

Advances in Organometallic Chemistry and Catalysis

The Silver/Gold Jubilee
International Conference on
Organometallic Chemistry
Celebratory Book

Edited by
Armando J. L. Pombeiro



WILEY

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CHEMISTRY AND CATALYSIS**

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PREFACE

1.1 ORGANOMETALLIC CHEMISTRY, THE SCIENCE AND APPLICATIONS

Organometallic chemistry concerns the compounds with *carbon–metal bonds*, but, in a *broader sense*, deals with (i) transformations of organic compounds with the assistance of metals or (ii) even organometallic-type compounds that bear a metalloid or a nonmetal instead of a metal. This wide meaning is followed in this book.

Although Prussian blue, nowadays known to concern cyano-iron complexes, is present in colored pigments that had already been used in the antiquity, the first organometallic synthesis appears to have been achieved (in 1760) at a military pharmacy in Paris by Cadet, who, when studying inks based on cobalt salts (containing As), obtained a malodorous fuming liquid containing cacodyl oxide $[(\text{Me}_2\text{As})_2\text{O}]$ and tetramethyldiarsine, compounds of organo-arsenium that were identified only later. However, the Zeise's salt $\text{Na}[\text{PtCl}_3(\eta^2\text{-C}_2\text{H}_4)]$, a π -complex of ethylene and Pt, prepared in 1827, is usually considered to be the first organometallic compound to be reported. The chemistry of the metal–carbon bond compounds has developed in a systematic manner since the middle of the nineteenth century, with works, for example, by Bunsen (who prepared and tasted (!) $[\text{Me}_2\text{AsCN}]$, in 1840) and his disciple Frankland (since 1849) who appears to have introduced the term “*organometallic*.” During the same century, a diversity of organometallic compounds were prepared by him and/or others (namely, Löwig, Schweizer, Hallwachs, Schafarik, Friedel, Crafts, Wanklyn, Schützenberger, Mond, and Berthelot), including organo-Zn, organo-Hg, organo-B, organo-Pb, organo-Al, organo-Si compounds and the first metal-carbonyls. The end of that century and beginning of the next one (the twentieth century) witnessed the development of organomagnesium compounds (by Barbier and his disciple Grignard) and the emergence of catalysis, in which organometallic chemistry played a fundamental role (e.g., Sabatier, Fischer, Tropsch, Roelen).

The *growth* of organometallic chemistry during the twentieth century was impressive (it is not possible in this short preface even to list the main achievements) and it became one of the fields of chemistry that has expanded mostly in the past decades, as attested, for example, by the good number of relevant international *journals*, huge number of *papers*, and prominent international *conferences* dealing with it, as well as by the many *Nobel prizes* awarded to scientists on account of their contributions within that overall field, namely, Grignard and Sabatier (1912); Ziegler and Natta (1963); Crowfoot-Hodgkin (1964); Fisher and Wilkinson (1973); Lipscomb (1976); Brown and Wittig (1979); Hoffmann and Fukui (1981); Taube (1983); Knowles, Noyori, and Sharpless (2001); Chauvin, Grubbs, and Schrock (2005); Heck, Negishi, and Suzuki (2010) (adding up already to nine prize winners in the current century!).

The *influence of organometallic chemistry* on the development of other fields of chemistry and other sciences has been growing in such an *interdisciplinary* way that nowadays organometallic chemistry interfaces with *most of branches of chemistry* and also with *materials science, biology, pharmacology, etc.*; so, naturally it should be viewed in a much broader sense than the strict requirement of M–C bonds, as mentioned above.

Catalysis conceivably provides the current highest contribution of chemistry toward *sustainable development*, and *organometallic catalysis*, in particular, promotes the use of carbon compounds and feedstocks for synthetic applications under milder conditions (*energy saving*) and superior selectivities (*waste reduction*), with resulting *cost savings*.

Development of systems operating under *environmentally benign conditions* toward the establishment of *sustainable energy* processes (e.g., artificial photosynthesis for conversion of carbon dioxide, dye-sensitized solar cells) is a scientific challenge that has been pursued by organometallic chemistry and catalysis.

Therefore, *Organometallic Chemistry* and *Catalysis* have grown in synergy and often indissoluble links can be disclosed. Organometallic compounds, under different perspectives, are involved in very important *applications*, such as

- *Activation* of small molecules with industrial, environmental, biological, or pharmacological significance, for example, alkanes (including natural gas and oil), olefins, carbon monoxide and carbon dioxide, and dihydrogen.

Hence, the *petrochemical industry* and *carbon dioxide fixation* (e.g., to prevent global warming) illustrate relevant fields of application of organometallic chemistry.

- *Synthesis* of important added value organic compounds, in both *commodity and fine chemistries* (large- and low-scale productions, respectively), namely, via catalytic processes where reactions are accelerated by organometallic catalysts. Examples of the former are polymers, carboxylic acids, aldehydes, alcohols, and ketones. Examples of the latter are compounds with biological/pharmacological activity.
- *New carbon materials* with a diversity of potential applications.

Apart from being widely used in industry, organometallic chemistry is also connected to *biology*, as there are enzymes that present organometallic active centers and catalyze organometallic reactions, which constitute inspiring biological motifs for development. Accordingly, *bioorganometallic chemistry* is a promising field with *pharmacological and biomedical applications*.

1.2 THIS BOOK AND THE INTERNATIONAL CONFERENCES ON ORGANOMETALLIC CHEMISTRY (ICOMC)

An important indicator of the strength and health of organometallic chemistry is the organization of a large number of important international conferences dealing with this science, the most representative ones being the prestigious series of *International Conferences on Organometallic Chemistry (ICOMC)*, which was launched in 1963 when the first conference was held in Cincinnati. This *book* follows the *XXV ICOMC*, which was held in Lisbon (2012) and gathered over 1200 delegates (circa 1100 being foreigners) from 54 countries, in spite of the world economic crisis and the competition with other relevant congresses in chemistry in the same year. It intends to celebrate the *Silver edition* (twenty-fifth edition) and the *Gold year* (fiftieth year since the first conference) of the series, constituting the major *Silver/Gold Jubilee celebratory* initiative of the ICOMCs.

The coinage of a *medal* (Fig. 1) on the occasion of the XXV ICOMC was another celebratory initiative, honoring the places where all these conferences have been held, and relevant landmarks in the history of this science: the ferrocene molecule (the conference logo) and the Chatt–Dewar–Duncanson model of ethylene coordination.

Further details on the XXV ICOMC, including the distributions of participants from countries and particulars of their contributions by scientific areas, as well as a review on representative works presented therein and concerning the platinum group metals are found in [1].



Figure 1 ICOMC Silver/Gold Jubilee medal.

Although the invited authors of this book have been Speakers at the XXV ICOMC, the book is *neither the Proceedings of the Conference nor a conventional book* with comprehensive and long chapters, but instead is *aimed* (i) to present *recent advances and hot topics of current interest* (with the concepts behind them, illustrative relevant cases, and their prospects) , (ii) to highlight the *synergy between Organometallic Chemistry and Catalysis*, and (iii) to show the versatility, richness, and potential of *Organometallic Chemistry (in the broad sense) and Catalysis*, including their relations with other sciences, that is, their boosting *interdisciplinarity*.

It provides an updated account of the scientific and applied interest and prospect of major fields of chemistry with high relevance in modern perspectives of science.

It can also be an inspiration for research topics for PhD and MSc theses, projects, and research lines. It is addressed to both expert and nonexpert readers, allowing the latter to get the sensitivity and encouragement for the field.

The main topics of the book follow the general *areas* of the XXV ICOMC itself. *Catalysis* was the most represented area (circa 22% of the total contributions), followed by *Fundamental Organometallic Chemistry* (circa 13%). Other areas (which, nevertheless can include the ones already mentioned or significantly overlap with them) can be ordered as follows: *Activation of Small Molecules, C–H and C–C Bond Activation and Functionalization, Metal-Mediated Synthesis* (each with circa 7%); *Organometallic and Green Chemistry, Bioorganometallic and Bioinorganic Chemistry, Organometallics-Related Chemistry* (each with circa 6%); *Organometallics for Materials* (circa 5%); *Polynuclear and Supramolecular Assemblies, Polymers, and Reaction Mechanisms* (circa 4% each); *Theoretical and Physical Methods, Electrochemistry*, and others.

These areas are assembled in the following main *sections of the Book*:

- Activation and Functionalization of Carbon Single Bonds and of Small Molecules;
- Organometallic Synthesis and Catalysis;
- Organometallic Polymerization Catalysis;
- Organometallic Polymers and Materials;
- Organometallic Chemistry and Sustainable Energy;
- Bioorganometallic Chemistry;
- Organometallic Electrochemistry.

Catalysis is the driving force within most of these sections (areas), thus being the most represented overall area of the book, also in accord with what turned out to be the main interest of the conference attendees, reflecting the current organometallic scientific community in general. However, the other areas are not neglected and some of them, with particularly promising prospects, are even emphasized herein relative to their quota at the conference.

The book ends with a postscript providing a brief historical summary of the ICOMCs.

As a recognition of the innovative character of Organometallic Chemistry and Catalysis, providing novel routes to the discoveries of science, the cover picture of this book is inspired on the *Monument of the Discoveries*, at the mouth of the river Tejo (Tagus), Belém, Lisboa, which, with its rising boat prow shape, celebrates the (Portuguese) discoveries of new lands and sea routes during the fifteenth and sixteenth centuries.

As editor of this book and Chairman of the XXV ICOMC, I acknowledge the authors of the various chapters for their valuable contributions (an asterisk has been assigned to the correspondence authors' names who have requested so), and the members of the International Advisory Board (IAB) of the ICOMC for having accepted my proposals for this and the other celebratory initiatives. The support of the Portuguese Electrochemical Society is also acknowledged. Special thanks are due to Dr. Fatima Guedes da Silva and Dr. Manas Sutradhar for their inestimable and generous editorial assistance. The support of the Portuguese Electrochemical Society is also acknowledged.

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PART I

ACTIVATION AND FUNCTIONALIZATION OF CARBON SINGLE BONDS AND OF SMALL MOLECULES

ORGANOMETALLIC COMPLEXES AS CATALYSTS IN OXIDATION OF C–H COMPOUNDS

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1.1 INTRODUCTION

Organometallic (i.e., containing π or σ metal–carbon bonds) derivatives of transition metals are known as *excellent catalysts* in reactions that do not involve the insertion of oxygen atoms [1]. They are used in (selected examples of recent publications are given) hydrogen/deuterium (H/D) exchange [2a], dehydrogenation [2b–e], homogeneous syngas conversion [2f], hydrosilylation [2g], carbonylation [2h], and homogeneous water gas shift reaction [2i]. In other recent works, complex [(Cp*)Ru(IPr*)Cl], where Cp* = η^5 -C₅Me₅ and IPr* = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene, was used as a catalyst in the racemization of chiral alcohols [2j], neutral η^6 -arene ruthenium complexes with monodentate P-donor ligands found to catalyze the transfer hydrogenation reaction [2k].

Organometallic catalysts were employed in oxidation reactions of some organic compounds. Thus, complex [CpMo(CO)₃CF₃] is a precatalyst for olefin epoxidation [3a], heterodinuclear ruthenium–iron complexes showed high activity for the catalytic oxidation of secondary alcohols with *tert*-butyl hydroperoxide to give ketones in aqueous media [3b]. In contrast, organometallic complexes were very rarely used as (pre)catalysts in oxygenation reactions of aromatic and saturated hydrocarbons [4a–e] (the latter can be called *noble gases of organic chemistry* because of their known inertness).

In various C–H oxygenation reactions, organometallic complexes can play the role of precatalyst. Compounds bearing carbon–metal bonds can also be some of intermediate compounds in the catalytic cycles. In this chapter, we discuss reactions in which an organometallic complex catalyzes the insertion of oxygen atoms into C–H bonds of hydrocarbons or other organic compounds. The focus will be made on the author's own works.

1.2 OXYGENATION REACTIONS WITH OXIDANTS OTHER THAN PEROXIDES

The first example of a metal-catalyzed oxygen atom insertion into the C–H bond was the reaction found by Shilov and Shteinman and their coworkers in 1972 (for reviews, see References 1h and 5). These authors demonstrated that Pt^{II}Cl₄²⁻ ion could catalyze H/D exchange in methane in a D₂O/CD₃COOD solution and, if Pt^{IV}Cl₆²⁻ is added, the latter oxidizes methane to methanol (Shilov chemistry). The catalytic cycle in which σ -methyl complexes of platinum(II) and platinum(IV) are involved is shown in Fig. 1.1.

Later, Periana and coworkers proposed (2,2'-bipyrimidyl)platinum(II)dichloride as a catalyst ("Periana system"; see a recent review [4d]). Fuming sulfuric acid is the oxidant in this case. A simplified scheme of the catalytic cycle is shown in Fig. 1.2. It can be seen that some intermediates contain σ -methyl-platinum bonds.

