sMMO in the hydroxylations of *n*-hexane and *n*-pentane, respectively [41].

A few multicopper(II) catalytic systems have been tested with oxidants other than H_2O_2. Hence, compounds $[Cu_2(py_2SSpy_2)](ClO_4)_2$ (**21**) [10], $[Cu_4(\mu_4\text{-}O)(\mu_3\text{-tea})_4(\mu_3\text{-BOH})_4][BF_4]_2$ (**32**) [18], and $\{[Cu(bmpa)Cl_2][Cu(bmpa)(H_2O)Cl][Cu(bmpa)Cl][CuCl_4]\}$ (**38**) [44] can catalyze the oxidation of C_6H_{12} by *tert*-butyl hydroperoxide (TBHP, aq. 70%) in MeCN solution, at 25–50 °C. However, the efficiency of all these systems in terms of total product yields (only up to 11% [44]) is significantly lower than that achieved by the same catalysts with H_2O_2 as oxidant.

Although dioxygen of air is typically involved to some extent in oxidation processes of C_6H_{12} with H_2O_2, the multicopper catalytic systems that can operate with O_2 as a sole oxidant under mild conditions are limited to two examples [9]. These concern the complexes $[K(18\text{-crown-}6)]_2[Cu_2(\mu\text{-}Cl)_6]$ (**20**) and $[Cu_4(\mu\text{-}Cl)_6(Cl)_2(18\text{-crown-}6)(H_2O)_2]$ (**37**) that are active in cyclohexane oxidation with O_2 (1 atm) in CH_2Cl_2 at 70 °C and in the presence of acetaldehyde, resulting in rather high product yields based on acetaldehyde [9]. It is believed that in these oxidation processes peroxyacetic acid acts as an oxidant, being generated in situ from acetaldehyde and O_2 [9].

3.2. Substrate versatility and mechanistic studies

A number of multicopper(II) catalytic systems have been tested in the mild oxidation of different alkane substrates which, apart from cyclohexane, also include other cyclic and linear alkanes. Hence, the catalysts or catalyst precursors that have been applied in the oxidation of more than one alkane substrate include compounds **7** [41], **18** [32], **19** [32], **22** [11], **24**–**26** [34,35], **30**–**32** [11,17,35,36], **50**–**53** [34–36], and **56** [37]. In the majority of cases, the second tested alkane was cyclopentane, the mild and efficient oxidation of which by H_2O_2 has been achieved in the presence of the heterometallic diethanolaminate complex **7** and various tri- (**24**–**26**), hexa- (**30**, **31**), and polynuclear (**50**–**53**) derivatives composed of tricopper(II) clusters with $\{Cu_3(\mu_3\text{-}OH)(\mu\text{-pz})_3\}^{2+}$ skeletons. These catalyst precursors typically lead to 30–36% total yields of cyclopentanol and cyclopentanone (selected systems are given in Table 8). As in the case of cyclohexane, the oxidation of cyclopentane by H_2O_2 proceeds in aqueous acetonitrile at r.t. in

Table 8
Selected multicopper catalytic systems for the oxidation of cyclopentane by H_2O_2, under mild conditions.[a]

Entry	Catalyst or catalyst precursor	Total yield (%)[b]	Ref.
1	$[Cu_2Co_2Fe_2(\mu\text{-dea})_6(NCS)_4(MeOH)_2]\cdot 3.2H_2O$ (**7**)	36	[41]
2	$[Cu_3(\mu_3\text{-OH})(\mu\text{-pz})_3(\mu\text{-buta})_2(MeOH)(H_2O)]_2$ (**30**)	30	[35]
3	$[Cu_3(\mu_3\text{-OH})(\mu\text{-pz})_3(\mu\text{-EtCOO})_2(EtOH)]_n$ (**51**)	31	[34,35]
4[c]	$[Cu(\mu_4\text{-dipic})_2\{Na_2(\mu\text{-}H_2O)_4\}]_n\cdot 2nH_2O$ (**56**)	10	[37]

[a] Typical reaction conditions: C_5H_{10} (1.0 mmol), aq. H_2O_2 (5.0 mmol), catalyst (10 μmol), $n(HNO_3)/n(\text{catalyst}) = 10{:}1$, MeCN solvent, 6 h, r.t.

[b] Moles of products (cyclopentanol + cyclopentanone)/100 mol of C_5H_{10}; typically determined by GC after the treatment with PPh_3.

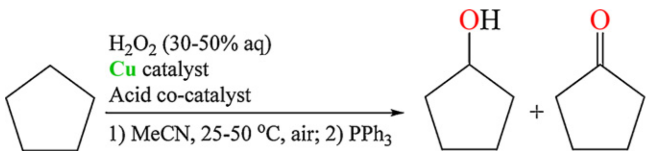
[c] C_5H_{10} (1.25 mmol), aq. H_2O_2 (2.5 mmol), 50 °C, in the absence of HNO_3.

air, and in the presence of HNO_3 as a co-catalyst (Scheme 2). The compound **56** [37] can also operate without any co-catalyst but with a modest product yield (10%). The oxidation of cycloheptane by H_2O_2 catalyzed by dicopper(II) Schiff base complexes **18** and **19** has also been reported [32].

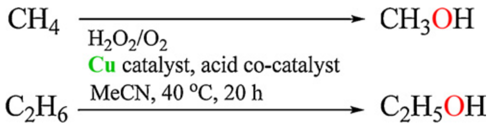
Apart from liquid alkanes, the multinuclear complexes $[Cu_3(\mu\text{-}H_2tea)_2(\mu\text{-poba})_2(H_2O)]\cdot 4H_2O$ (**22**) and $[Cu_4(\mu_4\text{-O})(\mu_3\text{-tea})_4(\mu_3\text{-BOH})_4][BF_4]_2$ (**32**) catalyze the oxidation of inert gaseous alkanes, such as methane and ethane (Scheme 3) [11], although less effectively than in the case of cyclohexane oxidation. For example, methanol (TON = 47, 2.2% yield) and ethanol (TON = 23, 2.1% yield) are obtained from CH_4 and C_2H_6, respectively, upon reaction of the alkane (30 atm) at 40 °C for 20 h with H_2O_2 in aqueous MeCN, in the presence of the **32**/HNO_3 catalytic system. The use of O_2 instead of H_2O_2 resulted in a marked decrease in the activity which, nevertheless, can still be catalytic [11].

In order to prove the radical type mechanism in Cu-catalyzed alkane oxidation by H_2O_2, the effects of radical trapping agents have been studied for selected catalytic systems (e.g., **5**, **7**, **9**, **22**, **25**, **40**, **53**, **56**), using either carbon radical traps like $CBrCl_3$ and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), or an oxygen radical trap such as diphenylamine. In all cases, the introduction of these radical scavengers into typical reaction mixtures of cyclohexane oxidation resulted in a strong decrease of the product yields. For example, in the C_6H_{12} oxidation catalyzed by the **5**/TFA [16] and **25**/HNO_3 [34] systems the total product yields decline from 38–28% to 1–5% (~80–95% yield drop) in the presence of any of the above-mentioned radical traps. Such a type of behavior and the detection of alkyl hydroperoxides (typical intermediates in radical type oxidation [16,17,47]) in considerable amounts reveal the involvement of both C- and O-centered radicals. For selected catalytic systems, the radical type mechanism has also been confirmed by additional studies, including experimental kinetic, selectivity, ESR and UV–vis methods [17].

Hence, the simplified mechanistic pathway (Scheme 4) in Cu-catalyzed alkane oxidation by H_2O_2 involves the H-abstraction from alkane (RH) conceivably by the hydroxyl radical $HO^\bullet$, formed via copper-assisted decomposition of H_2O_2 (reactions (1) and (2)), leading to the alkyl radical $R^\bullet$ (reaction (3)) [1,17,27,37,47–50]. Then $R^\bullet$ rapidly reacts with O_2 to give the organoperoxyl radical $ROO^\bullet$ (reaction (4)). The $ROO^\bullet$ can be reduced by a *L*Cu(I) species to the corresponding anion that is further converted into the main primary alkyl hydroperoxide product, ROOH (reactions (5) and (6)). This undergoes the copper-assisted homolytic decomposition furnishing the alkoxyl $RO^\bullet$ and alkylperoxyl $ROO^\bullet$ radicals (reactions (7) and (8)). The $RO^\bullet$ radicals are converted to the alcohol (ROH) by H-abstraction from the alkane (reaction (9)), whereas the peroxyl radicals dismutate (reaction (10)) to yield both the alcohol and the ketone ($R' = O$) [2a,17,27,47–51]. Although to a lesser extent, an alternative metal-free pathway for the decomposition of ROOH can also take place resulting in the formation of ROH and $R' = O$ [17].



