Alkane Oxidation

Deutsche Ausgabe: DOI: 10.1002/ange.201607216
Internationale Ausgabe: DOI: 10.1002/anie.201607216

Copper-Catalyzed Oxidation of Alkanes with H_2O_2 under a Fenton-like Regime

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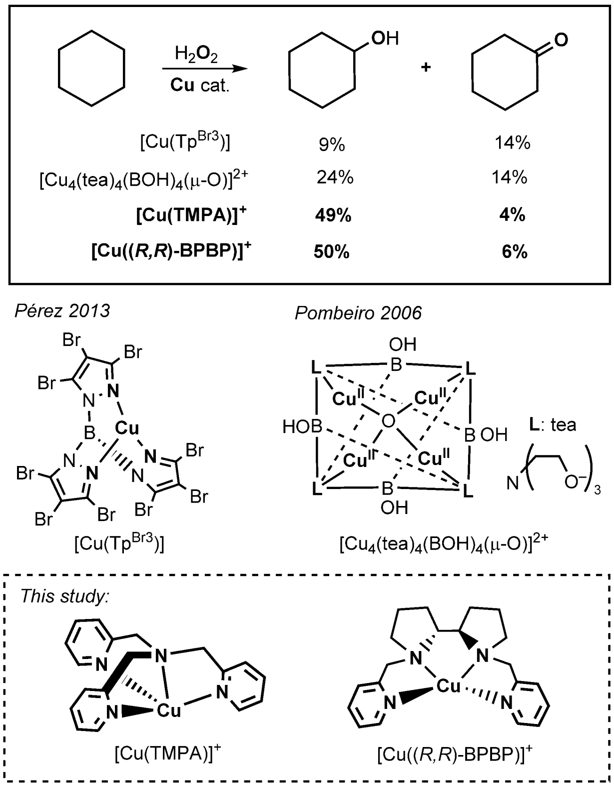
Abstract: *Copper complexes bearing readily available ligand systems catalyzed the oxidation of alkanes with H_2O_2 as the oxidant with high efficiency in remarkable yields (50–60 %). The reactions proceeded with unprecedented selectivity to give alkyl hydroperoxides as the major products. Detailed scrutiny of the reaction mechanism suggests the involvement of C-centered and O-centered radicals generated in a Fenton-like fashion.*

The oxidation of oil-derived building blocks, such as alkanes, is the first step in a majority of industrial chemical syntheses.[1] Owing to the intrinsic inertness of C–H bonds, harsh reaction conditions are often required (i.e. high temperatures, use of strong oxidants, and stoichiometric additives), which lead to poor selectivity, low yields, and undesired environmental and economic costs.[2] Iron- and copper-dependent metalloenzymes constitute a paradigmatic example of catalysts for selective C–H oxidation under mild conditions.[3,4] The activity of these enzymes inspired the development of small-molecule Fe catalysts for the oxidation of C–H substrates with excellent yields and selectivity.[4] Copper complexes have also emerged as efficient catalysts in C–H and C=C oxidative transformations.[5] However, the use of Cu in alkane oxidation has been limited.[6]

Barton et al. reported one of the first examples of copper-catalyzed C–H oxidation in a system that combined Cu powder, pyridine, acetic acid, and H_2O_2.[7] Alkane oxidation was found to occur by a radical chain mechanism leading to the formation of alkyl hydroperoxide intermediates.[8] However, oxidation products were obtained in very low yields (<5 %).[9] By using a similar approach, Sawyer and coworkers found that the use of a $[Cu^I(bpy)_2]$/pyridine mixture (bpy: 2,2′-bipyridine) led to a moderate increase in yield (<15 %).[10] A milestone contribution from Pombeiro and coworkers described a tetranuclear Cu cluster ($[Cu_4(tea)(BOH)_4(\mu\text{-}O)]^{2+}$) that promoted the peroxidation of cyclohexane with remarkable efficiency (yields up to 38 %; see Scheme 1).[11] Recently, Pérez and co-workers reported that mononuclear Cu complexes bearing a trispyrazolylborate ligand could also catalyze the oxidation of alkyl C–H bonds in moderate yields (Scheme 1).[12] Herein, we show that Cu salts, combined with commercially available ligand systems and H_2O_2, catalyze the oxidation of C–H bonds with unprecedented efficiency.