Complexes containing the fragment Cp*Ir (Cp* is pentamethylcyclopentadienyl) are active precatalysts in the C–H oxidation of *cis*-decalin and cyclooctane. Ceric ammonium nitrate was a sacrificial oxidant and water was the oxygen source

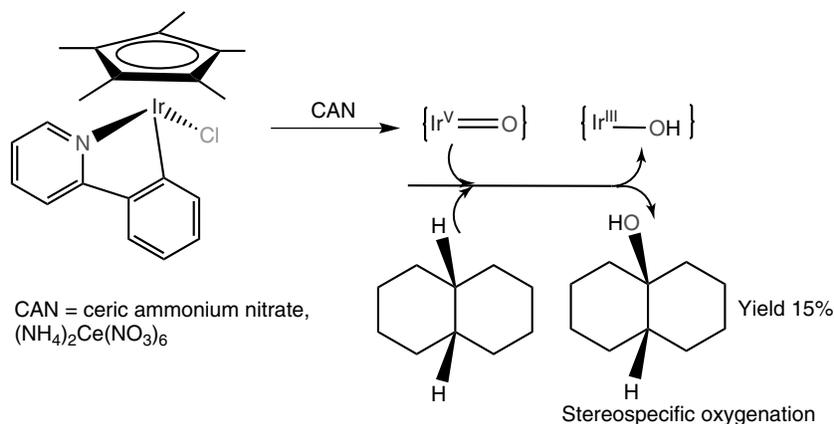


Figure 1.3 Stereospecific oxygenation of *cis*-decalin catalyzed by the Ir organometallic derivative [6].

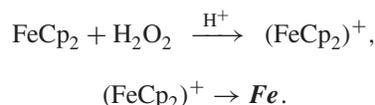
Indeed, organometallic precatalysts can be transformed during an induction period into catalytically active species that do not contain metal–carbon bonds. For example, molybdenum [7a] and tungsten [7b] carbonyls catalyze aerobic photooxygenation of cyclohexane to cyclohexyl hydroperoxide (primary product) and cyclohexanol and cyclohexanone (Fig. 1.4). The proposed mechanism is shown in Fig. 1.5. It includes the formation during the induction period of an oxo derivative. Complexes $\text{CpFe}(\pi\text{-PhH})\text{BF}_4$ and $(\pi\text{-durene})_2\text{Fe}(\text{BF}_4)_2$ also catalyzed the aerobic alkane photooxygenation [7c]. The mechanism has not been studied.

1.3 OXYGENATION OF C–H BONDS WITH PEROXIDES

In the course of our systematic studies of hydrocarbon oxidation with peroxides, we have found a few organometallic catalysts and systems based on organometallic compounds. In some cases, these systems turned out to be extremely efficient, much more efficient than systems containing “simple” salts of transition metals.

Recently, we have discovered [8], for the first time, that ferrocene (catalyst **1.1**) is an efficient (pre)catalyst for several types of oxidative transformations, namely, the oxidation of alkanes and benzene by H_2O_2 or *tert*-butyl hydroperoxide. The oxidation of gaseous and liquid alkanes to alkyl hydroperoxides by H_2O_2 proceeds in MeCN at 50 °C. An obligatory cocatalyst is pyrazine-2-carboxylic acid (PCA, or Hpca, where H is a proton and pca is the anion of PCA). In the cyclohexane oxidation, the yield and TON after 1.5 h attained 32% and 1200, respectively. In the ethane oxidation, TON reached 970. Maximum yield (58% based on the alkane) was obtained for the *n*-butane oxidation after 4 h.

The simplest kinetic scheme of the alkane oxygenation based on the kinetic data was proposed. In the first stage, ferrocene FeCp_2 is oxidized to ferricenium cation $(\text{FeCp}_2)^+$, which is in turn transformed into species *Fe* that is a fragment containing one iron ion.



These are the fast stages of the generation from FeCp_2 and H_2O_2 the main species, which is active in the catalytic process. Produced fragment *Fe* interacts with a PCA molecule to form the complex *Fe*(PCA):



Here (PCA) is a PCA fragment (possibly pyrazinecarboxylate, pca). The formed complex can react with the second PCA molecule yielding in this case an adduct containing two PCA fragments per one Fe ion:



Two adducts *Fe*(PCA) can dimerize to afford the dinuclear complex $\text{Fe}_2(\text{PCA})_2$:



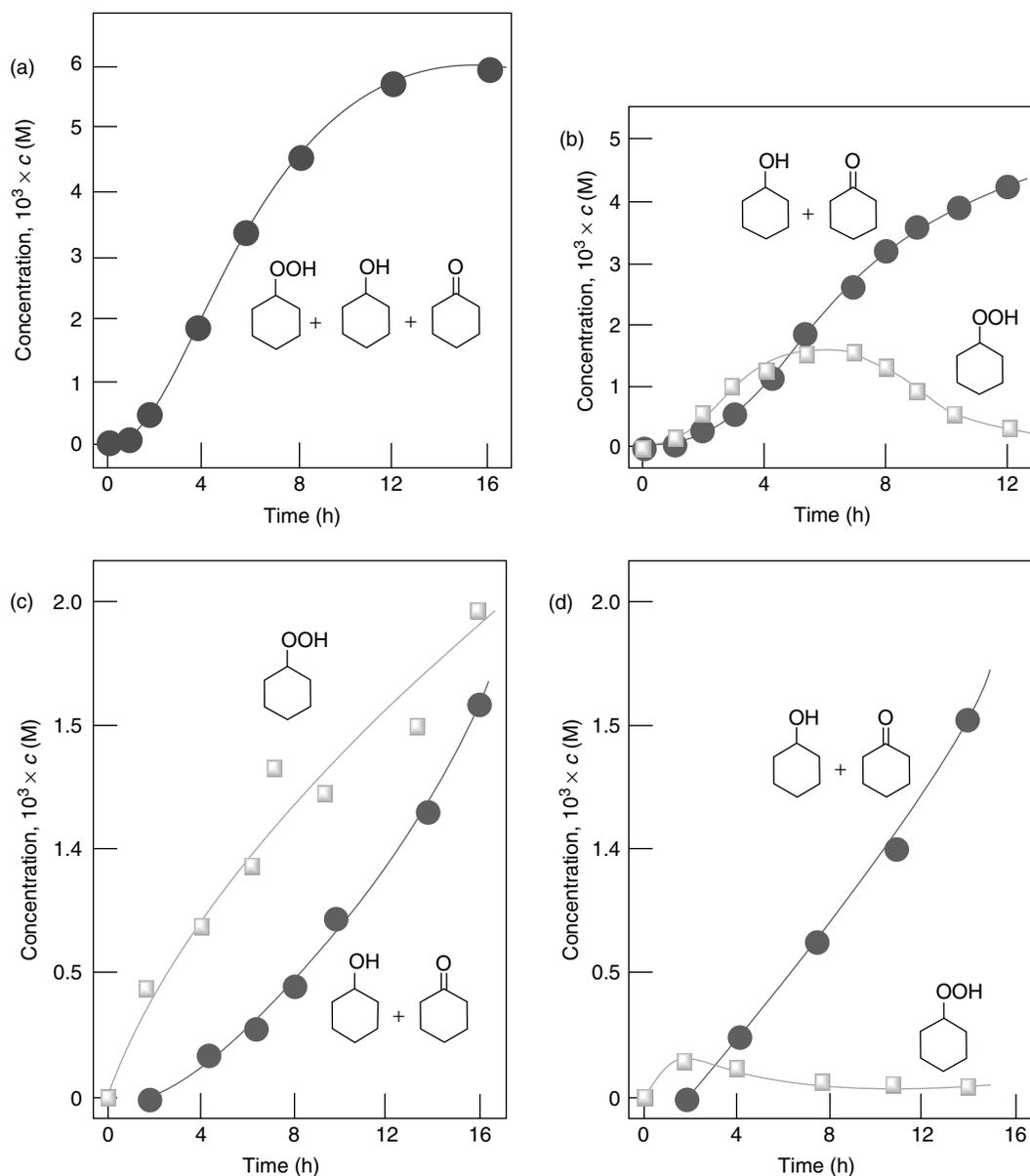


Figure 1.4 Oxidation of cyclohexane (CyH, 0.46 M) to cyclohexyl hydroperoxide, cyclohexanol, and cyclohexanone with air under irradiation with full light of high pressure Hg arc (1000 W) in MeCN (15 °C). Photocatalysts (5×10^{-4} M) : $M(CO)_6$ (where M = Mo, graph a [7a] and W, graph b [7b]) and complexes $CpFe(\pi-PhH)BF_4$ (graph c) and $(\pi-durene)_2Fe(BF_4)_2$ (graph d) [7c] are shown.

Complex $Fe_2(PCA)_2$ is a catalytically active species that produces hydroxyl radicals from H_2O_2 :



Hydroxyl radicals react in parallel routes with solvent (acetonitrile) and substrate (cyclohexane, RH):



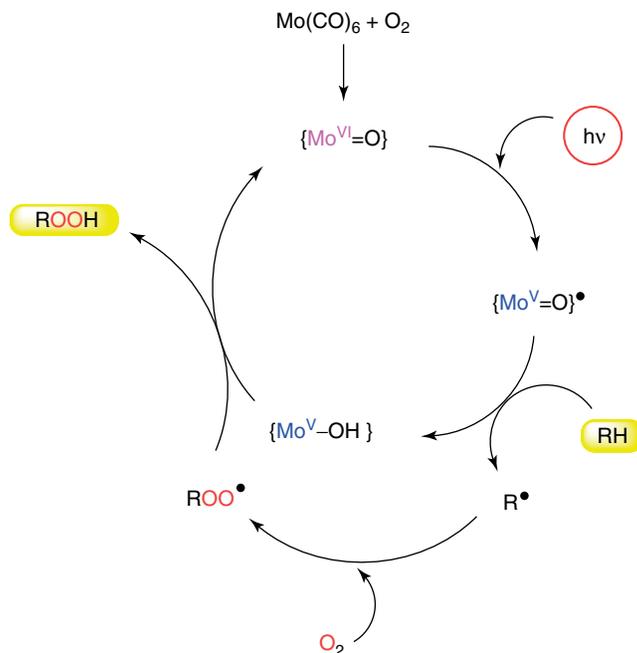


Figure 1.5 Mechanism proposed for the photooxygenation of alkanes, RH, in the presence of Mo or W carbonyls. (See insert for color representation of the figure.)

The last reaction is the rate-limiting step in the sequence of alkane transformations into cyclohexyl hydroperoxide. If we assume that the concentration of HO^\bullet is quasi-stationary and concentrations of all iron complexes are in quasi-equilibrium and take into account conditions $[\text{Fe}(\text{PCA})] \ll [\text{FeCp}_2]_0$ and $[\text{Fe}_2(\text{PCA})_2] \ll [\text{FeCp}_2]_0$, we obtain the equation for the initial reaction rate as follows:

$$W_0 = \frac{k_4[\text{Fe}_2(\text{PCA})_2][\text{H}_2\text{O}_2]_0}{1 + k_5[\text{MeCN}]/k_6[\text{RH}]_0},$$

where

$$[\text{Fe}_2(\text{PCA})_2] = K_3[\text{Fe}(\text{PCA})]^2,$$

and

$$[\text{Fe}(\text{PCA})] = \frac{K_1[\text{FeCp}_2]_0[\text{PCA}]_0}{1 + K_1K_2[\text{PCA}]_0^2}.$$

We can rewrite the equation for the initial reaction rate in the following form:

$$W_0 = \frac{\alpha[\text{PCA}]_0^2}{(1 + \beta[\text{PCA}]_0^2)^2},$$

where

$$\alpha = \frac{k_4[\text{H}_2\text{O}_2]_0(K_1[\text{FeCp}_2]_0)^2}{1 + k_5[\text{MeCN}]/k_6[\text{RH}]_0},$$

and

$$\beta = K_1K_2.$$

The following values $\alpha = 30 \text{ M}^{-1} \text{ s}^{-1}$ and $\beta = 1.1 \times 10^5 \text{ M}^{-2}$ have been calculated for the conditions of our experiments. Using these values for parameters α and β , the initial reaction rates (presented by a dotted curve) have been calculated at different concentrations of PCA under conditions described in the caption of Fig. 1.6b.