Scheme 2. Oxidation of cyclopentane to cyclopentanol and cyclopentanone, under mild conditions.



Scheme 3. Oxidation of methane and ethane to the corresponding alcohols under mild conditions.

The tetracopper triethanolaminate complex **32**, the most versatile catalyst, has also been tested [17,18] in the oxidation of methylcyclohexane (MCH), *cis*- and *trans*-1,2-dimethylcyclohexanes (*cis*- and *trans*-DMCH), *n*-heptane, and *n*-octane, using either H_2O_2 or TBHP as oxidants, aiming at studying bond, regio-, and stereoselectivity parameters (Table 9).

In the oxidation of *n*-heptane and *n*-octane by H_2O_2 with **32** or $Cu(NO_3)_2$, the regioselectivity parameters (Table 9, entries 1–5) are relatively low [C(1):C(2):C(3):C(4) ≈ 1:(4–8):(4–7):(3–6)], being typical to those of many other systems that oxidize alkanes with participation of hydroxyl radicals [2a,17,18,47,50,52]. Similarly, in the oxidation of methylcyclohexane and stereoisomeric 1,2-dimethylcyclohexanes, the bond selectivity 1°:2°:3° and stereoselectivity *trans*/*cis* parameters of 1:(5–13):(14–22) and 0.8–1.0, respectively (entries 1–3), are also rather low what, by analogy with other catalytic systems, suggests the involvement of hydroxyl radicals as active oxidizing species [17]. On the contrary, all the selectivity parameters are significantly higher in the catalytic systems operating without hydroxyl radicals, such as the dimanganese(IV) complex $[Mn_2(\mu\text{-O})_3(L^{16})_2](PF_6)_2$ (**Mn_2**) [52] or $NaAuCl_4$ [53] (Table 9, entries 6–8).

Interestingly, in the case of TBHP oxidant [18], complex **32** is active in the absence of any acid co-catalyst, and shows very

$$2LCu^{II} + H_2O_2 \rightarrow 2LCu^{I} + 2H^{+} + O_2 \qquad (1)$$
$$LCu^{I} + H_2O_2 \rightarrow LCu^{II} + HO^{\bullet} + HO^{-} \qquad (2)$$
$$RH + HO^{\bullet} \rightarrow R^{\bullet} + H_2O \qquad (3)$$
$$R^{\bullet} + O_2 \rightarrow ROO^{\bullet} \qquad (4)$$
$$ROO^{\bullet} + LCu^{I} \rightarrow ROO^{-} + LCu^{II} \qquad (5)$$
$$ROO^{-} + H^{+} \rightarrow ROOH \qquad (6)$$
$$ROOH + LCu^{I} \rightarrow RO^{\bullet} + LCu^{II} + HO^{-} \qquad (7)$$
$$ROOH + LCu^{II} \rightarrow ROO^{\bullet} + LCu^{I} + H^{+} \qquad (8)$$
$$RO^{\bullet} + RH \rightarrow ROH + R^{\bullet} \qquad (9)$$
$$2ROO^{\bullet} \rightarrow ROH + R'{=}O + O_2 \qquad (10)$$

Scheme 4. Simplified mechanism for the copper-catalyzed oxidation of alkanes (RH) by H_2O_2 to alkyl hydroperoxides (ROOH), alcohols (ROH), and ketones ($R' = O$). Multicopper catalyst precursor and derived species are schematically depicted as LCu^{II} and LCu^{I}.

Adapted from [17].

Table 9
Comparative representation of selectivity parameters in the oxidation of alkanes in acetonitrile by different systems.[a]

Entry	System	C(1):C(2):C(3):C(4)		1°:2°:3°	*trans*/*cis*	
		n-Heptane	*n*-Octane	MCH	*cis*-DMCH	*trans*-DMCH
1	**32**/HCl/H_2O_2		1:4:4:3	1:13:22	0.9	1.0
2	**32**/TFA/H_2O_2	1:8:7:5	1:5:5:4	1:5:14	0.8	0.8
3	**32**/HNO_3/H_2O_2	1:7:7:6			0.8	0.9
4	$Cu(NO_3)_2$/HNO_3/H_2O_2	1:7:6:5			0.9	0.7
5	**32**/TBHP	1:34:23:21	1:65:32:30	1:16:128	0.4	0.1
6[b]	**Mn$_2$**/MeCOOH/H_2O_2	1:46:35:34	1:29:25:24	1:26:200	0.3	4.1
7[b]	**Mn$_2$**/$(COOH)_2$/TBHP	1:14:13:12	1:17:12:11	1:0.3:0.6	0.2	7.3
8[c]	$NaAuCl_4$/H_2O_2	1:35:25:23	1:116:255			

Adapted from [17,18].

[a] All parameters were measured after reduction of the reaction mixtures with PPh_3 before GC analysis and calculated based on the ratios of isomeric alcohols. Parameters C(1):C(2):C(3):C(4) are relative normalized reactivities of H atoms at carbon atoms C(1), C(2), C(3) and C(4) of *n*-heptane or *n*-octane chain. Parameters 1°:2°:3° are relative normalized reactivities of hydrogen atoms at primary, secondary and tertiary carbon atoms of branched alkanes. Parameter *trans*/*cis* is determined as the ratio of the formed tertiary alcohol isomers with mutual *trans* and *cis* orientation of the methyl groups.

[b] For this system, see [52].

[c] For this system, see [53].

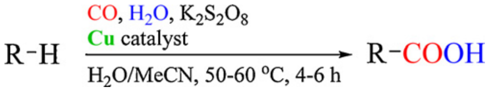
distinct selectivity parameters (entry 5) in comparison with those observed in the oxidation by H_2O_2 that require an acid promoter. The absence of an acid promoter eventually leads to the preservation of the original structure of **32**, with strongly hindered copper-containing reaction centers. As a consequence, the system exhibits a noticeable selectivity in the alkane oxidation [18]. In particular, the C(2) atom is the most reactive in linear alkane chains, as reflected by the regioselectivities C(1):C(2):C(3):C(4) of 1:34:23:21 and 1:65:32:30 for *n*-heptane and *n*-octane, respectively. These values are significantly higher than those observed for oxidation by H_2O_2, suggesting the possible involvement of different types of active oxidizing species, e.g., *tert*-butoxyl radicals [54]. Besides, the C(2) position is a preferable oxidation site in the biological hydroxylation of alkanes catalyzed by pMMO [55]. The presence of different oxidizing species is further indicated by the clearly distinct values of bond and stereoselectivities observed in alkane oxidation by the **32**/TBHP and **32**/co-catalyst/H_2O_2 systems (Table 9). Hence, in the **32**/TBHP system oxidation can possibly proceed in a hydrophobic pocket (cleft) containing some intermediate copper species, but their nature is still to be established [18]. All these features thus point out the complexity of Cu-catalyzed alkane oxidation, the mechanisms of which being affected by a diversity of factors, including the types of catalyst, promoter, and oxidant.