$[Cu(Tp^{Br3})]$	9%	14%
$[Cu_4(tea)_4(BOH)_4(\mu\text{-}O)]^{2+}$	24%	14%
$[Cu(TMPA)]^+$	**49%**	**4%**
$[Cu((R,R)\text{-}BPBP)]^+$	**50%**	**6%**

Scheme 1. Selected examples of copper-catalyzed cyclohexane oxidation with H_2O_2 as the oxidant. In this study, cyclohexyl hydroperoxide was obtained as the main oxidation product, which can be converted into cyclohexanol and cyclohexanone.

Inspired by the previous studies mentioned above, we decided to test the performance of different ligand systems in the oxidation of cyclohexane (Figure 1 and Table 1). Equimolar amounts of the desired ligand (L) and $[Cu^I(CH_3CN)_4](PF_6)$ (1 mol %) were mixed in CH_3CN. H_2O_2 (35 % in H_2O, 10 equiv) and cyclohexane (**S1**) were added sequentially, and the reaction mixture was stirred at room temperature for 6 h (see the Supporting Information for optimization of the reactions conditions and further details). GC analysis of the crude product mixture by the method described by Shul'pin[13] confirmed the formation of cyclohexyl hydroperoxide (**P1**) as the main product: When the crude product mixture was injected directly, a 1:1 mixture of cyclohexanol (**P2**) and cyclohexanone (**P3**) was observed;

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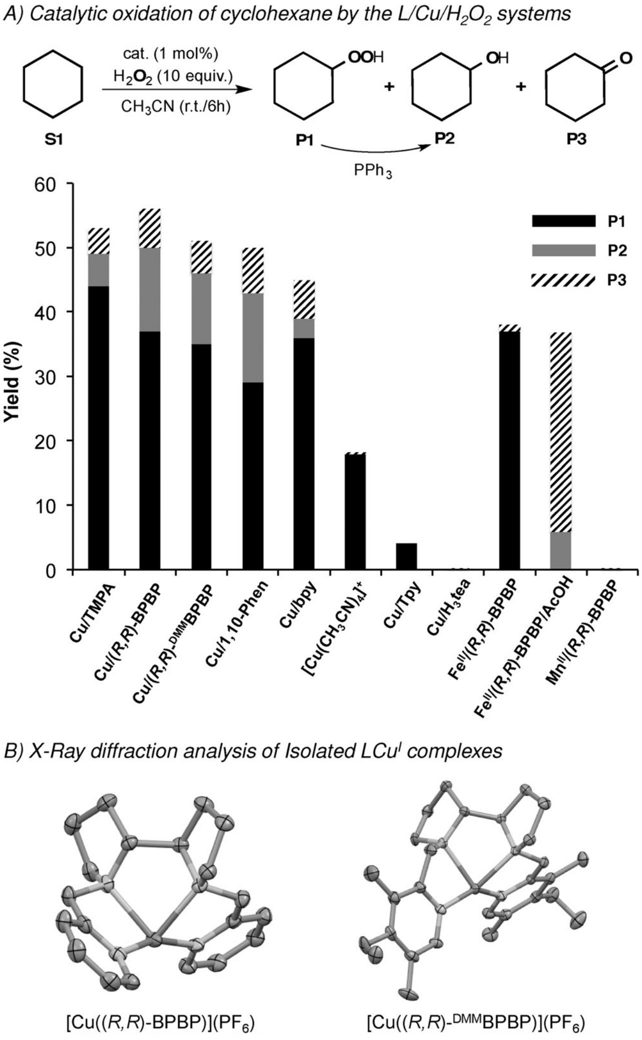
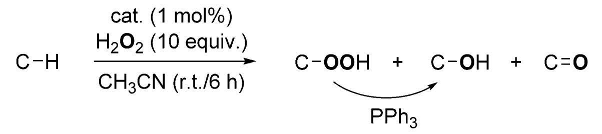
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201607216.



[Cu((*R,R*)-BPBP)](PF$_6$) [Cu((*R,R*)-^{DMM}BPBP)](PF$_6$)

Figure 1. A) Oxidation of cyclohexane (**S1**) by Cu/ligand catalysts with H_2O_2 as the oxidant and comparison of the yields obtained with the different Cu L$^-$ systems (see text and the Supporting Information for details). B) Displacement ellipsoid plots (50% probability level) of [Cu^I((*R,R*)-BPBP)]$^+$ and [Cu^I((*R,R*)-^{DMM}BPBP)]$^+$. For clarity, the PF$_6$ anions and the H atoms are not depicted. See the Supporting Information for synthetic details, structural features, and crystallographic data.