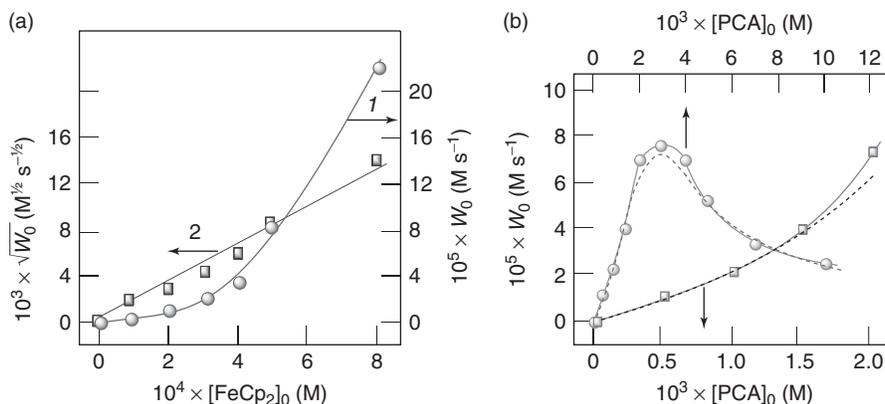


Figure 1.6 (a) Dependence of the initial rate W_0 of oxygenate accumulation in the cyclohexane oxidation with H_2O_2 catalyzed by ferrocene **1.1** in MeCN on the initial concentration of ferrocene (curve 1). Conditions: $[\text{PCA}]_0 = 3 \times 10^{-3} \text{ M}$, $[\text{H}_2\text{O}_2]_0 = 0.32 \text{ M}$, $[\text{cyclohexane}]_0 = 0.37 \text{ M}$, 50°C . Curve 2: linearization of curve 1 in coordinates $[\text{FeCp}_2]_0 - W_0^{1/2}$. (b) Dependence of the initial rate W_0 of oxygenate accumulation in the cyclohexane oxidation with H_2O_2 catalyzed by **1.1** in MeCN on the initial concentration of PCA (in the intervals $0 - 10 \times 10^{-3} \text{ M}$ and $0 - 2 \times 10^{-3} \text{ M}$). Conditions: $[\text{FeCp}_2]_0 = 5.0 \times 10^{-4} \text{ M}$, $[\text{H}_2\text{O}_2]_0 = 0.32 \text{ M}$, $[\text{cyclohexane}]_0 = 0.37 \text{ M}$, 50°C . Dotted curves present the simulated dependences.

tert-Butyl hydroperoxide (0.58 M; 70% aqueous) oxidizes cyclohexane (0.92 M) in MeCN at 50°C in the presence of **1.1** ($1 \times 10^{-3} \text{ M}$) and PCA ($25 \times 10^{-3} \text{ M}$), affording (after reduction with PPh_3) cyclohexanol (0.02 M) and cyclohexanone (0.001 M) after 4.5 h. Heating a solution of benzene (0.58 M) with H_2O_2 (1.28 M) in MeCN at 50°C in the presence of **1.1** ($5 \times 10^{-4} \text{ M}$) and PCA ($1 \times 10^{-2} \text{ M}$) gave phenol (0.038 M after 1 h). In the presence of 2,2'-bipyridine ($4 \times 10^{-3} \text{ M}$) instead of PCA, **1.1** ($5 \times 10^{-4} \text{ M}$) catalyzes the oxygenation with H_2O_2 (1.28 M) of benzene (0.58 M) to phenol (0.05 M after 3 h) with a long induction period.

We also found recently [8] the first example of alkane hydrocarboxylation in aqueous acetonitrile with the $\text{CO}/\text{S}_2\text{O}_8^{2-}/\text{H}_2\text{O}$ system catalyzed by an iron complex, that is, ferrocene (Table 1.1). For example, the reaction of propane (1 atm) with CO (10 atm) at 60°C during 4 h gave isomeric butyric acids in 60% total yield.

Another metallocene, namely, decamethylsilmocene, $(\text{Me}_5\text{C}_5)_2\text{Os}$ (catalyst **1.2**), turned out to be a good precatalyst in a very efficient oxidation of alkanes with hydrogen peroxide in acetonitrile at $20 - 60^\circ\text{C}$ [9]. The reaction proceeds with a substantial lag period that can be reduced by the addition of pyridine in a small concentration. Alkanes, RH, are oxidized primarily to the corresponding alkyl hydroperoxides, ROOH. TONs attain 51,000 in the case of cyclohexane (maximum turnover frequency was 6000 h^{-1}) and 3600 in the case of ethane. The oxidation of benzene and styrene afforded phenol and benzaldehyde, respectively. A kinetic study of cyclohexane oxidation catalyzed by **1.2** and selectivity parameters (measured in the oxidation of *n*-heptane, methylcyclohexane, isooctane, *cis*-dimethylcyclohexane, and *trans*-dimethylcyclohexane) indicated that the oxidation of saturated, olefinic, and aromatic hydrocarbons proceeds with the participation of hydroxyl radicals.

We discovered [10] that triosmium dodecacarbonyl (compound **1.3**, Fig. 1.7) catalyzes a very efficient oxidation of alkanes by H_2O_2 in MeCN to afford alkyl hydroperoxides (primary products) as well as alcohols and ketones (aldehydes) at 60°C if pyridine is added in a low concentration. TONs attained 60,000 (Fig. 1.8a) and turnover frequencies were up to $24,000 \text{ h}^{-1}$. A plateau in the dependence of W_0 on initial concentration of cyclooctane, [RH] (Fig. 1.8b), indicates that there is a competition between RH and another component of the reaction mixture for a transient oxidizing species. Indeed, at high concentration of the hydrocarbon, all oxidizing species are accepted by RH and the maximum possible oxidation rate is attained. This concurrence can be described by the following kinetic scheme:



TABLE 1.1 Hydrocarboxylation of Alkanes by the 1.1/CO/K₂S₂O₈ System^a

Alkane ^b , atm; mmol	CO, atm	Products	Yield, %	Total Yield, %
Cyclohexane ^c				
1.0	20	<i>c</i> -C ₆ H ₁₁ COOH	18.3	19.4
		<i>c</i> -C ₆ H ₁₁ OH	0.8	
		<i>c</i> -C ₆ H ₁₀ O	0.3	
<i>n</i> -Heptane ^d				
1.0	20	Me(CH ₂) ₆ COOH	0.3	9.2
		MeCH(COOH)(CH ₂) ₄ Me	3.6	
		EtCH(COOH)(CH ₂) ₃ Me	3.5	
		Me(CH ₂) ₂ CH(COOH)(CH ₂) ₂ Me	1.8	
<i>n</i> -Hexane ^d				
1.0	20	Me(CH ₂) ₅ COOH	0.4	8.3
		MeCH(COOH)(CH ₂) ₃ Me	4.0	
		EtCH(COOH)(CH ₂) ₂ Me	3.9	
<i>n</i> -Pentane ^d				
1.0	20	Me(CH ₂) ₄ COOH	0.8	12.6
		MeCH(COOH)(CH ₂) ₂ Me	8.2	
		EtCH(COOH)Et	3.6	
<i>n</i> -Butane				
0.75 ^e	10	EtCH(Me)COOH	19	21
		Me(CH ₂) ₃ COOH	2	
Propane				
6	20	Me ₂ CHCOOH	17	19
		Me(CH ₂) ₂ COOH	2	
1 ^e	10	Me ₂ CHCOOH	51	60
		Me(CH ₂) ₂ COOH	9	
Ethane				
10	20	EtCOOH	9	9
1 ^e	10	EtCOOH	15	15

Adapted from Reference 8.

^aConditions. Amounts: ferrocene 1.1, 4×10^{-3} mmol; K₂S₂O₈, 1.5 mmol; MeCN, 4 ml; H₂O, 2 ml; 60 °C, 4 h. Volume of the autoclave was 13 ml. Yield is based on the alkane.

^bAmounts as pressure for gaseous ethane, propane, and *n*-butane and as mmol for other alkanes are given.

^cAt 50 °C; CH₃CN, 3 ml; H₂O, 3 ml.

^dRegioselectivity parameters C(1):C(2):C(3):C(4) for pentane, hexane, and heptane are 1:15:14, 1:15:15, and 1:18:18:18, respectively.

^eK₂S₂O₈, 1.0 mmol.



where W_i is the rate of generation of oxidizing species X. The analysis of this scheme in a quasi-stationary approximation relative to species X leads to the following equation:

$$W_0 = \frac{d[\text{ROOH}]}{dt} = \frac{W_i}{1 + \frac{k_2[\text{py}] + k_3[\text{H}_2\text{O}_2] + k_4[\text{MeCN}]}{k_1[\text{RH}]}}$$

In accord with the last equation, we can see the linear dependence of the experimentally measured reciprocal parameter $1/W_0$ on reciprocal concentration $1/[\text{RH}]_0$ (Fig. 1.8c). The tangent of this straight line slope angle corresponds to the value

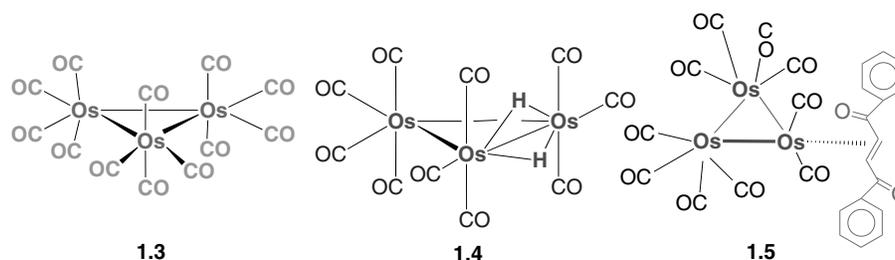


Figure 1.7 Efficient oxidation catalysts based on osmium carbonyls.

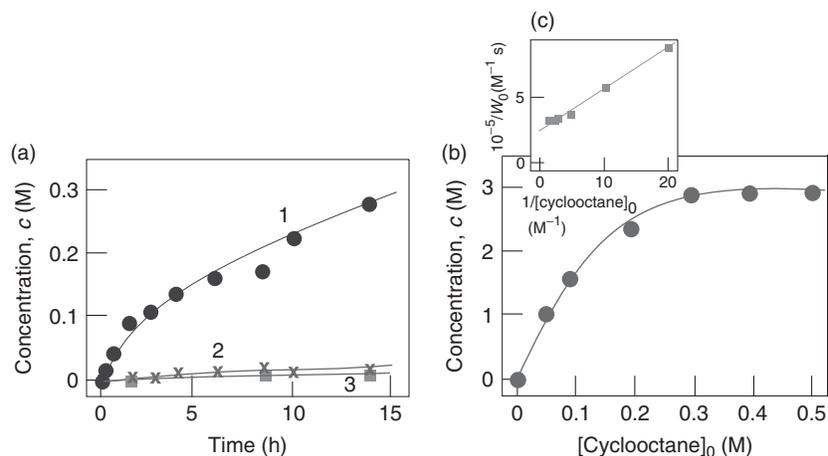


Figure 1.8 (a) Kinetic curves of accumulation of cyclooctyl hydroperoxide (curve 1), cyclooctanone (curve 2), and cyclooctanol (curve 3) in the cyclooctane (0.5 M) oxidation with H_2O_2 catalyzed by $\text{Os}_3(\text{CO})_{12}$ (**1.3**) in MeCN at 60°C . Concentrations of the three products were measured using a simple method, previously developed by us [10–12] with the reduction of samples with PPh_3 . (b) Dependence of W_0 on the initial concentration of cyclooctane ($[\mathbf{1.3}]_0 = 5 \times 10^{-5}$ M). (c) Linearization of dependence shown in (b) using coordinates $1/W_0 - 1/[\text{cyclooctane}]_0$. Adapted from Reference 10(a).

$(k_2[\text{py}] + k_3[\text{H}_2\text{O}_2] + k_4[\text{MeCN}])/k_1 W_i$. The segment that is cut off by the line on Y-axis is equal to $1/W_i$. Thus, we can calculate the following value:

$$\frac{k_2[\text{py}] + k_3[\text{H}_2\text{O}_2] + k_4[\text{MeCN}]}{k_1} = 0.14.$$

At our conditions $[\text{py}] = 0.1$ M, $[\text{H}_2\text{O}_2] = 2$ M, and $[\text{MeCN}] \approx 18$ M, we can calculate the following parameters (s^{-1}) for different data found in the literature: $k_2[\text{py}] = 2.3 \times 10^8$ or 4.5×10^8 , $k_3[\text{H}_2\text{O}_2] = (9 \pm 2.8) \times 10^7$, and $k_4[\text{MeCN}] = 6.4 \times 10^7$ or 3.9×10^8 . It follows from this estimation that the most probable competitors of cyclooctane for hydroxyl radicals are pyridine and acetonitrile. Rate constants ($\text{M}^{-1} \text{s}^{-1}$) can be calculated as follows: $k_1 = 1.6 \times 10^9$ or 3.2×10^9 in the case of pyridine and $k_1 = 4.5 \times 10^8$ or 2.8×10^9 in the case of acetonitrile. These values are typical for the reactions of hydroxyl radicals with alkanes: $k_1 = 1.2 \times 10^9$ for cyclopentane, $k_1 = 1.3 \times 10^9$ for cyclohexane, and $k_1 = 1.6 \times 10^9$ for cycloheptane in aqueous solution. It can be seen that the experimentally found competition is in good agreement with the assumption that the oxidizing species in our system is hydroxyl radical. Radical HO^\bullet attacks the hydrocarbon RH to generate alkyl radical R^\bullet , which very rapidly reacts with molecular oxygen.