4. Hydrocarboxylation of alkanes

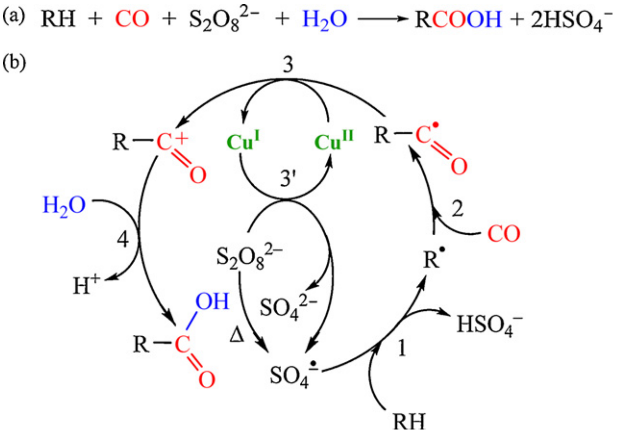
Among the different alkane functionalization reactions [1,2], their direct carboxylation by CO to give carboxylic acids in a single-pot is particularly attractive [4,19–26,56], since aliphatic carboxylic acids are important commodity chemicals with an increasing demand [3]. Their common synthetic procedures 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) requirement of harsh reaction conditions (high temperatures and pressures), involvement of multi-stage transformations and use of costly metal catalysts, and (iii) low conversions, poor selectivity, and need of a complex work-up [3,20]. These limitations have stimulated intensive research [50,57,58] aiming at the improvement and optimization of the alkane carboxylation method initially developed by Fujiwara [56,59], which is based on reacting an alkane with CO and peroxodisulfate, at 80 °C in absolute TFA and in the presence of a metal catalyst [19]. In spite of significant improvements [58], a main limitation of this method consists in the use of TFA solvent in view of its corrosive character, cost, difficult reutilization, and consumption along the reaction.

However, in recent years we have developed a new cleaner protocol for the direct and highly efficient conversion of C_n alkanes into the corresponding C_{n+1} carboxylic acids [19,60]. This route is based on the hydrocarboxylation of an alkane with carbon monoxide and water in the presence of peroxodisulfate (Schemes 5 and 6a). In contrast to state-of-the-art alkane carboxylation methods [56–59], the present approach eliminates the use of absolute trifluoroacetic acid (TFA) as a solvent, and proceeds efficiently at mild temperatures (50–60 °C) and in aqueous acid-solvent-free medium (H_2O/MeCN mixed solvent) [19]. Moreover, interestingly, water also plays a main role as a reagent (Scheme 6a), besides being a mere solvent component [19].

Although these hydrocarboxylation processes occur to some extent in metal-free systems, the reaction can be significantly improved by the use of metal catalysts or promoters. Among the variety of tested Cu, Fe, V, Mn, Re, Cr, and other transition metal catalysts, multicopper(II) complexes or coordination polymers are

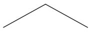
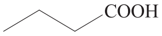
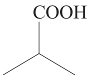
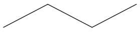
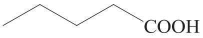
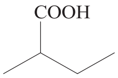


Scheme 5. Hydrocarboxylation of C_n alkanes to C_{n+1} carboxylic acids.



Scheme 6. (a) Hydrocarboxylation of alkanes (RH) to carboxylic acids (RCOOH) with $S_2O_8^{2-}$ as oxidant. (b) Proposed mechanism for the copper-catalyzed reaction. Adapted from [19,25]. ΔH_s (plane text) and $\Delta H_s^{\neq}$ (bold text) values (in kcal/mol) from DFT calculations for $R = C_2H_5$: reactions: (1) −8.6, **6.9**; (2) −12.8, **3.3**; (3) $[Cu^{II} = \{Cu(H_2O)_4Cl\}^+]$ −27.0; (4) [(4′) for reaction of RCO^+ with H_2O to give $RC(OH)OH^+$ −27.4, **7.39**; (4″) for reaction of $RC(OH)OH^+$ with H_2O to give RCOOH −9.4].

Table 10
Cu-catalyzed single-pot hydrocarboxylation of gaseous C_n ($n = 2–4$) alkanes into the corresponding C_{n+1} carboxylic acids, under mild conditions.[a]

Entry	Alkane	Carboxylic acid product	Catalyst	Product yield (%)[b]			Selectivity[d]	Ref.
				C(1)	C(2)	Total[c]		
1	 ethane	 C(1)	**23**	29.0	–	29.0	–	[23]
2			**46**	15.2	–	15.2	–	[25]
3	 propane	 C(1)  C(2)	**44**	7.8	70.6	78.4	1:27	[21]
4			**46**	8.1	66.5	74.6	1:25	[25]
5	 *n*-butane	 C(1)  C(2)	**44**	4.7	90.5	95.2	1:29	[21]
6			**46**	4.4	61.0	65.4	1:21	[25]

[a] Typical reaction conditions: alkane (1.0 atm; 0.266 mmol), Cu catalyst (4.0 μmol), $p(CO) = 10$ atm, $K_2S_2O_8$ (1.0 mmol), H_2O (2.0 mL)/MeCN (4.0 mL), 60 °C, 4–6 h, 13 mL autoclave.

[b] Moles of product/100 mol of alkane.

[c] Yield of all products.

[d] Bond 1°:2° or C(1):C(2) regioselectivity parameters.

typically the most active ones [19,20], affording 2–5 higher product yields than those in the metal-free systems. In particular, the hydrosoluble tetracopper(II) complex $[Cu_4(\mu_4\text{-}O)(\mu_3\text{-}tea)_4(\mu_3\text{-}BOH)_4][BF_4]_2$ (**32**) was initially applied as a reference catalyst in the hydrocarboxylation of ethane, propane, *n*-butane, *n*-pentane, cyclopentane, *n*-hexane, and cyclohexane [19,60]. Subsequently, the hydrocarboxylation has been optimized further [4,20,22] and extended to various alkanes and other multicopper catalysts or catalyst precursors, namely the dimer $[Cu_2(\mu\text{-}Hedea)_2(NCS)_2]$ (**4**) [24], the trimer $[Cu_3(\mu_3\text{-}BO)(\mu\text{-}H_3bts)_3][BF_4]\cdot 2H_2O$ (**23**) [23], the tetramer $[Li(H_2O)_4][Cu_4(\mu\text{-}Hbes)_4(\mu\text{-}ba)]\cdot H_2O$ (**33**) [25], and the polymers $[Cu_4(\mu_3\text{-}Hbes)_2(\mu\text{-}Hbes)_2(\mu\text{-}phba)\{Na(H_2O)_4\}]_n$ (**43**) [21], $[Cu_4(\mu_3\text{-}Hbes)_4(\mu\text{-}ba)(Na)]_n$ (**44**) [21], $[Cu_4(\mu_3\text{-}Hbes)_4(\mu\text{-}mba)\{Na(H_2O)_2\}]_n\cdot nH_2O$ (**45**) [21], $[Cu_4(\mu_3\text{-}Hbes)_4(\mu\text{-}mhba)\{Li(H_2O)_2\}]_n\cdot 3nH_2O$ (**46**) [25], $[Cu_4(\mu_3\text{-}Hbes)_4(\mu\text{-}dhba)\{Li(H_2O)_2\}]_n\cdot 3nH_2O$ (**47**) [25], and $[Cu_2Mg_2(\mu\text{-}Htea)_2(\mu_6\text{-}pma)(H_2O)_6]_n\cdot 6nH_2O$ (**57**) [26]. In contrast to oxidation, the hydrocarboxylation reactions of alkanes in the presence of these copper compounds do not require an acid co-catalyst. Hence, the most active catalytic systems for the hydrocarboxylation of gaseous, liquid linear, and cyclic alkanes are summarized in Tables 10–12, respectively, and discussed in the following sub-sections. In this discussion, all the % yields are expressed as moles of products per 100 mol of alkane substrate.