Table 1: Catalytic oxidation of alkanes by Cu complexes with H_2O_2.[a]



Entry	Substrate	Catalyst	Yield [%] C–OH$^{(COOH)}$/C=O	Total yield [%]
1	cyclohexane	[Cu(TMPA)]$^+$	49$^{(44)}$/4	53
2	cyclohexane	[Cu((*R,R*)-BPBP)]$^+$	50$^{(37)}$/6	56
3	cyclohexane	[Fe((*R,R*)-BPBP)]$^{2+}$	37$^{(37)}$/1	38
4	cyclohexane	[Fe((*R,R*)-BPBP)]$^{2+}$[b]	6$^{(0)}$/31	37
5	cyclopentane	[Cu(TMPA)]$^+$	32$^{(28)}$/7	39
6	cyclopentane	[Cu((*R,R*)-BPBP)]$^+$	29$^{(24)}$/7	36
7	cycloheptane	[Cu(TMPA)]$^+$	36$^{(28)}$/6	42
8	cycloheptane	[Cu((*R,R*)-BPBP)]$^+$	39$^{(31)}$/8	47
9	cyclooctane	[Cu(TMPA)]$^+$	43$^{(37)}$/4	47
10	cyclooctane	[Cu((*R,R*)-BPBP)]$^+$	40$^{(36)}$/3	43
11	*n*-hexane	[Cu(TMPA)]$^+$	2.1$^{(1.9)}$/0.4 (C1) 11.1$^{(9.5)}$/2.4 (C2) 13.1$^{(10.6)}$/3.3 (C3)	32
12	*n*-hexane	[Cu((*R,R*)-BPBP)]$^+$	2.6$^{(2.1)}$/0.3 (C1) 10.9$^{(8.3)}$/1.2 (C2) 11.8$^{(9.0)}$/1.5 (C3)	28

[a] Reaction conditions: alkane (0.33 M), Cu/L (3.3 mM, 1 mol%), H_2O_2 (3.3 M, 10 equiv), CH_3CN (1.5 mL), room temperature, 6 h. [b] Acetic acid was used as a cocatalyst (see Ref. [15] and the Supporting Information).

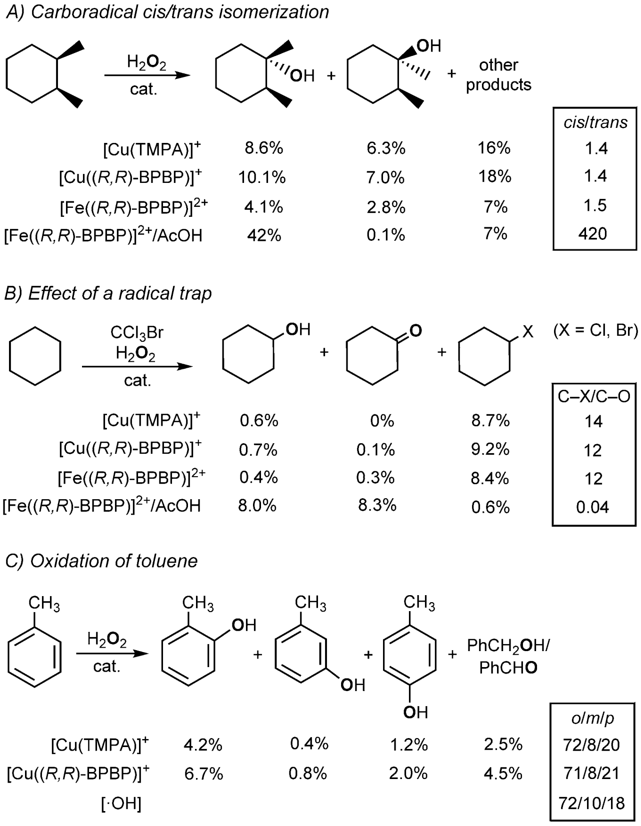
treatment of the crude reaction mixture with excess PPh$_3$ prior to GC analysis led to the observation of cyclohexanol as the main product, indicative of the presence of **P1** in solution (see the Supporting Information). A series of tetra-, tri-, bi-, and monodentate ligands were tested, and the Cu^I/TMPA (tris(2-pyridylmethyl)amine) and Cu^I/(*R,R*)-BPBP ((2*R*,2′*R*)-1,1′-bis(2-pyridylmethyl)-2,2′-bipyrrolidine) systems gave the best catalytic performance (51–56% yield).