Similar trinuclear carbonyl hydride cluster, $\text{Os}_3(\text{CO})_{10}(\mu\text{-H})_2$ (compound **1.4**), catalyzes the oxidation of cyclooctane to cyclooctyl hydroperoxide by hydrogen peroxide in acetonitrile solution [12]. Selectivity parameters obtained in oxidations of various linear and branched alkanes as well as kinetic features of the reaction indicated that the alkane oxidation occurs with the participation of hydroxyl radicals. A similar mechanism operates in the transformation of benzene into phenol and styrene into benzaldehyde. The system also oxidizes 1-phenylethanol to acetophenone. The kinetic study

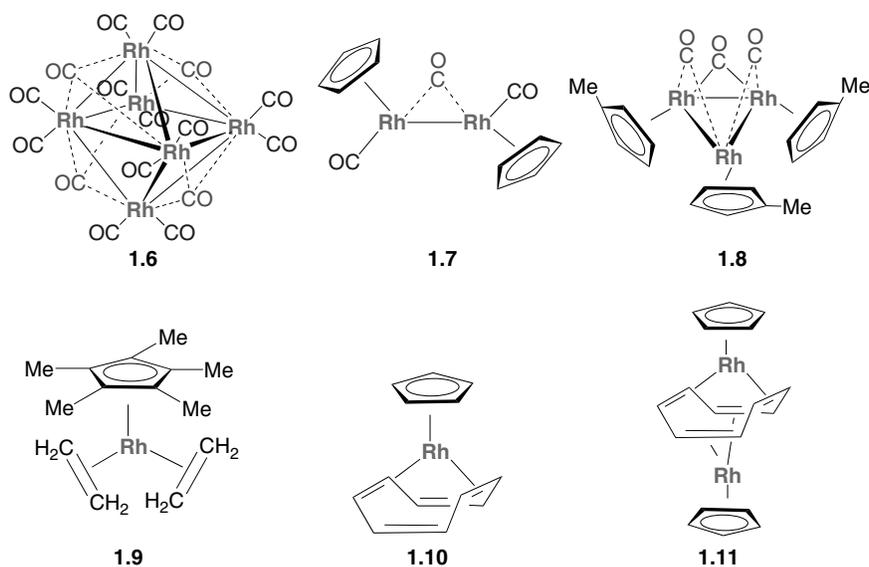


Figure 1.9 Compound **1.6** is an efficient catalyst for the benzene oxidation, compounds **1.7** and **1.8** are less efficient, and compounds **1.9**, **1.10**, and **1.11** are inactive.

led to a conclusion that the oxidation of alcohols does not involve hydroxyl radicals as the main oxidizing species and apparently proceeds with the participation of osmyl species, “Os = O.” Finally, a carbonyl osmium(0) complex with π -coordinated olefin, (2,3- η -1,4-diphenylbut-2-en-1,4-dione)undecacarbonyl triangulotriosmium (**1.5**, Fig. 1.7), catalyzes the oxygenation of alkanes (cyclohexane, cyclooctane, *n*-heptane, isooctane, etc.) with hydrogen peroxide, as well as with *tert*-butyl hydroperoxide and *meta*-chloroperoxybenzoic acid in acetonitrile solution [13]. “Simple” osmium salts (OsCl₃, Na₂OsCl₆) also catalyze (especially in the presence of pyridine or other N-bases) alkane hydroperoxidation with H₂O₂ in acetonitrile [14a] or water [14b], but these reactions are less efficient in comparison with processes catalyzed by organoosmium compounds.

Hexanuclear rhodium carbonyl cluster, Rh₆(CO)₁₆ (compound **1.6**, Fig. 1.9), catalyzes benzene hydroxylation with hydrogen peroxide in acetonitrile solution [15a]. Phenol and quinone (in less concentration) are formed with the maximum attained total yield and TON of 17% and 683, respectively. It is noteworthy that certain other rhodium carbonyl complexes, containing cyclopentadienyl ligands, Rh₂Cp₂(CO)₃ (**1.7**) and Rh₃(CpMe)₃(CO)₃ (**1.8**), are less efficient catalysts, whereas cyclopentadienyl derivatives of rhodium, which do not contain the carbonyl ligands, Rh(CpMe₅)(CH₂=CH₂)₂ (**1.9**), RhCp(cyclooctatetraene) (**1.10**) and Rh₂Cp₂(cyclooctatetraene) (**1.11**), turned out to be absolutely inactive in the benzene hydroxylation. In the presence of compound **1.6**, styrene is transformed into benzaldehyde and (in less concentration) acetophenone and 1-phenylethanol. Addition of acids is known to accelerate some metal-catalyzed oxidation reactions. In our case, when trifluoroacetic acid was added to the reaction solution catalyzed by cluster **1.6**, the initial reaction rate was approximately three times higher. It should be emphasized that no oxygenated products have been detected when alkanes were used as substrates in the **1.6**-catalyzed oxidation. Ethyl groups in ethylbenzene were also not oxygenated. It has been tentatively assumed that the interaction of cluster **1.6** with hydrogen peroxide leads to splitting Rh–Rh and Rh–CO bonds to form vacant sites that coordinate benzene molecules. Possibly, the **Rh**–CO fragment is oxidized in the initial period of the reaction to afford **Rh**–C(O)OH and **Rh**–C(O)OOH species. The catalytic cycle presented in Fig. 1.10 was proposed for the oxidation reaction. In the initial period, a rhodium complex under the action of hydrogen peroxide and water is transformed into a hydroxy derivative **A**. The interaction of species **A** with hydrogen peroxide affords a hydroperoxo derivative **B**. The latter forms a π -arene complex **C**. Species **C** can be converted into rhodadioxolane **D**, which decomposes further to produce phenol and initial catalytically active species **A**.

Cyclopentadienylbenzeneiridium(III) tetrafluoroborate [π -C₅H₅Ir(π -C₆H₆)](BF₄)₂ (complex **1.12**) was completely inactive in oxidation with hydrogen peroxide and *tert*-butyl hydroperoxide but exhibited a moderate activity in oxidation with *m*-chloroperoxybenzoic acid at room temperature [15b]. The H₂O₂–**1.12** system showed a moderate activity in the oxidation of secondary alcohols. For example, cyclohexanol was oxidized at room temperature to cyclohexanone (30% yield for 6 h) when a fourfold excess of PCA as a cocatalyst was added to the reaction solution.

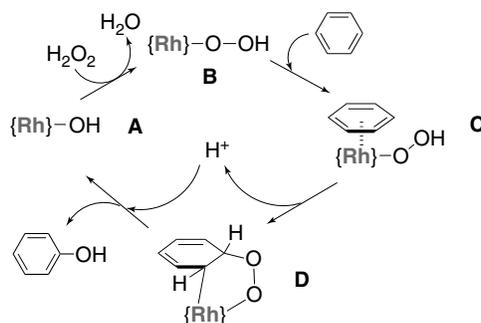


Figure 1.10 A catalytic cycle proposed for the benzene hydroxylation catalyzed by a rhodium complex ($\{\text{Rh}\}$ is a Rh-containing fragment). Adapted from Reference 15a.

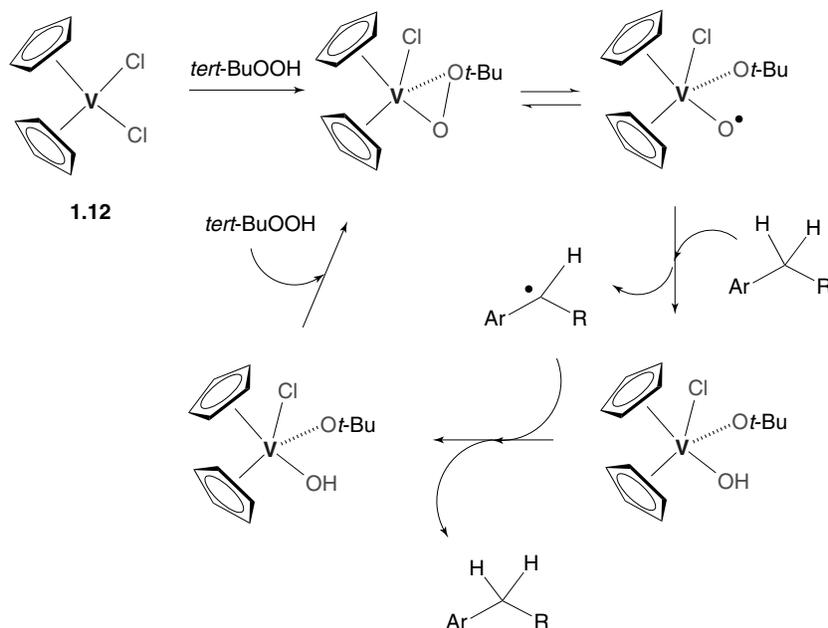


Figure 1.11 A catalytic cycle proposed for the benzyl hydroxylation catalyzed by vanadium complex **1.12**. Adapted from Reference 16.

It has been shown recently that cyclopentadienyl vanadium complexes catalyze the oxidation of benzylic groups by *tert*-BuOOH [16]. Compound Cp_2VCl_2 (**1.12**) catalyzes benzylic C–H oxidation selectively and effectively, giving no aromatic oxidation products. The authors assume that intermediate catalytically active species contain Cp rings (Fig. 1.11).

1.4 CONCLUSIONS AND OUTLOOK

It is clearly seen from this chapter that organometallic complexes are not leading catalysts for various reactions that afford valuable oxygenates from hydrocarbons and other C–H compounds. Such complexes are usually expensive and their synthesis is often not simple. However, in some cases, organometallics outrival commercially available inorganic salts in activity and selectivity. One can expect that the research on the application of organometallic catalysts in oxidation reactions will continue in the future.

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TOWARD FUNCTIONALIZATION OF ALKANES UNDER ENVIRONMENTALLY BENIGN CONDITIONS

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2.1 INTRODUCTION

Alkanes are very rich carbon compounds but their use as raw materials for organic synthesis has been hampered by their high inertness. Their conversion into organic products with an added value (for reviews, see e.g., [1–15]), is a challenge in modern chemistry, and alkanes are used generally as fuels (full oxidation to CO₂), with complete loss of carbon to the atmosphere and resulting noxious environmental effects associated with carbon dioxide accumulation therein.

The development of mild and green processes for their partial oxidation and functionalization would promote the potential of their application toward alternative raw materials for organic synthesis. Single-pot methods to achieve functionalized products, such as carboxylic acids, would be highly advantageous also in terms of simplicity, in comparison with the current multistage and energy-demanding processes used in industry.

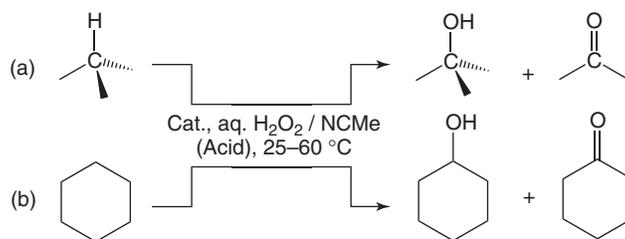
Of particular significance to achieve environmentally benign systems would be the use of water as a solvent, but this is also challenging in view of the lack of solubility of the alkanes and, commonly, also of the metal catalysts. The approach followed in the author's group often involves the use of hydrosoluble ligands at appropriate metal centers, which can lead to the formation of water-soluble catalyst precursors. Examples are indicated in the following sections.

2.2 PEROXIDATIVE OXIDATIONS OF ALKANES TO ALCOHOLS AND KETONES, CATALYZED BY TRANSITION METAL COMPLEXES

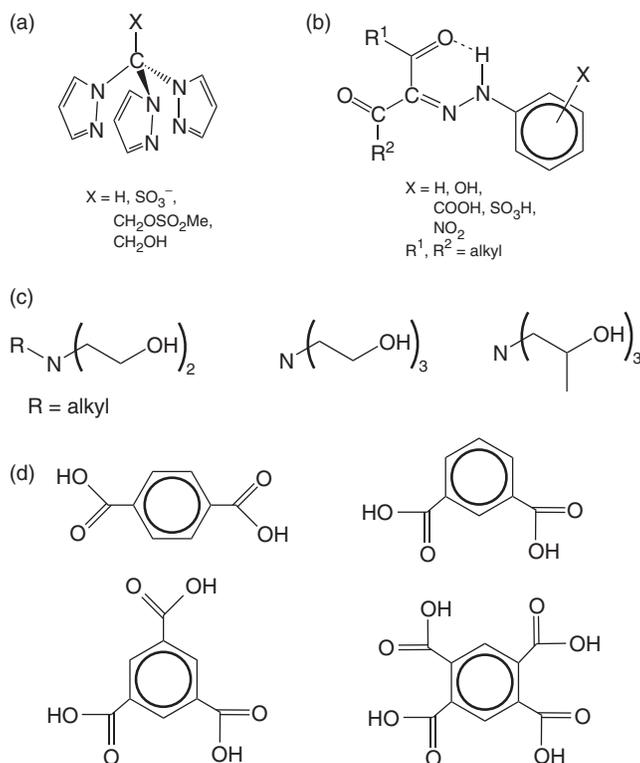
Both cyclic and acyclic alkanes undergo partial oxidation to alcohols and ketones, with hydrogen peroxide and under mild conditions (Scheme 2.1a) in the catalytic systems discussed herein, but the oxidation of cyclohexane to cyclohexanol and cyclohexanone (Scheme 2.1b) has been typically used as the model reaction, in view, for example, of its simplicity (cyclohexane bears only one type of carbon atoms) and its industrial significance (the mixture of cyclohexanol and cyclohexanone obtained by such a reaction is used for the preparation of adipic acid, a key intermediate for the production of nylon-6,6).