4.1. Gaseous alkanes

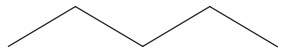
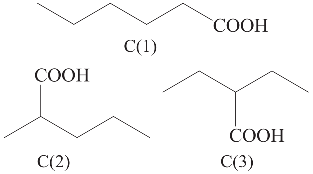
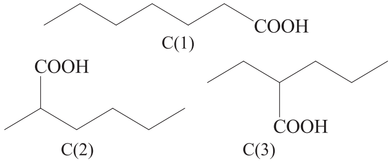
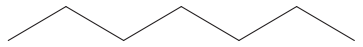
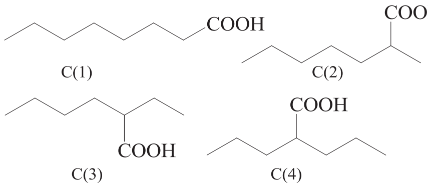
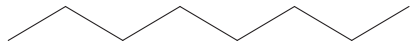
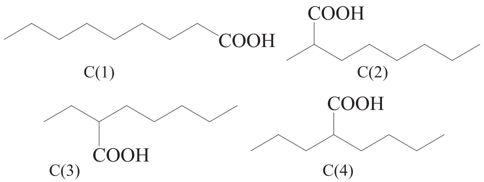
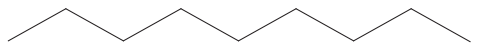
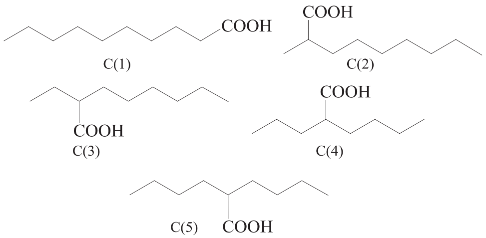
The compounds **23**, **32**, **33**, and **43**–**47** catalyze the hydrocarboxylation of ethane to propanoic acid, propane to 2-methylpropanoic and butanoic acids, and *n*-butane to 2-methylbutanoic and pentanoic acids (Table 10), whereas the attempted transformation of methane to acetic acid has so far been unsuccessful [4,19]. Due to the presence of only primary carbon atoms, C_2H_6 is the least reactive alkane, typically leading to yields of propanoic acid below 15% (based on ethane), although a higher yield of 29% can be achieved with **23** (Table 10, entry 1). Despite the fact that in the reactions with C_3H_8 and $n\text{-}C_4H_{10}$ as substrates the yields of linear carboxylic acids (butanoic and pentanoic acids) also do not exceed 5–9%, the presence of significantly more reactive secondary carbon atoms in these alkanes allows their efficient transformation into the branched acids (main products), with typical bond selectivity 1°:2° parameters of 1:(21–27). In these hydrocarboxylation processes [21,25], the hydrosoluble compounds **33** and **43**–**47** are highly active and show comparable levels of product yields owing to the presence of resembling tetracopper(II) $\{Cu_4(\mu\text{-}Hbes)(\mu\text{-}COO)\}^-$ cores. Among all the tested catalytic systems in the hydrocarboxylation of propane and *n*-butane, the highest yields of 2-methylpropanoic (71%) and 2-methylbutanoic (91%) acids are obtained with **44** (Table 10, entries 3 and 5), whereas the maximum total yields based on these alkane substrates attain values of 78 and 95%, respectively [21].

Complex **32** that possesses a different tetracopper(II) core also shows a pronounced activity, although leading to inferior total yields of carboxylic acids, i.e., 58 and 87% based on alkanes for the reactions with C_3H_8 and $n\text{-}C_4H_{10}$, respectively [4]. The effects of various reaction parameters have been studied in the hydrocarboxylation of ethane, propane and *n*-butane with **32**. In particular, solvent composition is a very important reaction parameter [4,19], since hydrocarboxylation reactions practically do not proceed in either only water or only acetonitrile, or in the absence of both of them. Acetonitrile solubilizes the organic species, while water dissolves catalyst and peroxodisulfate oxidant, also providing the main source of the hydroxyl group for the carboxylic acid. The optimal solvent compositions typically consist of 1:2 or 1:1 H_2O/MeCN volumetric ratios [4,19].

The reaction temperature also has an important effect. The hydrocarboxylation reactions occur even at 30 °C but with rather modest yields, which are sharply enhanced by heating until the optimum 60 °C temperature. Substantial formation of carboxylic acids can already be observed after 1 h, but longer reaction times (4–6 h) are typically required to achieve the best product yields [4,19]. Although alkane carboxylations in TFA are known to proceed

Table 11

Cu-catalyzed single-pot hydrocarboxylation of linear C_n ($n = 5–9$) alkanes into the corresponding C_{n+1} carboxylic acids, under mild conditions.[a]

Entry	Alkane	Carboxylic acid product	Catalyst	Product yield (%)[b]					Regioselectivity C(1):C(2):C(3):C(*n*)	Ref.
				C(1)	C(2)	C(3)	C(4)	Total[c]		
1	 *n*-pentane	 C(1) C(2) C(3)	**4**	1.6	26.0	10.9	–	38.5	1:24:20	[24]
2			**32**	1.3	34.8	1.3	–	39.2	1:40:7	[22]
3	 *n*-hexane	 C(1) C(2) C(3)	**23**	1.2	15.7	15.5	–	32.4	1:20:19	[23]
4			**32**	1.3	23.0	21.6	–	45.9	1:27:25	[22]
5	 *n*-heptane	 C(1) C(2) C(3) C(4)	**4**	1.1	10.0	9.6	4.1	24.8	1:14:13:11	[24]
6			**46**	0.8	10.6	10.3	4.4	26.1	1:20:19:17	[25]
7	 *n*-octane	 C(1) C(2) C(3) C(4)	**4**	0.7	7.6	7.0	6.9	22.2	1:16:15:15	[24]
8			**32**	0.5	5.5	5.1	5.1	16.2	1:16:15:15	[22]
9	 *n*-nonane	 C(1) C(2) C(3) C(4) C(5)	**32**	0.5	5.7	5.0	4.9 (2.1)[d]	18.2	1:17:15:14:13	[22]
10			**47**	0.5	4.9	4.7	4.7 (1.6)[d]	16.4	1:15:14:14:12	[25]

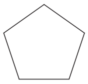
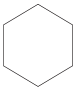
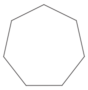
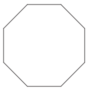
[a] Typical reaction conditions: alkane (1.00 mmol), Cu catalyst (4.0 μmol), p(CO) = 20 atm, $K_2S_2O_8$ (1.50 mmol), H_2O (2.0 mL)/MeCN (4.0 mL), 60 °C, 4–6 h in an autoclave (13.0 mL capacity).

[b] Moles of product/100 mol of alkane.

[c] Yield of all products.

[d] Yield of the C(5) product is given in brackets.

Table 12
Cu-catalyzed single-pot hydrocarboxylation of C_n ($n = 5–8$) cycloalkanes into the corresponding C_{n+1} cycloalkanecarboxylic acids, under mild conditions.[a]

Entry	Cycloalkane	Catalyst	Product yield (%)[b]			Ref.
			Carboxylic acid	Ketone + alcohol	Total[c]	
1		**23**	41.8	3.1	44.9	[23]
2		**46**	42.0	5.2	47.2	[25]
3		**32**	72.3	4.6	76.9	[19,20]
4		**33**	44.8	2.3	47.1	[25]
5		**23**	25.2	11.6	36.8	[23]
6		**33**	28.5	9.6	38.1	[25]
7		**4**	9.8	13.7	23.5	[24]
8		**57**	13.7	12.5	26.2	[26]

[a] Typical reaction conditions: cycloalkane (1.00 mmol), Cu catalyst (4.0 μmol), $p(CO) = 20$ atm, $K_2S_2O_8$ (1.50 mmol), H_2O/MeCN (2.0/4.0 or 3.0/3.0 mL), 50–60 °C, 4–6 h, 13 mL autoclave.

[b] Moles of product/100 mol of alkane.

[c] Yield of all products; cyclic ketones and alcohols are also formed as products of cycloalkane oxidation.

even in the absence of CO (with TFA acting then as the carbonylating agent [57,58]), the hydrocarboxylation reactions of gaseous alkanes in H_2O/MeCN medium do not undergo to any extent unless CO is added, because no other carbonylating reagent is present [4,19,25]. Carbon monoxide is typically introduced into the reaction mixture in a tenfold excess relative to substrate to generate the highest product yields. The use of potassium peroxodisulfate is also indispensable, since it acts as both a radical initiator and an oxidant, and the hydrocarboxylation reactions do not occur in its absence or upon its substitution for O_2, H_2O_2, or *t*-BuOOH [4,19,25]. However, $K_2S_2O_8$ is almost quantitatively transformed during the reaction to give $KHSO_4$ [19,20] which, upon cooling the reaction mixture, can be easily crystallized and separated by filtration, and potentially reconverted to peroxodisulfate via established electrochemical processes [61]. Other peroxodisulfate salts, for example, $(NH_4)_2S_2O_8$, can also be applied providing similar yields [20].