Under these reaction conditions, simple ligands, such as bpy and 1,10-phenanthroline (1,10-Phen), were also found to lead to remarkable yields (up to 50%). Other similar scaffolds, such as 2,2′:6′,2′′-terpyridine (Tpy), led to yields lower than those observed with Cu^I in the absence of a ligand (the catalytic performance of other ligand systems is included in the Supporting Information). Strikingly, the ligand used by Pombeiro and co-workers[11a] (H$_3$tea: triethanolamine) was found to be inactive under our reaction conditions, thus indicating that the Cu cluster assembly is required for the peroxidation.

In a seminal report, White and co-workers reported that a [Fe^{II}((*S,S*)-BPBP)]$^{2+}$ complex was able to oxidize cyclohexane to cyclohexanone in high yield (90%), although a high catalyst loading (15 mol%) and acetic acid (1.5 equiv) were required.[14] Surprisingly, under the peroxidative conditions described herein, the Cu catalysts were found to give the oxidation products in higher yields than the Fe analogues. Cyclohexanol, derived from cyclohexyl hydroperoxide, was the major product, whereas the ketone was obtained as the major product in the presence of acetic acid (Fe^{II}/(*R,R*)-BPBP)/AcOH in Figure 1 and Table 1).[15] Another advantage of our approach is that the catalysts can be generated in situ during the reaction, and no isolation of the Cu^I complexes before their use is required. Similar yields were observed when the LCu^I complexes were isolated (Figure 1B) and used as catalysts (see the Supporting Information).

Other alkanes were also oxidized under the LCu/H_2O_2 conditions described herein (Table 1). Cyclopentane, cycloheptane, and cyclooctane were oxidized to the corresponding secondary alcohols and ketones in remarkable yields (36–47%) with good selectivity, without the formation of overoxidized products. The linear substrate *n*-hexane was also oxidized to the corresponding C–OH and C=O products (20–30% yield), with preferential activation of internal positions over the terminal C−H bonds (C1/C2/C3 1:5:5). To the best of our knowledge, the yields observed for these systems have no precedent in copper-catalyzed oxidation reactions of non-activated C−H bonds.[5a]

As described above, alkyl hydroperoxides are the major products under our reaction conditions. This outcome is indicative of the involvement of C-centered- and O-centered-radical formation.[16] To obtain further evidence of radical formation, we carried out the oxidation of *cis*-1,2-dimethylcyclohexane (Scheme 2a). In general, if C−H oxidation at a tertiary C center by a high-valent metal–oxo species occurs through hydrogen-atom abstraction and fast OH rebound, retention of the configuration at that center is observed with respect to the C−C bonds.[17] Under our reaction conditions, we observed a mixture of *cis*/*trans* products derived from scrambling of one of the stereocenters, thus confirming the formation and diffusion of C-centered radicals. Surprisingly, the analogue $[Fe^{II}((R,R)\text{-BPBP})]^{2+}$ also led to radical formation, which was avoided when acetic acid was used as a cocatalyst.[18] The formation of radical species in our systems was also confirmed by adding radical traps under oxidative conditions (Scheme 2b). The addition of CCl_3Br to the LCu/H_2O_2/C_6H_{12} mixture led to the formation of cyclohexyl bromide and cyclohexyl chloride as the main products (C−X/C−O ratio: 12–14), which are indicative of the generation of C-centered radicals (e.g. cyclohexyl radical) during the course of the reaction. Moreover, a substantial decrease in the reaction yield was observed (< 30%) in the presence of CCl_3Br, thus suggesting the formation of O-centered radicals during catalytic turnover.[19] Further proof of the formation of O-centered radicals was obtained when toluene was oxidized under our reaction conditions (Scheme 2c). The distribution of the phenolic products obtained (*o*-/*m*-/*p*-cresol) was very similar to the mixture obtained in a reaction between hydroxyl radical and toluene.[20]



Scheme 2. Mechanistic studies on the oxidation of different C−H substrates by the LCu/H_2O_2 system.