2.2.1 Scorpionate Complexes as Catalyst Precursors

In contrast to boron-based scorpionates, such as *tris*(pyrazolyl)borate and derivatives, those based on carbon, namely *tris*(pyrazolyl)methane, HC(pz)₃, and hydrosoluble-derived ones (Scheme 2.2a), are still underexplored, in spite of their potential, when suitably functionalized, to form *water-soluble complexes*. A good example is the sulfonate derivative, that is, *tris*(pyrazolyl)methane sulfonate (Tpms), which is hydrolytically stable over a wide pH range and leads to sandwich



Scheme 2.1 Peroxidative oxidation of an alkane (a) and, in particular, of cyclohexane (b) to the corresponding alcohol and ketone, with aqueous H_2O_2 , catalyzed by a transition metal catalyst (Cat.), under typical mild reaction conditions of this work.

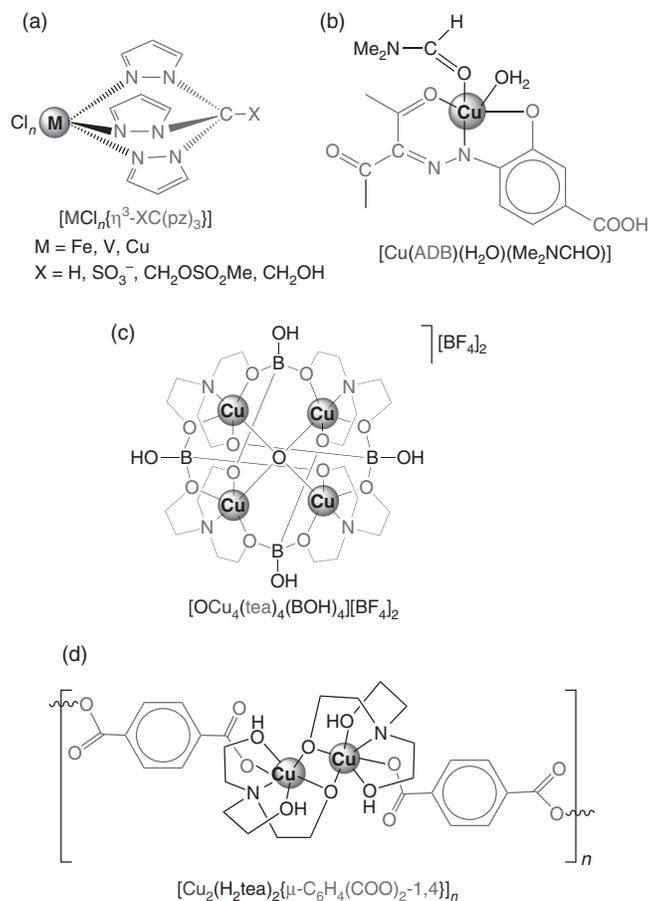


Scheme 2.2 Examples of types of ligands (or their precursors) in metal catalysts for the peroxidative oxidation of alkanes: (a) C-based scorpionates, (b) azoderivatives or arylhydrazones of β -diketones, (c) aminopolyalcohols, and (d) benzene polycarboxylic acids.

and/or half-sandwich complexes with various transition metals. The *half-sandwich compounds of iron, vanadium, and copper*, bearing this or a related scorpionate ligand (Scheme 2.3a) [16–20], act as good catalyst precursors for the partial oxidation of alkanes to the corresponding alcohols and ketones, in acetonitrile, with aqueous hydrogen peroxide as an oxidant, under mild conditions (e.g., 20–40 °C), typically in acidic medium.

This is illustrated for the peroxidative oxidation of cyclohexane to a mixture of cyclohexanol and cyclohexanone (Scheme 2.1b), a reaction with industrial application (see above). The conditions required in the industrial process (quite higher temperatures) are much harsher than ours, and the conversions are rather low in order to achieve a good selectivity. In our systems based on a half-sandwich complex, turnover numbers (TONs, moles of product per mole of catalyst precursor) up to 690 and yields up to 25% have been achieved with the Fe precatalyst $[\text{Fe}(\text{Cl})_2(\text{Tpms})]$ [20].

In a few cases (with Fe or Cu hydrosoluble precatalysts), the system can operate in the absence of any added organic solvent (even acetonitrile) [20], a feature that is noteworthy toward the development of a green catalytic system. However, our catalysts are not effective when using air (or dioxygen) instead of hydrogen peroxide as the oxidant, a disadvantage relative to the industrial process.



Scheme 2.3 Examples of transition metal catalyst precursors for the peroxidative oxidation of alkanes, bearing (a) a C-scorpionate [16–20], (b) an azoderivative of a β -diketone [21], (c) an aminopolyalcohol derivative (tea^{3-} = deprotonated form of triethanolamine, H_3tea) [33, 34], and (d) a benzene dicarboxylate [33, 34] ligand.

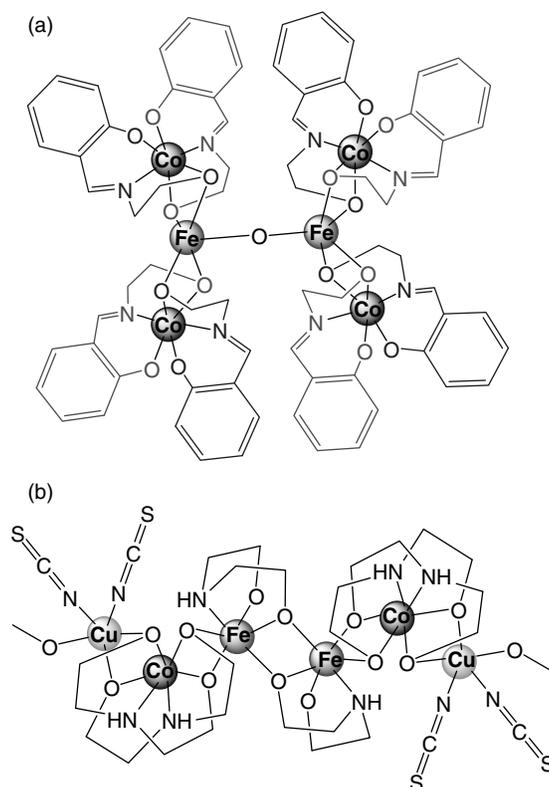
A broader discussion on the use of scorpionate complexes in catalysis is given in Chapter 22.

2.2.2 Azoderivatives of β -Diketone Complexes as Catalyst Precursors

Suitably functionalized azoderivatives of β -diketones (ADB or arylhydrazones of β -diketones, AHBD) (Scheme 2.2b) are also convenient hydrosoluble species toward water-soluble catalyst precursors in this field and of particular interest are those bearing an acid substituent (carboxylic or sulfonic group) [21], which can operate without requiring the common presence of an added acid promoter. The acidic moiety conceivably has two main roles: provides water solubility and acts as the acid promoter. Hence, the complexes $[Cu(ADB)(H_2O)(Me_2NCHO)]$ (Scheme 2.3b) and $[\{Cu(\mu-ADB)(MeOH)\}_2][ADB = p-COOH$ substituted (2-hydroxy-phenylhydrazone)pentane-2,4-dione] appear to behave as *dual-role* catalyst precursors, in *acid-free* medium, combining, in each molecule, an active copper center and an acid site (TONs and yields up to 163 and 14%, respectively, are achieved for the model oxidation of cyclohexane, in NCMe/aqueous H_2O_2 , at $50^\circ C$) [21].

2.2.3 Multinuclear Complexes as Catalyst Precursors

Although the mononuclear Cu half-sandwich scorpionate complexes (see above) are commonly less active than the Fe ones, copper complexes can be more effective in *multinuclear assemblies* (including coordination polymers) and our approach for these species concerns their *self-assembly synthesis* by using a suitable combination of a metal source, a main chelating ligand, a spacer or linker, apart from a pH regulator. A wide discussion on the types of self-assembled multicopper complexes and their use for alkane functionalization is presented in Chapter 3, and only a very brief overall view is outlined here.



Scheme 2.4 Direct self-assembled *heterometallic* catalyst precursors for the peroxidative oxidation of alkanes: (a) $[\text{Co}_4\text{Fe}_2\text{O}(\text{Sae})_8]$ (H_2Sae = salicylidene-2-ethanolamine) [35] and (b) $[\text{FeCuCo}(\mu\text{-L})_3(\text{NCS})_2(\text{MeOH})_2]$ (H_2L = diethanolamine) [36].

Typical examples of chelating ligands and spacers applied for self-assembly of multicopper coordination compounds and polymers include (see above) AHBD [21–24], aminopolyalcohols, and benzenepolycarboxylic acids [25–34] (Scheme 2.2b–d).

A diversity of 1D, 2D, or 3D copper assemblies can be obtained, including coordination polymers, as well as multi- or mononuclear species with discrete molecules. Among the latter, the tetranuclear μ -oxo complex derived from triethanolamine $[\text{OCu}_4(\text{tea})_4(\text{BOH})_4][\text{BF}_4]_2$ (Scheme 2.3c) is particularly active (TONs or yields up to 380 or 39%, respectively, for the conversion of cyclohexane to cyclohexanol and cyclohexanone) [33, 34]. It is also active (although less effectively, by one order of magnitude) for the oxidation of methane and ethane to methanol and ethanol, respectively [34].

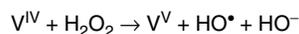
Heterometallic species can be conveniently obtained, in particular by *direct self-assembly*, from a metal powder, and they can exhibit a metal synergic effect with a remarkable catalytic activity. Hence, the hexanuclear heterodimetallate $\text{Co}^{\text{III}}_4\text{Fe}^{\text{III}}_2$ Schiff base complex $[\text{Co}_4\text{Fe}_2\text{O}(\text{Sae})_8]$ (H_2Sae = salicylidene-2-ethanolamine) (Scheme 2.4), without copper, self-assembled from Co powder, FeCl_2 , H_2Sae , and Et_3N under air, exhibits an outstanding TON of 3.6×10^3 (corresponding to a turnover frequency of $1.1 \times 10^4 \text{ h}^{-1}$), for the oxidation of cyclohexane in NCMe/aqueous H_2O_2 , at room temperature [35].

A good activity with a synergic effect is also achieved (TON and yield up to 100 and 25%, respectively) by the heterotrimetallic Fe/Cu/Co complex $[\text{FeCuCo}(\mu\text{-L})_3(\text{NCS})_2(\text{MeOH})_2]$ (H_2L = diethanolamine) [36].

2.2.4 Role of Water

The use of water as a solvent, even when mixed with an organic one, is a positive feature of a catalytic system, which aims to be of environmental significance.

However, the role of water can lie beyond that of a mere solvent, as suggested by the observation, in some cases, that water promotes the catalytic activity, and attested by theoretical density functional theory (DFT) calculations [37–40]. This was studied in detail for the aqueous H_2O_2 –NCMe systems based on the oxo–Re complex $[\text{MeReO}_3]$ (methyl trioxo-rhenium, MTO) [37] and on the vanadate (VO_3^-) or vanadatane ($[\text{VO}\{\text{N}(\text{CH}_2\text{CH}_2\text{O})_3\}]$) [38] catalyst precursors, which are effective



Scheme 2.5 Overall reactions involved in a vanadium(V/IV)-assisted generation of hydroxyl radical (HO^\bullet) from hydrogen peroxide. The $V^V + OH^-$ products can stand for $V^V=O + H^+$.

for the peroxidative oxidation of alkanes to the corresponding alcohols and ketones. The vanadate system was initially established by Shul'pin et al. [41] and included pyrazinecarboxylic acid (PCAH) as a promoter.

As indicated by radical trap experiments, various types of selectivity (regio-, bond-, and stereo-selectivity), and kinetic and theoretical studies [18–24, 27, 29, 33–40], these peroxidative oxidations of alkanes occur via radical mechanisms. They are believed to proceed via free hydroxyl radical (HO^\bullet) that acts as an H-abstractor from the alkane RH to yield the corresponding alkyl radical R^\bullet . Fast reaction of R^\bullet with O_2 generates the alkylperoxyl radical ROO^\bullet , which, following known pathways [38, 39, and references therein], lead to the formation of the final alcohol (ROH) and the corresponding ketone via the alkylperoxide ROOH.

The hydroxyl radical is generated on metal-assisted reduction of H_2O_2 (see Scheme 2.5, for a $V^{V/IV}$ catalytic system) [38, 40–42].

The concerned overall H_2O_2 reactions involve proton-transfer steps, for example, from ligated H_2O_2 to an oxo ligand, which are promoted by water on bridging both ligands with the formation of six-membered transition states (TSs) that are thus stabilized [37–40]. This is exemplified by $[VO_3(HOOH \cdots OH_2 \cdots)(PCA)]^\ddagger$, the TS involved in such a proton transfer in the VO_3^- -pyrazinecarboxylate (PCA) system (Scheme 2.6) [38]. The assistance of water, which acts as a *catalyst*, lowers (Scheme 2.6a) the activation barrier by 7–11 kcal/mol, in comparison with the four- or five-membered TSs that would form if the proton transfer would occur [41–43] with the assistance of the PCA ligand (Shul'pin “robot-type mechanism,” Scheme 2.6b) or directly from the H_2O_2 ligand to an oxo ligand. Hence, water, in a controlled amount, can be more effective for this purpose than the more complex PCA ligand.

A similar effect of water has been proposed for other types of reactions without involving alkanes, for example, olefin epoxidations catalyzed by cyclopentadienyl–Mo systems [44], and thus it can be of a considerable generality.