The partial oxidation of C_n alkanes to C_n carboxylic acids (e.g., ethane to acetic acid) or the conversion of MeCN solvent to acetic acid do not proceed [4,19], thus allowing a high selectivity to be achieved. Interestingly, the substitution of **32** for a simple copper salt, $Cu(NO_3)_2{\cdot}2.5H_2O$, in *n*-butane hydrocarboxylation, resulted in a strong inhibiting effect. This fact indicates the particular relevance of the N,O-ligands and their intricate arrangement in the multicopper(II) core of **32** [4].

Compared with industrial synthetic methods for low aliphatic $C_3–C_5$ carboxylic acids [3], the Cu-catalyzed hydrocarboxylation processes of gaseous alkanes represent a number of remarkable features, such as the possibility of operating under mild conditions in aqueous acid-solvent-free medium and leading, in a single step, to high selectivities and product yields based on alkane substrates [4,19,21,25]. In this regard, note that low aliphatic $C_3–C_5$ carboxylic acids are important commodity chemicals that are in increasing demand, being used in a wide variety of applications [3]. Their large-scale production is mainly based on the carbonylation of ethylene, oxidation of propanal or naphtha (for propanoic acid), liquid-phase oxidation of butyraldehydes (for butyric acids), and carbonylation of olefins or alcohols (for C_5 acids) [3]. However, there are still a number of general limitations of those methods, including: (i) the common use of raw materials that are considerably more expensive than alkanes and require prior production, (ii) the required multistage transformations, and the need for harsh reaction conditions and expensive metal catalysts, and (iii) the low product yields and/or poor selectivity and complex workup [4].

4.2. *Liquid linear alkanes*

Similarly to gaseous alkanes, multicopper(II) catalytic systems are efficient in the hydrocarboxylation of linear $C_5–C_9$ alkane substrates [19,22,24–26], allowing to generate from three to five isomeric monocarboxylic acid products (Table 11). The branched acids derived from the reactions at different secondary C(2), C(3), C(4), and C(5) carbon atoms within the hydrocarbon chain constitute the major products, whereas the corresponding linear (fatty) acids are only formed in minor amounts (<1.6% yield based on alkane). Isomeric carboxylic acids produced from linear alkanes include the following ones: (i) 2-methylpentanoic, 2-ethylbutanoic, and hexanoic acids from *n*-C_5H_{12}, (ii) 2-methylhexanoic, 2-ethylpentanoic, and heptanoic acids from *n*-C_6H_{14}, (iii) 2-methylheptanoic, 2-ethylhexanoic, 2-propylpentanoic, and octanoic acids from *n*-C_7H_{16}, (iv) 2-methyloctanoic, 2-ethylheptanoic, 2-propylhexanoic, and nonanoic acids from *n*-C_8H_{18}, and (v) 2-methylnonanoic, 2-ethyloctanoic, 2-propylheptanoic, 2-butylhexanoic, and decanoic acids from *n*-C_9H_{20} (see Table 11 for structural formulae) [25].

The linear C_5 and C_6 alkanes appear to be the most reactive and their hydrocarboxylation reactions, catalyzed by **32**, lead to 39 and 46% total yields (based on alkanes) of carboxylic acid products, respectively (entries 2 and 4), upon optimization of the reaction conditions [22]. The dicopper(II) complex **4** also exhibits rather high activity with overall yields in the 32–39% range (entries 1 and 3). The hydrocarboxylation of higher alkanes is less efficient [22,24,25], resulting in the maximum total yields of 26% (*n*-C_7H_{16}), 22% (*n*-C_8H_{18}), and 18% (*n*-C_9H_{20}), when using catalysts **46**, **4**, and **32**, respectively (entries 6, 7 and 9).

In the linear $C_6–C_9$ alkanes, all the secondary carbon atoms are typically carboxylated without noticeable preference to any particular one, as attested by the C(1):C(2):C(3):C(*n*) regioselectivities (normalized for the relative number of H atoms [62]) of 1:27:25 (Table 11, entry 4), 1:20:19:17 (entry 6), 1:16:15:15 (entry 7), and 1:17:15:14:13 (entry 9) observed in the reactions catalyzed by **32**, **46**, **4**, and **32**, respectively [22,24,25]. However, the C(2) atom in *n*-pentane appears to be more reactive (entries 1 and 2).

The observed regioselectivity parameters in the hydrocarboxylation of linear C_5–C_9 alkanes [22,24,25] are significantly higher than those reported for the oxidation of such alkanes by the **32**/co-catalyst/H_2O_2 system (Table 9, entries 1–3) operating with the participation of hydroxyl radicals [17], but somewhat comparable to the regioselectivities achieved in the oxidation reactions of these alkanes by the **32**/TBHP (Table 9, entry 5) that involve *tert*-butoxy radicals as oxidizing species [18]. These and other related examples are indicative of the involvement of the sulfate radical $SO_4{}^{\bullet-}$ as an active species in Cu-catalyzed alkane hydrocarboxylation.

The substrate scope of hydrocarboxylation is also extendable to branched alkanes. For example, the hydrocarboxylation of 3-methylhexane in the presence of **32** resulted in 19% overall yield of carboxylic acids [22]. Among various isomeric C_8 carboxylic acids, 2-methyl-2-ethylpentanoic (reaction at the tertiary carbon atom), 2,3-dimethylhexanoic, 3-methyl-2-ethylpentanoic, and 2,4-dimethylhexanoic acids (reaction at the secondary carbon atoms) are the main products, as attested by the bond selectivity 1°:2°:3° of 1:16:31 [22].

Moreover, a high overall selectivity (97–99%) toward carboxylic acids was observed for all the C_5–C_9 alkanes tested, since the generation of alcohols and ketones as by-products of partial alkane oxidation was negligible (only their traces below 1% total yield can be detected in some cases) in the hydrocarboxylation reactions. No other by-products were detected [19,22,24,25].

Furthermore, the observed efficiency (up to 46% total yields) of Cu-catalyzed alkane hydrocarboxylation is very high in comparison with the conventional routes for C_6–C_{10} aliphatic carboxylic acids. For example, their commercial synthesis via the oxidation of naphtha [1b,3] is characterized by yields inferior to 15%, poor selectivities and severe reaction conditions (high temperatures and pressures). A noteworthy feature of hydrocarboxylation also consists in the possibility of obtaining a variety of isomeric carboxylic acids as a mixture of reaction products, thus opening up its use, without the need for isolation of each isomer, in antibacterial, antifungicide, and sanitizing compositions, typical to those described in other state-of-the-art systems [22].

4.3. Cycloalkanes

Various multicopper(II) compounds also catalyze the hydrocarboxylation of unsubstituted C_5–C_8 cycloalkanes (Table 12) to the corresponding cycloalkanecarboxylic acids [19,20,23–26]. Owing to the presence of a single type of carbon atoms in the cycloalkane, the formation of only one carboxylic acid product is detected. As in the case of liquid linear C_5 and C_6 alkanes, the most reactive cycloalkanes are cyclopentane and cyclohexane. Their hydrocarboxylation reactions [20,23,25] result in cyclopentanecarboxylic and cyclohexanecarboxylic acids formed in up to 42% (with **23** and **46**) and 72% (with **32**) yields based on these alkane substrates, respectively (Table 12, entries 1–3). The hydrocarboxylation reactions of cycloheptane and cyclooctane are less efficient [25,26], and the highest yields of cycloheptanecarboxylic (29%) and cyclooctanecarboxylic (14%) acids are achieved in the systems catalyzed by **33** and **57**, respectively (entries 6 and 8). A particular characteristic of the transformations involving cycloalkanes as substrates [19,20,23–26] consists in the formation of the oxidation products (cyclic ketones and alcohols) in up to 14% overall yields (Table 12). On the contrary, the total yields of ketones and alcohols are negligible (typically below 1%) in the reactions of gaseous and liquid linear alkanes [4,19,22,25].