Kinetic analysis of the peroxidation reaction catalyzed by the Cu/TMPA system was also carried out (Figure 2A, top). The initial rates of cyclohexyl hydroperoxide (**P1**) production were determined from time profiles under various conditions (see the Supporting Information). The initial rate of **P1** formation was found to be proportional to the initial concentration of both H_2O_2 and the Cu complex. On the other hand, the reaction rate did not depend on the initial cyclohexane concentration. These results, combined with the mechanistic data (Scheme 2), point towards the peroxidation mechanism depicted in Figure 2B. The resting state of the catalyst, LCu^{II}, is generated by oxidation of the initial LCu^{I} complex (see the Supporting Information).[21] LCu^{II} reacts with H_2O_2 to generate LCu^{III}–OH and a hydroxyl radical in

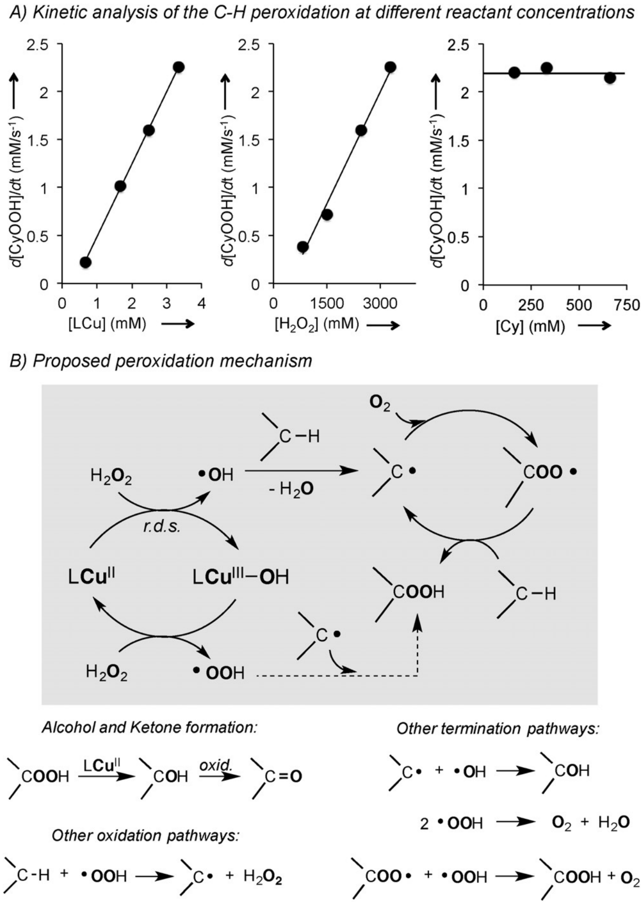


Figure 2. A) Kinetic analysis of cyclohexane oxidation promoted by the $[Cu(TMPA)]^+/H_2O_2$ system at different initial concentrations of the catalyst, oxidant, and substrate (see the Supporting Information). B) Proposed reaction mechanism for the peroxidation of alkanes by the Cu catalysts.

a Fenton-like fashion. This step is the rate-determining step, as confirmed by the kinetic analysis described above. The $^{\bullet}OH$ species initiates a radical chain mechanism by reacting with the alkane to generate a C-centered radical species. The LCu^{II} state can be regenerated when the LCu^{III}–OH complex is reduced by H_2O_2, with the generation of a $^{\bullet}OOH$ radical. A similar mechanism was recently proposed for the oxidation of benzene to phenol with the catalyst $[Cu^{II}(TMPA)]^{2+}$ in H_2O_2/acetone mixtures.[22]

The cyclohexyl hydroperoxide product can be generated by termination of the radical chain ($R^{\bullet}+{}^{\bullet}OOH$) or by hydrogen abstraction of an alkane by the $ROO^{\bullet}$ intermediate, which can be generated by a reaction between the C-centered radical and the O_2 present in solution. When the reaction was carried out under Ar, a significant decrease in the reaction yield was observed (34 versus 55 %).[21] The selectivity of the present system towards the formation of the cyclohexyl hydroperoxide is quite remarkable. We envision that this selectivity is due to the ability of the Cu^{II} complexes to discriminate between H_2O_2 (in excess) and the cyclohexyl hydroperoxide product, thus avoiding the formation of cyclohexanol and cyclohexanone and their overoxidation products.

In the chemical industry, cyclohexane is oxidized to cyclohexanone with a homogeneous Co^{III} catalyst under harsh conditions (150 °C, 12 atm O_2) with low conversion (4 %).[2b] The copper catalysts described herein constitute a first step in the development of cheap, environmentally sustainable, and efficient synthetic methodologies that could eventually replace traditional oxidation processes.

Experimental Section

See the Supporting Information for experimental details. CCDC 1495023 and 1495024 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgements

This research was supported by The Robert A. Welch Foundation (Grant N-1900).

Keywords: alkanes · bioinorganic chemistry · copper · homogeneous catalysis · oxidation

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 12873–12876
Angew. Chem. **2016**, *128*, 13065–13068

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Received: July 26, 2016