It is noteworthy to mention that the involvement of a second metal center can also promote the proton transfer, as believed to occur in di- or oligovanadate catalysts, which exhibit a higher activity than monovanadate [40]. In such systems, six-membered oxo–divanadium TSs (Scheme 2.6c) can be formed, lowering the energy barrier by circa 4.2 kcal/mol relatively to the proton transfer at a monovanadate center [40].

Furthermore, water can have an even deeper role in alkane functionalization, as a hydroxylating reagent, which will be discussed in Section 4.

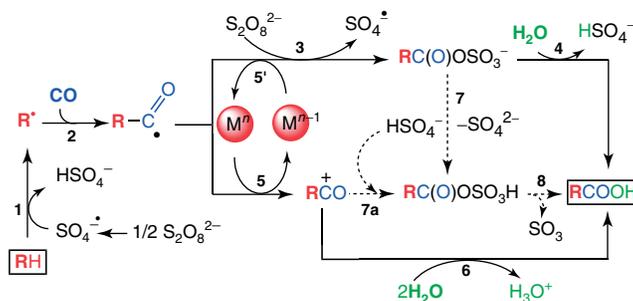
2.2.5 Nontransition Metal Catalyzed Alkane Oxidation

When thinking on green catalysis, one is encouraged to try to avoid the use of any transition metal catalyst that commonly has an environmentally nonbenign character (although, in some cases, namely with Fe, Cu, or V catalysts, they can be tolerated). Of significance toward this aim is the recognition by Mandelli and Shul'pin [45] that aluminum, a nontransition metal, can replace a transition metal catalyst, as shown by the $Al(NO_3)_3-H_2O_2-NCMe-H_2O$ system, which catalyzes the oxidation of octane and heptane to the corresponding alcohols and ketones.

This is particularly interesting in the view that a redox-inactive metal is replacing a redox-active metal, in oxidation catalysis, and was investigated by DFT calculations [46].

These theoretical studies indicate the crucial role played by the intermediate $[Al(OOH)(HOOH)(H_2O)_4]^{2+}$, bearing (i) an highly activated hydrogen peroxide ligand with a dramatically decreased HO–OH bond energy (6.1 kcal/mol) in comparison with free H_2O_2 (39.4 kcal/mol), and (ii) a ligated monodeprotonated form (HOO^-). At this intermediate, this latter ligand reduces (intramolecular redox process) hydrogen peroxide to hydroxide (HO^-) and hydroxyl (HO^\bullet), being itself oxidized to the hydroperoxyl radical (HOO^\bullet), a labile ligand that liberates from the metal (Scheme 2.7) [46].

Therefore, the transition metal is avoided in this H_2O_2 –Al catalytic system on account of a suitable redox-active co-ligand (HOO^-) that can play the redox role of the transition metal, by acting as a reducing agent of H_2O_2 toward the generation of the hydroxyl radical. The generality of such an interesting behavior is worth to be investigated.



Scheme 2.8 Main radical mechanism of the hydrocarboxylation of alkanes with peroxydisulfate, CO, and water, in aqueous ($\text{H}_2\text{O}/\text{MeCN}$) medium [51]. The minor 7 (or 7a) to 8 alternative pathway does not concern water as the hydroxylating agent. (See insert for color representation of the figure.)

The system is active for both liquid and gaseous alkanes, but with a rather low activity for methane. Although operating under metal-free conditions, it is also metal-promoted namely by some copper complexes that act as catalyst precursors for the oxidation of alkanes with hydrogen peroxide, typically the abovementioned tetranuclear μ -oxo triethanolamine complex $[\text{OCu}_4(\text{tea})_4(\text{BOH})_4][\text{BF}_4]_2$.

The mechanism is also radical, as indicated by the suppression of acid (RCOOH) formation by a radical trap and the preferable carbonylation at a secondary carbon relative to a primary one. According to DFT calculations [51], it proceeds mainly as shown in Scheme 2.8.

Peroxydisulfate acts as a radical source and as an oxidant (a third minor role as a hydroxylating agent is mentioned below). The first role concerns its homolysis that leads to the sulfate radical $\text{SO}_4^{\bullet-}$, which abstracts hydrogen from the alkane (RH) forming the alkyl radical R^{\bullet} (step 1, Scheme 2.8). This is carbonylated by CO to give the acyl radical $\text{RC}^{\bullet}\text{O}$ (step 2), which is oxidized either by peroxydisulfate (its second role) with coupling to sulfate to give the acyl sulfate $\text{RC}(\text{O})\text{OSO}_3^-$ (step 3, metal-free pathway) or by the metal promoter to form the acyl cation RCO^+ (step 5, metal-promoted route) [51].

Nucleophilic attack of water, either at the acyl sulfate or at the acyl cation (step 4 or 6, respectively), leads to the formation of the carboxylic acid RCOOH , as the final product [51]. Hence, apart from being a solvent, water also plays a fundamental role as a stoichiometric nucleophilic reagent toward alkane-derived acyl species.

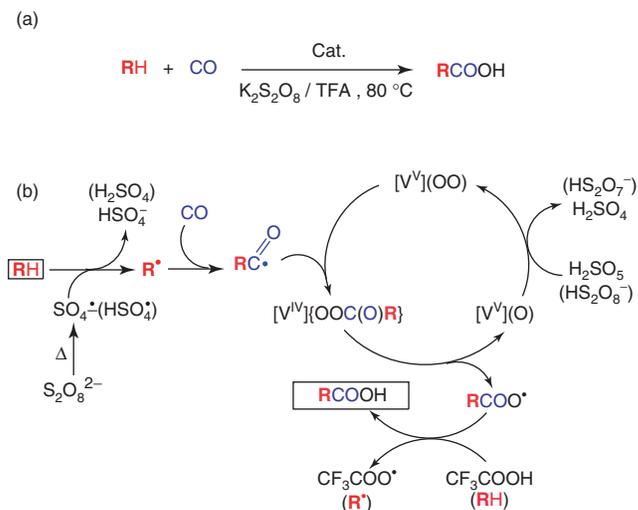
When using H_2^{18}O , a minor amount of nonlabeled RCOOH is also obtained, which can be accounted for by steps 7 (or 7a) and 8, where HSO_4^- (derived from peroxydisulfate), instead of water, acts as the hydroxylating agent [51].

This alkane-hydrocarboxylating system can be considered as a development toward the “green” direction of a previous carboxylation system based on the use of peroxydisulfate in trifluoroacetic acid (TFA) at 80°C (Scheme 2.9a), which was pioneered by Fujwara [12, 15], and further improved by the author’s group [52–60] by finding more active and convenient metal catalysts, and establishing the mechanism of the catalysis. In fact, the water–acetonitrile mixture, in the above alkane-hydrocarboxylating system (Eq. 2.1, Scheme 2.8), has replaced successfully the noxious TFA as a solvent in the latter carboxylation system, the operating conditions became much milder and environmentally tolerable, and a role of water as a reagent was found. However, peroxydisulfate could not be replaced by a greener oxidant, such as H_2O_2 .

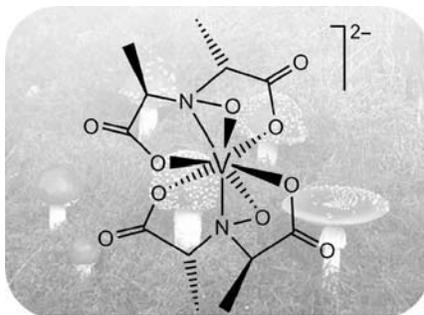
In the $\text{S}_2\text{O}_8^{2-}/\text{TFA}$ system, vanadium catalysts were found to be the most active, in particular amavadin (also spelled amavadine) and its models [52–54, 57, 59, 61]. Amavadin is the nonoxo–vanadium complex $[\text{V}(\text{HIDPA})_2]^{2-}$ [HIDPA = deprotonated basic form of *N*-(hydroxyimino)dipropionic acid] (Scheme 2.10) that is present in some toadstools (*amanita muscaria*), but its biological role still remains undiscovered [61]. Its catalytic activity, and those of its models, such as $[\text{V}(\text{HIDA})_2]^{2-}$ [HIDA = deprotonated basic form of *N*-(hydroxyimino)diacetic acid] and related vanadatrane $[\text{VO}\{\text{N}(\text{CH}_2\text{CH}_2\text{O})_3\}]$, are so high (TONs up to over 10^4 or carboxylic acids yields up to over 90%, for the most inert alkanes, methane, or ethane) [52, 53] that amavadin and the toadstools where it is found have been considered by this author as a *kind of magic* (inspired on a well-known Queen band song) and the latter were called elsewhere [62] as “magic mushrooms, new catalysts from Nature.”

The initial steps of the mechanism of the alkane (RH) carboxylation (Scheme 2.9b) [52, 53] are identical to those of the hydrocarboxylation, discussed above, with $\text{S}_2\text{O}_8^{2-}$ as the source of the sulfate radical, which acts as H-abstractor from the alkane to give the alkyl radical R^{\bullet} , and CO as the carbonylating agent of this radical to yield the acyl radical $\text{RC}^{\bullet}\text{O}$.

However, peroxydisulfate, instead of water, provides the source of the hydroxyl oxygen as substantiated by DFT calculations [52, 53], which indicate the plausible addition of the acyl radical to a peroxo-V intermediate to form a



Scheme 2.9 Alkane carboxylation with CO and $\text{K}_2\text{S}_2\text{O}_8$, in TFA: (a) General reaction [12, 15, 52–60] and (b) proposed mechanism for an oxo-vanadium catalyst [52, 53]. (See insert for color representation of the figure.)



Scheme 2.10 Amavadin complex $[\text{V}(\text{HIDPA})_2]^{2-}$ [HIDPA = deprotonated basic form of *N*-(hydroxyimino)dipropionic acid] with its natural source, *amanita muscaria*.

percarboxylate ligand, $\text{RC}(\text{O})\text{OO}$, which, on O–O bond homolysis, generates the carboxyl radical RCOO^\bullet that, via H-abstraction from the alkane or from TFA, yields the acid RCOOH .

It is noteworthy to mention that both the hydrocarboxylation and the carboxylation of alkanes processes discussed herein provide single-pot routes to carboxylic acids that are much simpler and operate under much milder conditions in comparison with the industrial processes. This is well illustrated for the case of the industrial production of acetic acid [63, 64], which involves three distinct stages under energy-demanding and environmentally nontolerable conditions: high temperature catalytic steam reforming of methane or coal to CO and dihydrogen, high temperature catalytic conversion of synthesis gas into methanol, and carbonylation of methanol with expensive Rh or Ir catalysts (Monsanto or Cativa process, respectively), still at a considerably elevated temperature.

Moreover, amavadin also catalyses the abovementioned peroxidative oxidation of alkanes, as well as their peroxidative halogenations [65], although with a much lower activity.

2.4 FINAL REMARKS

Steps have been taken toward eco-friendly catalytic systems active in alkane functionalization under mild conditions, preferably in aqueous media, by using *hydrosoluble catalysts* obtained from ligands that are water soluble. Systems can operate usually with a *green oxidant* (aqueous hydrogen peroxide) and in partially *aqueous media*.

Moreover, *water* can play a fundamental role beyond that of a mere solvent, acting as a *promoter* of the catalytic activity (by favoring proton-transfer steps) or even as a *reagent*, that is, the hydroxylating reagent in the alkane functionalization.

A transition metal can be avoided, by using a *nontransition metal* catalyst, provided a suitable redox-active co-ligand is present.

A *metal-free* system was already established for the carboxylation of alkanes with CO and water, operating in water–acetonitrile and under *acid-free* conditions. The latter feature (no added acid) is common to a few other catalytic systems active for alkane hydroxylation, namely by taking advantage of a ligand bearing an acid group (“dual-role catalyst”).

The alkane functionalization reactions proceed via *radical mechanisms*, with a *high chemoselectivity*, although with low regio-, bond-, and stereo-selectivities as expected for the involvement of the hydroxyl radical, features that were not discussed in this chapter.

Theoretical DFT studies allow to disclose conceivable reaction mechanisms.

The systems exhibit a *high simplicity* and provide the oxidized and carboxylated (carboxylic acids) products in a *single-pot* process, thus contrasting with the higher complexity of the industrial synthetic processes for the same products.

In addition, a number of the developed catalysts are also active, under different experimental conditions, in *oxidations of other substrates*, in particular some of the copper catalysts for alcohol aerobic (TEMPO-mediated) or peroxidative oxidations [21, 22]. The reactions may be microwave-assisted (details are given in Chapter 18).

It is also worth mentioning the *biological significance* of these studies and the inspiration of biology on their development. In fact, pMMO (particulate methane monooxygenase), a main enzyme in the metabolic pathway of methanotrophs, is a membrane multicopper enzyme that catalyzes the oxidation of alkanes to the corresponding alcohols [66–68], which is mimicked by the multinuclear copper systems.

Moreover, *amavadin*, a water-soluble natural vanadium complex, still with an undisclosed biological role in the mushrooms where it is accumulated, has been successfully applied as a remarkably effective catalyst precursor in the field of alkane carboxylation, although under conditions that are not found in biological systems. Concerning the peroxydisulfate/TFA system for alkane carboxylation, this acid solvent has already been replaced by a mixture of water/acetonitrile, operating under milder conditions, but a cheaper and less noxious oxidant (hydrogen peroxide or dioxygen) conceivably has yet to be found before the process gains a widespread use.