The hydrocarboxylation of cyclopentane and cyclohexane in the presence of **32** has been optimized to a variety of reaction parameters, including solvent composition, temperature, time, CO pressure, and relative amounts of substrate, oxidant, and catalyst [20]. The best reaction conditions are very close to those obtained after optimization of the hydrocarboxylation involving gaseous [4,19] and liquid linear [22] alkanes. The differences concern the preferable use of the H_2O/MeCN solvent in the 1:1 volumetric ratio and slightly inferior reaction temperature (50 °C) in cycloalkane hydrocarboxylation [20]. In the cyclohexane hydrocarboxylation, the best activity exhibited by **32** (72% yield) is higher than those achieved when using the mononuclear complexes [Cu(H_3L^{17})(NCS)] and [Cu(H_2tea)(N_3)] and copper(II) nitrate (21–33% yields) [19,20,24].

The hydrocarboxylation catalyzed by **32** is also extendable to different cycloalkanes that contain a tertiary carbon atom [20]. Hence, methylcyclohexane and adamantane can be transformed into the mixture of isomeric C_{n+1} cycloalkanecarboxylic acids with the overall yields of 21 and 7% based on alkanes, and the bond selectivities of 1:10:42 (1°:2°:3°) and 1:14 (2°:3°), correspondingly. In a comparable way, *cis*- and *trans*-1,2-dimethylcyclohexanes afford the respective acid products in 13–14% overall yields and the stereoselectivity parameters *trans*/*cis* of 0.62 (partial retention of *cis* configuration) and 0.43 (substantial inversion of *trans* configuration), respectively, which also support the involvement of the sulfate radical $SO_4{}^{\bullet-}$ as an active species [20].

4.4. Reaction mechanism

Based on the combination of experimental data, namely including analysis of various selectivity parameters [4,19,20,22,24], tests with radical traps [4,19,20] and ^{18}O-labeled H_2O [19], with DFT calculations (for ethane hydrocarboxylation by model mononuclear aqua complexes of copper [19]) and other studies [19,57,58], the simplified mechanistic pathway shown in Scheme 6 has been proposed [19,25,26] for the Cu-catalyzed hydrocarboxylation of various alkanes (RH).

The mechanism [19–26] bears the following steps: (1) the generation of the alkyl radicals $R^\bullet$ from an alkane [formed upon H abstraction by sulfate radical $SO_4{}^{\bullet-}$ derived from homolysis of $K_2S_2O_8$], (2) the carbonylation of $R^\bullet$ by CO to furnish the acyl radicals $RCO^\bullet$, (3) the oxidation of $RCO^\bullet$ by copper(II) species to the acyl cations RCO^+ [via the Cu(II)/Cu(I) redox couple], (3′) the regeneration of the Cu(II) form upon oxidation of Cu(I) by $K_2S_2O_8$, and (4) the hydrolysis of RCO^+ to yield the carboxylic acids. The last step was also confirmed [19] on the basis of experiments with ^{18}O-labeled H_2O in cyclohexane hydrocarboxylation and theoretical calculations on ethane hydrocarboxylation.

While the active role of sulfate radical $SO_4{}^{\bullet-}$ has been confirmed by various selectivity tests, the involvement of alkyl radicals was also proved by performing the carboxylation of alkanes (e.g., propane and cyclohexane) in the presence of the carbon-centered radical trap $CBrCl_3$, which resulted in the full suppression of carboxylic acid formation and the appearance of the corresponding alkyl bromides as main products [4,20]. The radical pathway is also supported by the inhibiting effect of O_2 [20]. In fact, the hydrocarboxylation processes do not proceed with O_2 as the sole oxidant, and when dioxygen is used together with peroxodisulfate, a significant decrease in the yield of carboxylic acids is detected. This is indicative that O_2 acts as a radical scavenger, reacting with the alkyl radicals to give the peroxyl radicals, thus promoting the formation of oxidation products (alcohols and ketones) [20].

5. Conclusions and outlook

The present study provides a summary of recent advances in homogeneous oxidative functionalization of alkanes catalyzed by multicopper systems, showing that mild, efficient, and selective protocols for the oxidation and hydrocarboxylation of inert alkanes can be developed. Although a rational design of highly active and versatile catalysts is still a difficult task, the performed herein analysis of multicopper systems that have already found notable applications in oxidative transformations of alkanes allows to identify a number of preferable requirements for a prospective homogeneous Cu-based catalyst. These requirements include (i) the presence of N,O-ligands or environment, (ii) low coordination numbers (i.e., 4 and/or 5) of Cu centers that preferably possess labile ligands, (iii) high stability of the multinuclear metal cores with relatively close separations of Cu atoms, (iv) solubility and stability of catalysts in water and/or aqueous acetonitrile medium, and (v) their easy preparation from simple, cheap, and commercially available chemicals.

The catalytic systems described for the oxidative functionalization of alkanes show a number of important features. In particular, very high product yields (up to 95% based on alkane) can be attained in alkane hydrocarboxylation [19–26], especially considering the exceptional inertness of these hydrocarbons and the fact that such reactions involve C—H bond cleavage, C—C bond formation, and proceed in an acid-solvent-free H_2O/MeCN medium (water plays a main role as a reagent, besides being a mere solvent component) and at very mild temperatures (50–60 °C). Besides, these hydrocarboxylation reactions contrast with most of the state-of-the-art processes [1,2] for the relatively mild transformations of alkanes that require the use of strongly acidic reaction media, such as concentrated trifluoroacetic or sulfuric acid, or a superacid. However, the exploration of both alkane oxidation and hydrocarboxylation to overcome some limitations of the current systems, such as the use of $K_2S_2O_8$ as an oxidant (in hydrocarboxylation) and MeCN as a solvent component, should be continued.

Hence, further research should envisage the application of other cheaper and cleaner oxidants (e.g., air, O_2, or H_2O_2), carbonylating agents (e.g., CO_2), recyclable catalysts, and more favorable reaction conditions. The extension of both synthetic and catalytic directions, by widening the type of multicopper(II) compounds and by broadening the substrate versatility of the catalytic transformations, should also be pursued. Furthermore, a different direction consists in the heterogenization of the most promising catalysts on various supports and the establishment of their catalytic potential toward oxidative functionalization of alkanes under heterogeneous conditions.

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References

[1] (a) A.E. Shilov, G.B. Shul'pin, Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes, Kluwer Acad. Publ., Dordrecht, 2000;
(b) G.A. Olah, Á. Molnár, Hydrocarbon Chemistry, Wiley, Hoboken, NJ, 2003;
(c) G.B. Shul'pin, in: M. Beller, C. Bolm (Eds.), Transition Metals for Organic Synthesis, vol. 2, 2nd ed., Wiley-VCH, Weinheim/New York, 2004, p. 215;
(d) R.A. Sheldon, J.K. Kochi, Metal-catalyzed Oxidations of Organic Compounds, Academic Press, New York, 1981.
[2] For selected reviews on alkane functionalization, see:
(a) G.B. Shul'pin, Mini-Rev. Org. Chem. 6 (2009) 95;
(b) M.M. Díaz-Requejo, P.J. Pérez, Chem. Rev. 108 (2008) 3379;
(c) J.A. Labinger, J.E. Bercaw, Nature 417 (2002) 507;
(d) A.A. Fokin, P.R. Schreiner, Chem. Rev. 102 (2002) 1551;
(e) A. Sen, Acc. Chem. Res. 31 (1998) 550;
(f) A.E. Shilov, G.B. Shul'pin, Chem. Rev. 97 (1997) 2879.
[3] (a) Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., Wiley-VCH, Weinheim, 2002;
(b) Encyclopedia of Chemical Technology, 5th ed., Wiley, New York, 2004;
(c) H. Wittcoff, B.G. Reuben, J.S. Plotkin, Industrial Organic Chemicals, 2nd ed., Wiley, New York, 2004.
[4] M.V. Kirillova, A.M. Kirillov, A.J.L. Pombeiro, Chem. Eur. J. 16 (2010) 9485.
[5] (a) R.S. Brissos, S. Garcia, A. Presa, P. Gamez, Comment Inorg. Chem. 32 (2011) 219;
(b) P. Gamez, P.G. Aubel, W.L. Driessen, J. Reedijk, Chem. Soc. Rev. 30 (2001) 376;
(c) L.M. Mirica, X. Ottenwaelder, T.D.P. Stack, Chem. Rev. 104 (2004) 1013;
(d) E.A. Lewis, W.B. Tolman, Chem. Rev. 104 (2004) 1047.
[6] (a) S. Itoh, in: J.A. McCleverty, T.J. Meyer, L. Que, W.B. Tolman (Eds.), Comprehensive Coordination Chemistry, vol. 8, 2nd ed., Elsevier, Dordrecht, 2003, p. 369 (Chapter 8.15);
(b) D.H. Lee, in: J.A. McCleverty, T.J. Meyer, L. Que, W.B. Tolman (Eds.), Comprehensive Coordination Chemistry, vol. 8, 2nd ed., Elsevier, Dordrecht, 2003, p. 437 (Chapter 8.17);
(c) J.J.R. Fraústo da Silva, R.J.P. Williams, The Biological Chemistry of the Elements, Oxford University Press, Oxford, 2001.
[7] (a) R.A. Himes, K.D. Karlin, Curr. Opin. Chem. Biol. 13 (2009) 119;
(b) R.L. Lieberman, A.C. Rosenzweig, Nature 434 (2005) 177;
(c) S.I. Chan, V.C.-C. Wang, J.C.-H. Lai, S.S.-F. Yu, P.P.-Y. Chen, K.H.-C. Chen, C.-L. Chen, M.K. Chan, Angew. Chem. Int. Ed. 46 (2007) 1992;
(d) S.J. Elliot, M. Zhu, L. Tso, H.-H.T. Nguyen, J.H.-K. Yip, S.I. Chan, J. Am. Chem. Soc. 119 (1997) 9949.
[8] (a) S.I. Chan, S.S.F. Yu, Acc. Chem. Res. 41 (2008) 969;
(b) A.C. Rosenzweig, M.H. Sazinsky, Curr. Opin. Struct. Biol. 16 (2006) 729.
[9] S. Murahashi, N. Komiya, Y. Hayashi, T. Kumano, Pure Appl. Chem. 73 (2001) 311.
[10] T. Ohta, T. Tachiyama, K. Yoshizawa, T. Yamabe, T. Uchida, T. Kitagawa, Inorg. Chem. 39 (2000) 4358.
[11] A.M. Kirillov, M.N. Kopylovich, M.V. Kirillova, M. Haukka, M.F.C.G. da Silva, A.J.L. Pombeiro, Angew. Chem. Int. Ed. 44 (2005) 4345.
[12] 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. 348 (2006) 159.
[13] Y.Y. Karabach, A.M. Kirillov, M.F.C.G. da Silva, M.N. Kopylovich, A.J.L. Pombeiro, Cryst. Growth Des. 6 (2006) 2200.
[14] Y.Y. Karabach, A.M. Kirillov, M. Haukka, M.N. Kopylovich, A.J.L. Pombeiro, J. Inorg. Biochem. 102 (2008) 1190.
[15] A.M. Kirillov, Y.Y. Karabach, M. Haukka, M.F.C. Guedes da Silva, J. Sanchiz, M.N. Kopylovich, A.J.L. Pombeiro, Inorg. Chem. 47 (2008) 162.
[16] K.R. Gruenwald, A.M. Kirillov, M. Haukka, J. Sanchiz, A.J.L. Pombeiro, Dalton Trans. (2009) 2109.
[17] M.V. Kirillova, Y.N. Kozlov, L.S. Shul'pina, O.Y. Lyakin, A.M. Kirillov, E.P. Talsi, A.J.L. Pombeiro, G.B. Shul'pin, J. Catal. 268 (2009) 26.
[18] M.V. Kirillova, A.M. Kirillov, D. Mandelli, W.A. Carvalho, A.J.L. Pombeiro, G.B. Shul'pin, J. Catal. 272 (2010) 9.
[19] M.V. Kirillova, A.M. Kirillov, M.L. Kuznetsov, J.A.L. Silva, J.J.R. Fraústo da Silva, A.J.L. Pombeiro, Chem. Commun. (2009) 2353.
[20] M.V. Kirillova, A.M. Kirillov, A.J.L. Pombeiro, Adv. Synth. Catal. 351 (2009) 2936.
[21] A.M. Kirillov, J.A.S. Coelho, M.V. Kirillova, M.F.C. Guedes da Silva, D.S. Nesterov, K.R. Gruenwald, M. Haukka, A.J.L. Pombeiro, Inorg. Chem. 49 (2010) 6390.
[22] M.V. Kirillova, A.M. Kirillov, A.J.L. Pombeiro, Appl. Catal. A: Gen. 401 (2011) 106.
[23] A.M. Kirillov, Y.Y. Karabach, M.V. Kirillova, M. Haukka, A.J.L. Pombeiro, Dalton Trans. 40 (2011) 6378.
[24] A.M. Kirillov, M.V. Kirillova, L.S. Shul'pina, P.J. Figiel, K.R. Gruenwald, M.F.C. Guedes da Silva, M. Haukka, A.J.L. Pombeiro, G.B. Shul'pin, J. Mol. Catal. A: Chem. 350 (2011) 26.
[25] M.V. Kirillova, A.M. Kirillov, A.N.C. Martins, C. Graiff, A. Tiripicchio, A.J.L. Pombeiro, Inorg. Chem. 51 (2012) 5224.
[26] A.M. Kirillov, Y.Y. Karabach, M.V. Kirillova, M. Haukka, A.J.L. Pombeiro, Cryst. Growth Des. 12 (2012) 1069.
[27] K.T. Mahmudov, M.N. Kopylovich, M.F.C. Guedes da Silva, P.J. Figiel, Y.Y. Karabach, A.J.L. Pombeiro, J. Mol. Catal. A: Chem. 318 (2010) 44.
[28] M.N. Kopylovich, K.T. Mahmudov, M.F.C. Guedes da Silva, P.J. Figiel, Y.Y. Karabach, M.L. Kuznetsov, K.V. Luzyanin, A.J.L. Pombeiro, Inorg. Chem. 50 (2011) 918.
[29] M.N. Kopylovich, A.C.C. Nunes, K.T. Mahmudov, M. Haukka, T.C.O. Mac Leod, L.M.D.R.S. Martins, M.L. Kuznetsov, A.J.L. Pombeiro, Dalton Trans. 40 (2011) 2822.
[30] M. Salavati-Niasari, Z. Salimi, M. Bazarganipour, F. Davar, Inorg. Chim. Acta 362 (2009) 3715.
[31] G. Ceyhana, C. Celik, S. Urus, I. Demirtas, M. Elmastas, M. Tumer, Spectrochim. Acta A 81 (2011) 184.
[32] S. Basak, S. Sen, P. Roy, C.J. Gomez-Garcia, D.L. Hughes, R.J. Butcher, E. Garribba, S. Mitra, Aust. J. Chem. 63 (2010) 479.
[33] P. Roy, M. Manassero, Dalton Trans. 39 (2010) 1539.
[34] C. Di Nicola, Y.Y. Karabach, A.M. Kirillov, M. Monari, L. Pandolfo, C. Pettinari, A.J.L. Pombeiro, Inorg. Chem. 46 (2007) 221.
[35] C. Di Nicola, F. Garau, Y.Y. Karabach, L.M.D.R.S. Martins, M. Monari, L. Pandolfo, C. Pettinari, A.J.L. Pombeiro, Eur. J. Inorg. Chem. (2009) 666.
[36] S. Contaldi, C. Di Nicola, F. Garau, Y.Y. Karabach, L.M.D.R.S. Martins, M. Monari, L. Pandolfo, C. Pettinari, A.J.L. Pombeiro, Dalton Trans. (2009) 4928.
[37] M.V. Kirillova, A.M. Kirillov, M.F.C. Guedes da Silva, A.J.L. Pombeiro, Eur. J. Inorg. Chem. (2008) 3423.
[38] P.J. Figiel, A.M. Kirillov, Y.Y. Karabach, M.N. Kopylovich, A.J.L. Pombeiro, J. Mol. Catal. A: Chem. 305 (2009) 178.