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SELF-ASSEMBLED MULTICOPPER COMPLEXES AND COORDINATION POLYMERS FOR OXIDATION AND HYDROCARBOXYLATION OF ALKANES

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3.1 INTRODUCTION

The selective and atom-efficient oxidative functionalization of alkanes under mild conditions, toward the synthesis of various added-value organic products (alcohols, ketones, aldehydes, and carboxylic acids), constitutes a challenge to modern chemistry because of the exceptionally high inertness of these hydrocarbons [1, 2]. An important research direction is toward the search for new bioinspired catalytic systems [1a–3] that are capable of converting alkanes into different oxidation products. Given the recognized biological function of copper and its presence in the active sites of many oxidation enzymes [3, 4], including the multicopper particulate methane monooxygenase (pMMO) [5], the development of new bioinspired multicopper catalysts and efficient alkane functionalization protocols thereof constitutes a subject of high importance.

Recently, we have developed a versatile aqueous medium self-assembly method for the generation of diverse multicopper(II) complexes and coordination polymers derived from cheap and commercially available ligands such as aminoalcohols and benzenecarboxylates [6–15]. The obtained compounds were applied as highly efficient and versatile catalysts or catalyst precursors in two different alkane functionalization reactions. These include the mild oxidation of alkanes (typically cyclohexane as a model substrate) by hydrogen peroxide into alkyl hydroperoxides, alcohols, and ketones [6–9, 11, 16, 17], 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 [12–15, 18–22].

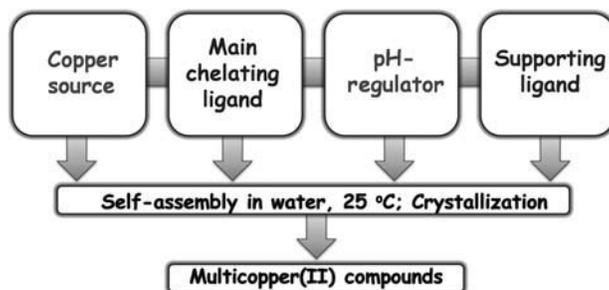
Hence, in this chapter, we describe the principle of aqueous medium self-assembly synthesis, the selected self-assembled aminoalcoholate multicopper(II) complexes and coordination polymers, and their catalytic application in homogeneous oxidative functionalization of alkanes.

3.2 SELF-ASSEMBLY SYNTHESIS IN AQUEOUS MEDIUM

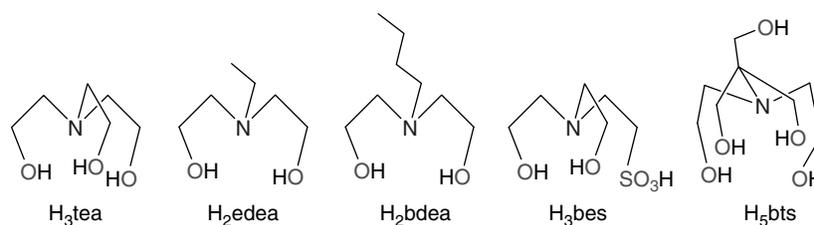
From the environmental and economical viewpoints, water is the ideal green solvent for both the synthesis of coordination compounds and the catalytic transformations of organic molecules including the oxidative functionalization of alkanes [23]. However, the performance of catalytic reactions in aqueous medium typically requires the use of hydrosoluble catalysts that often mimic the functions of enzymes. Although various bioinspired multicopper complexes were synthesized as models of pMMO and related copper-based enzymes [3–5a], those catalysts were often not soluble in water, exhibited modest activities, or were almost not tested in oxidative transformations wherein alkanes are used as substrates.

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Scheme 3.1 General scheme of self-assembly synthesis. Adapted from Reference 10.



Scheme 3.2 Aminoalcohols applied in self-assembly synthesis of multicopper(II) compounds.

Bearing the above-mentioned points in mind, we have developed a simple and versatile self-assembly protocol for the synthesis of diverse multicopper(II) complexes and coordination polymers in aqueous medium, under ambient conditions, and using simple and commercially available chemicals (Scheme 3.1). This self-assembly method is based on a combination with water, at room temperature (rt) and in air, of copper source, main chelating ligand, pH-regulator, and supporting ligand or spacer, followed by crystallization [10–15]. As a metal source, simple copper salts such as copper(II) nitrate or acetate were used, whereas triethanolamine (H_3tea) and closely related aminoalcohols [*N*-ethyl- and *N*-butyldiethanolamine (H_2edea , H_2bdea), *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (H_3bes), or bis(2-hydroxyethyl)amino-tris(hydroxymethyl)methane (H_5bts)] were applied as main chelating ligands (Scheme 3.2). Alkali or alkaline earth metal hydroxides [$NaOH$, $LiOH$, or $Mg(OH)_2$] were utilized as pH-regulators, while the supporting ligands were selected from benzenecarboxylates (e.g., benzoic, terephthalic, or pyromellitic acids), simple inorganic anions (azide, thiocyanate, or tetrafluoroborate), or cyanometallates (e.g., $[Fe(CN)_6]^{3-/4-}$) [6, 8–15, 24].

By modifying the type of main chelating ligand, pH-regulator or supporting ligand, we have synthesized a considerable number of aminoalcoholate multicopper compounds, ranging from discrete di-, tri-, and tetracopper(II) complexes, to 1D, 2D, and 3D coordination polymers [6–15, 24]. Many of the obtained compounds are water soluble and have also been tested as catalysts or catalyst precursors in the oxidative functionalization of alkanes. Although some parent compounds are not soluble in water, they can also act as catalyst precursors of active hydrosoluble species on treatment with an acid promoter and/or oxidant [7, 9, 15, 24]. The representative examples of highly active di-, tri-, tetra-, and polynuclear copper catalysts or catalyst precursors are summarized in Table 3.1 and their structures and catalytic behavior are briefly described in the following sections.

3.3 AMINOALCOHOLATE MULTICOPPER COMPLEXES AND COORDINATION POLYMERS

The dicopper(II) complexes $[Cu_2(\mu-H_2tea)_2(ba)_2] \cdot 2H_2O$ (**1**), $[Cu_2(\mu-Hedea)_2(NCS)_2]$ (**2**), and $[Cu_2(\mu-Hbdea)_2(N_3)_2]$ (**3**) composed of related dicopper cores were easily self-assembled by the treatment of $Cu(NO_3)_2$ and respective aminoalcohols (H_3tea , H_2edea , or H_2bdea) with benzoic acid (for **1**), sodium thiocyanate (**2**), or sodium azide (**3**) in alkaline aqueous solution (Table 3.1) [6, 9, 11]. As a representative example, the structure of **3** is given in Fig. 3.1. It bears two five-coordinate copper atoms that adopt distorted square-pyramidal geometries, being filled by *N*, O_2 -tridentate μ -*Hbdea* ligands and azide moieties [11].

The discrete tricopper(II) complexes $[Cu_3(\mu-H_2tea)_2(\mu-poba)_2(H_2O)] \cdot 4H_2O$ (**4**) and $[Cu_3(\mu_3-BO)(\mu-H_3bts)_3][BF_4] \cdot 2H_2O$ (**5**) self-assembled from triethanolamine (H_3tea) or Bis-Tris (H_5bts) aminoalcohols are particularly interesting

TABLE 3.1 Selected Self-Assembled Multicopper(II) Compounds as Catalysts or Catalyst Precursors in Oxidation and Hydrocarboxylation of Alkanes

Compound Number	Formula	Alkane Substrates ^a	References
1	[Cu ₂ (μ-H ₂ tea) ₂ (ba) ₂] · 2H ₂ O	C ₆ H ₁₂	6, 7
2	[Cu ₂ (μ-Hedea) ₂ (NCS) ₂]	Cyclic and linear C ₅ –C ₈ ^b	9
3	[Cu ₂ (μ-Hbdea) ₂ (N ₃) ₂]	C ₆ H ₁₂	11
4	[Cu ₃ (μ-H ₂ tea) ₂ (μ-poba) ₂ (H ₂ O)] · 4H ₂ O	C ₆ H ₁₂ , CH ₄ , C ₂ H ₆	6, 7
5	[Cu ₃ (μ ₃ -BO)(μ-H ₃ bts) ₃][BF ₄] · 2H ₂ O	Linear C ₂ –C ₈ ^b , cyclic C ₅ –C ₈ ^b	13
6	[Cu ₄ (μ ₄ -O)(μ ₃ -tea) ₄ (μ ₃ -BOH) ₄][BF ₄] ₂	C ₆ H ₁₂ , CH ₄ , C ₂ H ₆ , MCH, DMCH, <i>n</i> -C ₇ H ₁₆ , <i>n</i> -C ₈ H ₂₀ ; linear C ₂ –C ₈ ^b , cyclic C ₅ –C ₈ ^b	6, 7, 16–21
7	[Li(H ₂ O) ₄][Cu ₄ (μ-Hbes) ₄ (μ-ba)] · H ₂ O	Linear C ₂ –C ₉ ^b , cyclic C ₅ –C ₈ ^b	14
8	[Cu ₂ (μ-H ₂ tea) ₂ (μ ₂ -tpa)] _n · 2nH ₂ O	C ₆ H ₁₂	6, 7
9	[Cu ₂ (μ ₃ -H ₂ tea) ₂ (μ ₄ -pma){Na ₂ (H ₂ O) ₄ }] _n · 10nH ₂ O	C ₆ H ₁₂	8, 9
10	[Cu ₆ (μ-H ₂ tea) ₆ {Fe(μ-CN) ₆ }] _n (NO ₃) _{2n} · 6nH ₂ O	C ₆ H ₁₂	24
11	[Cu ₄ (μ ₃ -Hbes) ₂ (μ-Hbes) ₂ (μ-phba){Na(H ₂ O) ₄ }] _n	C ₃ H ₈ , <i>n</i> -C ₄ H ₁₀ ^b	12
12	[Cu ₄ (μ ₃ -Hbes) ₄ (μ-ba)(Na)] _n	C ₃ H ₈ , <i>n</i> -C ₄ H ₁₀ ^b	12
13	[Cu ₄ (μ ₃ -Hbes) ₄ (μ-mhba){Li(H ₂ O) ₂ }] _n · 3nH ₂ O	Linear C ₂ –C ₉ ^b , cyclic C ₅ –C ₈ ^b	14
14	[{Cu(H ₃ tea) ₂ (μ ₄ -pma)] _n	C ₆ H ₁₂	9
15	[Cu ₂ Mg ₂ (μ-Htea) ₂ (μ ₆ -pma)(H ₂ O) ₆] _n · 6nH ₂ O	Linear C ₅ –C ₉ ^b , cyclic C ₅ –C ₈ ^b	15

^aUnless stated otherwise, the substrates were used in oxidation reactions.

^bSubstrates were used in hydrocarboxylation reactions.

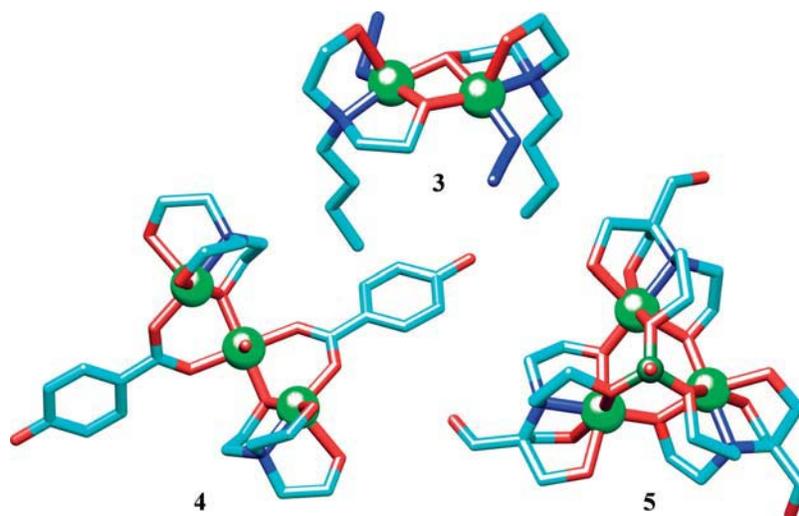


Figure 3.1 X-ray crystal structures of complexes [Cu₂(μ-Hbdea)₂(N₃)₂] (3), [Cu₃(μ-H₂tea)₂(μ-poba)₂(H₂O)] · 4H₂O (4), and [Cu₃(μ₃-BO)(μ-H₃bts)₃][BF₄] · 2H₂O (5). All H atoms, [BF₄][−] anion (in 5), and crystallization H₂O molecules (in 4, 5) are omitted for clarity. Color codes: Cu, green balls; O, red; N, blue; C, cyan; B, dark green ball. Adapted from References 6, 11, and 13. (See insert for color representation of the figure.)

examples because of their solubility in water, unusual structural features, and good substrate versatility in the oxidative functionalization of alkanes [6, 7, 13]. The structure of 4 (Fig. 3.1) possesses three five-coordinate Cu(II) atoms that are clustered by two μ-O atoms of H₂tea and two μ-COO groups of 4-oxybenzoate(2−) into a nonplanar {Cu₃(μ-O)₂(μ-COO)₂} core, wherein the “central” Cu atom has a labile H₂O ligand [6]. The structure of 5 (Fig. 3.1) possesses a [Cu₃(μ₃-BO)(H₃L)₃]⁺ cluster cation, wherein the six-coordinate Cu centers are interconnected by the μ-O atoms from three pentadentate H₃bts ligands acting in a *N*,*O*₄-coordination mode [13]. An additional stabilization of the structure is achieved by a μ₃-BO moiety that simultaneously binds to other μ-O atoms from H₃bts [13].