[39] (a) R.A. Sheldon, Green Chem. 7 (2005) 267;
(b) U.M. Lindström, Chem. Rev. 102 (2002) 2751;
(c) W.A. Herrmann, B. Cornils (Eds.), Aqueous-Phase Organometallic Catalysis: Concepts and Applications, Wiley-VCH, Weinheim, 2004;
(d) R.A. Sheldon, Chem. Commun. (2008) 3352.
[40] Y.Y. Karabach, M.F.C. Guedes da Silva, M.N. Kopylovich, B. Gil-Hernández, J. Sanchiz, A.M. Kirillov, A.J.L. Pombeiro, Inorg. Chem. 49 (2010) 11096.
[41] D.S. Nesterov, V.N. Kokozay, V.V. Dyakonenko, O.V. Shishkin, J. Jezierska, A. Ozarowski, A.M. Kirillov, M.N. Kopylovich, A.J.L. Pombeiro, Chem. Commun. (2006) 4605.
[42] T.F.S. Silva, G.S. Mishra, M.F.C. Guedes da Silva, R. Wanke, L.M.D.R.S. Martins, A.J.L. Pombeiro, Dalton Trans. (2009) 9207.
[43] M. Casarin, C. Corvaja, C. Di Nicola, D. Falcomer, L. Franco, M. Monari, L. Pandolfo, C. Pettinari, F. Piccinelli, Inorg. Chem. 44 (2005) 6265.
[44] A.C. Silva, T.L. Fernandez, N.M.F. Carvalho, M.H. Herbst, J. Bordinhão, A. Horn Jr., J.L. Wardell, E.G. Oestreicher, O.A.C. Antunes, Appl. Catal. A: Gen. 317 (2007) 154.
[45] For recent reviews on the use of coordination polymers in catalysis, see:
(a) L.-Q. Ma, C. Abney, W.-B. Lin, Chem. Soc. Rev. 38 (2009) 1248;
(b) J.-Y. Lee, O.K. Farha, J. Roberts, K.A. Scheidt, S.T. Nguyen, J.T. Hupp, Chem. Soc. Rev. 38 (2009) 1450;
(c) D. Farrusseng, S. Aguado, C. Pinel, Angew. Chem. Int. Ed. 48 (2009) 7502;
(d) A. Corma, H. Garcia, F.X.L. Xamena, Chem. Rev. 110 (2010) 4606;
(e) M. Ranocchiari, J.A. van Bokhoven, Phys. Chem. Chem. Phys. 13 (2011) 6388.
[46] U. Schuchardt, D. Cardoso, R. Sercheli, R. Pereira, R.S. da Cruz, M.C. Guerreiro, D. Mandelli, E.V. Spinace, E.L. Pires, Appl. Catal. A: Gen. 211 (2001) 1.
[47] (a) G.B. Shul'pin, J. Mol. Catal. A: Chem. 189 (39) (2002);
(b) G.B. Shul'pin, C.R. Chim. 6 (2003) 163.
[48] (a) G. Süss-Fink, G.V. Nizova, S. Stanislas, G.B. Shul'pin, J. Mol. Catal. A: Chem. 130 (1998) 163;
(b) G.B. Shul'pin, M.V. Kirillova, T. Sooknoi, A.J.L. Pombeiro, Catal. Lett. 123 (2008) 135.
[49] (a) M.L. Kuznetsov, A.J.L. Pombeiro, Inorg. Chem. 48 (2009) 307;
(b) M.V. Kirillova, A.M. Kirillov, P.M. Reis, J.A.L. Silva, J.J.R. Fraústo da Silva, A.J.L. Pombeiro, J. Catal. 248 (2007) 130.
[50] (a) G.B. Shul'pin, Y.N. Kozlov, G.V. Nizova, G. Suss-Fink, S. Stanislas, A. Kitaygorodskiy, V.S. Kulikova, J. Chem. Soc. Perkin Trans. 2 (2001) 1351;
(b) G.B. Shul'pin, J. Mol. Catal. A: Chem. 227 (2005) 247;
(c) Y.N. Kozlov, V.B. Romakh, A. Kitaygorodskiy, P. Buglyo, G. Suss-Fink, G.B. Shul'pin, J. Phys. Chem. A 211 (2007) 7736.
[51] (a) M. Costas, M.P. Mehn, M.P. Jensen, L. Que Jr., Chem. Rev. 104 (2004) 939;
(b) M. Costas, K. Chen, L. Que Jr., Coord. Chem. Rev. 200–202 (2000) 517.
[52] (a) Y.N. Kozlov, G.V. Nizova, G.B. Shul'pin, J. Phys. Org. Chem. 21 (2008) 119;
(b) G.B. Shul'pin, G. Süss-Fink, L.S. Shul'pina, J. Mol. Catal. A: Chem. 170 (2001) 17;
(c) G.B. Shul'pin, M.G. Matthes, V.B. Romakh, M.I.F. Barbosa, J.L.T. Aoyagi, D. Mandelli, Tetrahedron 64 (2008) 2143;
(d) G.B. Shul'pin, Y.N. Kozlov, S.N. Kholuiskaya, M.I. Plieva, J. Mol. Catal. A: Chem. 299 (2009) 77.
[53] G.B. Shul'pin, G. Süss-Fink, A.E. Shilov, Tetrahedron Lett. 42 (2001) 7253.
[54] G.B. Shul'pin, J. Gradinaru, Y.N. Kozlov, Org. Biomol. Chem. 1 (2003) 3611.
[55] (a) R.L. Lieberman, A.C. Rosenzweig, Crit. Rev. Biochem. Mol. Biol. 39 (2004) 147;
(b) K.-Y. Ng, L.-C. Tu, Y.-S. Wang, S.I. Chan, S.S.-F. Yu, ChemBioChem 9 (2008) 1116.
[56] C. Jia, T. Kitamura, Y. Fujiwara, Acc. Chem. Res. 34 (2001) 633.
[57] (a) P.M. Reis, J.A.L. Silva, A.F. Palavra, J.J.R. Fraústo da Silva, T. Kitamura, Y. Fujiwara, A.J.L. Pombeiro, Angew. Chem. Int. Ed. 42 (2003) 821;
(b) A.M. Kirillov, M. Haukka, M.V. Kirillova, A.J.L. Pombeiro, Adv. Synth. Catal. 347 (2005) 1435;
(c) P.M. Reis, J.A.L. Silva, A.F. Palavra, J.J.R. Fraústo da Silva, A.J.L. Pombeiro, J. Catal. 235 (2005) 333.
[58] (a) M.V. Kirillova, M.L. Kuznetsov, J.A.L. da Silva, M.F.C. Guedes da Silva, J.J.R. Fraústo da Silva, A.J.L. Pombeiro, Chem. Eur. J. 14 (2008) 1828;
(b) M.V. Kirillova, J.A.L. da Silva, J.J.R. Fraústo da Silva, A.J.L. Pombeiro, Appl. Catal. A: Gen. 332 (2007) 159;
(c) M.V. Kirillova, M.L. Kuznetsov, P.M. Reis, J.A.L. da Silva, J.J.R. Fraústo da Silva, A.J.L. Pombeiro, J. Am. Chem. Soc. 129 (2007) 10531;
(d) M.V. Kirillova, J.A.L. da Silva, J.J.R. Fraústo da Silva, A.F. Palavra, A.J.L. Pombeiro, Adv. Synth. Catal. 349 (2007) 1765.
[59] Y. Fujiwara, K. Takaki, Y. Taniguchi, Synlett (1996) 591.
[60] A.J.L. Pombeiro, M.V. Kirillova, A.M. Kirillov, J.A.L. Silva, J.J.R. Fraústo da Silva, Int. Patent Appl. WO/2008/088234 (2008).
[61] G.B. Balazs, J.F. Cooper, T.E. Shell, J. Appl. Electrochem. 29 (1999) 285.
[62] For a recent review on regioselectivity, see: G.B. Shul'pin, Org. Biomol. Chem. 8 (2010) 4217.