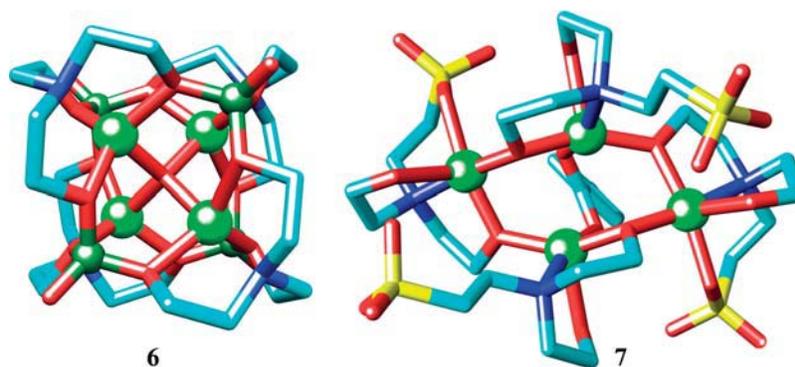


Figure 3.2 X-ray crystal structures of complexes $[\text{Cu}_4(\mu_4\text{-O})(\mu_3\text{-tea})_4(\mu_3\text{-BOH})_4][\text{BF}_4]_2$ (**6**) and $[\text{Li}(\text{H}_2\text{O})_4][\text{Cu}_4(\mu\text{-Hbes})_4(\mu\text{-ba})] \cdot \text{H}_2\text{O}$ (**7**). All H atoms, $[\text{BF}_4]^-$ anions (in **6**), $[\text{Li}(\text{H}_2\text{O})_4]^+$ cations, and crystallization H_2O molecules (in **7**) are omitted for clarity. Color codes: Cu, green balls; O, red; N, blue; C, cyan; B, dark green balls. Adapted from References 6 and 14. (See insert for color representation of the figure.)

There are also two different aminoalcoholate tetracopper(II) cores in the discrete tetracopper(II) complexes, $[\text{Cu}_4(\mu_4\text{-O})(\mu_3\text{-tea})_4(\mu_3\text{-BOH})_4][\text{BF}_4]_2$ (**6**) and $[\text{Li}(\text{H}_2\text{O})_4][\text{Cu}_4(\mu\text{-Hbes})_4(\mu\text{-ba})] \cdot \text{H}_2\text{O}$ (**7**) [6, 14]. The triethanolamine Cu(II) complex **6** is the most remarkable multicopper catalyst, in view of its high solubility and stability in aqueous medium, facile self-assembly synthesis from simple and cheap chemicals [6], recyclability [7], high efficiency, and substrate versatility for the oxidation [6, 7, 16, 17] and hydrocarboxylation [18–21] of various alkanes [17, 18]. The intricate cage-like structure of **6** (Fig. 3.2) features four Cu(II) atoms that are clustered via the triethanolamine $\mu_3\text{-O}$ atoms and $\mu_3\text{-BOH}$ groups, being further stabilized by the “central” $\mu_4\text{-O}$ oxo atom [6]. The hydrosoluble tetracopper(II) compound **7** [14] derived from a well-known biobuffer H_3bes (Scheme 3.2) bears the $[\text{Cu}_4(\mu\text{-Hbes})_4(\mu\text{-ba})]^-$ anion, which is constructed from two pairs of Cu atoms, four $\mu\text{-O}$ bridging Hbes ligands, and one $\mu\text{-COO}$ benzoate ligand (Fig. 3.2). All four Cu atoms act as square pyramids fused via common vertexes into the $\{\text{Cu}_4(\mu\text{-O})_4(\mu\text{-COO})\}$ cluster cores, wherein the copper centers are almost coplanar [14].

A number of aminoalcoholate copper(II) coordination polymers were applied as catalyst precursors in oxidative functionalization of alkanes [6–9, 14, 15, 22, 24]. Although coordination polymers are typically used in heterogeneous catalysis [25], compounds that are soluble in aqueous and/or organic medium can also act as catalyst precursors in homogeneous catalysis. Selected examples of coordination polymers obtained by aqueous medium self-assembly protocol concern the compounds **8–15** (Table 3.1), several types of which can be identified on the basis of the nature of ligands and nuclearity of the Cu-containing building blocks. The first type includes the polymers $[\text{Cu}_2(\mu\text{-H}_2\text{tea})_2(\mu_2\text{-tpa})]_n \cdot 2n\text{H}_2\text{O}$ (**8**) [6], $[\text{Cu}_2(\mu_3\text{-H}_2\text{tea})_2(\mu_4\text{-pma})\{\text{Na}_2(\text{H}_2\text{O})_4\}]_n \cdot 10n\text{H}_2\text{O}$ (**9**) [8], and $[\text{Cu}_6(\mu\text{-H}_2\text{tea})_6\{\text{Fe}(\mu\text{-CN})_6\}]_n(\text{NO}_3)_{2n}6n\text{H}_2\text{O}$ (**10**) [24]. These bear dimeric $[\text{Cu}_2(\mu\text{-aminoalcoholate})_2]^{2+}$ units (similar to those in **1–3**), which are assembled into 1D (**8**), 2D (**9**), and 3D (**10**) coordination networks through different linkers (Fig. 3.3) based on aromatic carboxylates or $[\text{Fe}(\text{CN})_6]^{4-}$ moieties [6, 8, 24]. A particularly interesting example concerns the highly water-soluble compound **9** assembled from dicopper(II) triethanolamine and aqua-sodium building blocks, and μ_4^- pyromellitate linkers (Fig. 3.3) [8].

The coordination polymers **11–13** represent another type of compounds that contain tetracopper(II) $[\text{Cu}_4(\mu\text{-Hbes})_4(\mu\text{-benzenecarboxylate})]^-$ building blocks similar to that of the discrete complex **7**, but assembled into 1D (**11**) or 3D (**12,13**) coordination networks through bridging and charge-balancing $\{\text{Na}\}^+$, $\{\text{Na}(\text{H}_2\text{O})_4\}^+$, or $\{\text{Li}(\text{H}_2\text{O})_2\}^+$ moieties [12, 14]. Other coordination polymers also include the 1D network $[\{\text{Cu}(\text{H}_3\text{tea})\}_2(\mu_4\text{-pma})]_n$ (**14**) built from the cationic monocopper $\{\text{Cu}(\text{H}_3\text{tea})\}^{2+}$ units and $\mu_4\text{-pma}(4-)$ linkers [9]. In the related compound $[\text{Cu}_2\text{Mg}_2(\mu\text{-Htea})_2(\mu_6\text{-pma})(\text{H}_2\text{O})_6]_n \cdot 6n\text{H}_2\text{O}$ (**15**), two $\{\text{Cu}(\mu\text{-Htea})\}^+$ fragments are clustered with a $\{\text{Mg}(\text{H}_2\text{O})_2\}^{2+}$ moiety and $\mu_6\text{-pma}(4-)$ spacer, forming an unusual heterometallic $\{\text{Cu}_2\text{Mg}(\mu\text{-O})_2(\mu\text{-COO})_2\}^-$ core [15]. Such cores are further assembled by $\{\text{Mg}(\text{H}_2\text{O})_4\}^{2+}$ linkers and $\mu_6\text{-pma}$ ligands into 2D metal–organic sheets [15].

3.4 APPLICATION IN ALKANE OXIDATION

The multicopper(II) complexes and coordination polymers **1, 3, 4, 6, 8–10**, and **14** (Table 3.1) act as efficient catalyst or catalyst precursors toward the mild oxidation of cyclohexane by hydrogen peroxide. This cycloalkane is typically used as a

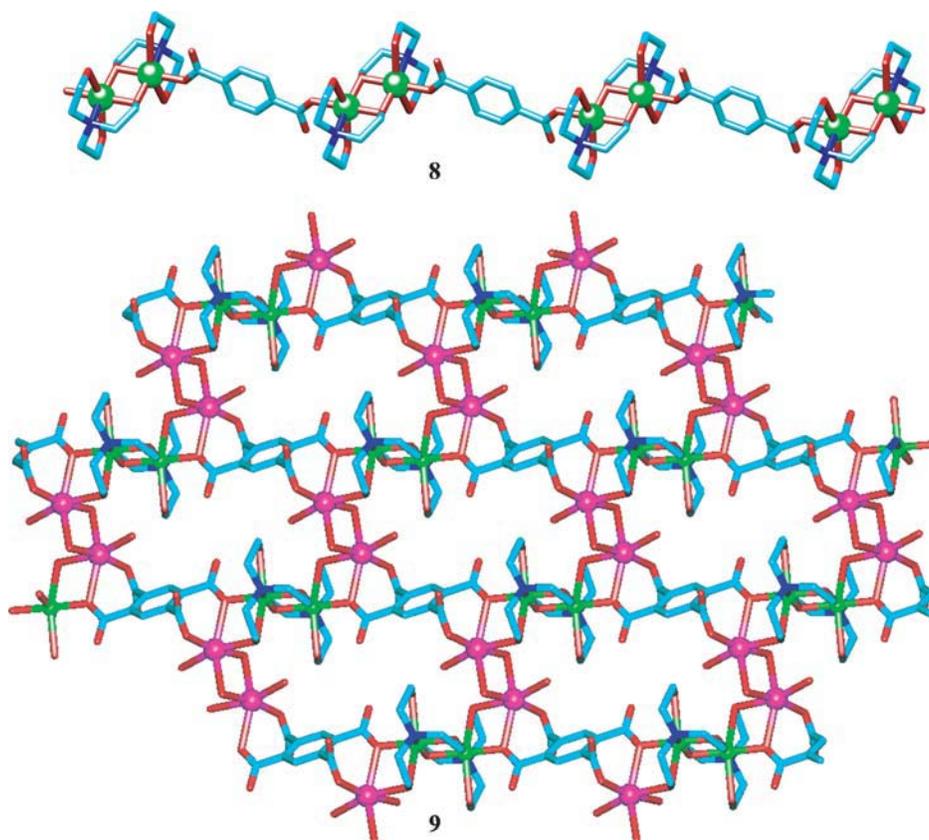
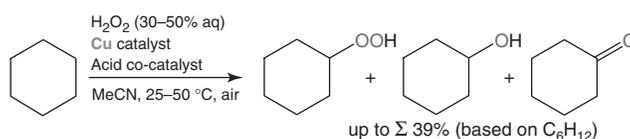


Figure 3.3 X-ray crystal structures of 1D and 2D polymers $[\text{Cu}_2(\mu\text{-H}_2\text{tea})_2(\mu_2\text{-tpa})]_n \cdot 2n\text{H}_2\text{O}$ (**8**) and $[\text{Cu}_2(\mu_3\text{-H}_2\text{tea})_2(\mu_4\text{-pma})\{\text{Na}_2(\text{H}_2\text{O})_4\}]_n \cdot 10n\text{H}_2\text{O}$ (**9**), respectively. All H atoms and crystallization H_2O molecules are omitted for clarity. Color codes: Cu, green balls; O, red; N, blue; C, cyan; Na, magenta. Adapted from References 6 and 8. (See insert for color representation of the figure.)



Scheme 3.3 Mild oxidation of cyclohexane to cyclohexyl hydroperoxide (primary product), and cyclohexanol and cyclohexanone (final products). Adapted from Reference 11.

recognized model substrate, in view of the importance of its oxidation products. In fact, cyclohexanol and cyclohexanone are intermediates in nylon-6,6' and polyamide-6 production [26, 27]. Although the industrial Dupont process undergoes at approximately 150°C using air as oxidant (~ 12 atm) and cobalt(III) naphthenate as a homogeneous catalyst, its main limitation consists in achieving only 4% cyclohexane conversion with 85% selectivity to the main products [7, 27]. Therefore, the search for new, more efficient, and selective protocols of cyclohexane oxidation continues to be an important research direction.

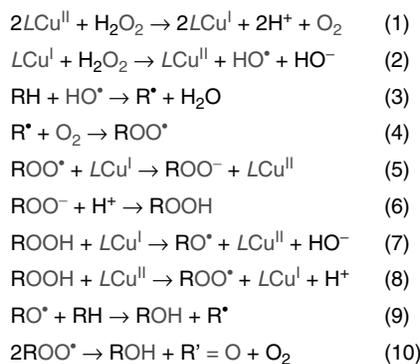
Hence, in the presence of various multicopper catalytic systems [6, 7, 9, 11, 16, 24], C_6H_{12} is oxidized by aq. H_2O_2 into a mixture of cyclohexyl hydroperoxide (CyOOH, main primary product), cyclohexanol and cyclohexanone that are the major final products after the autodecomposition of CyOOH or its reduction with PPh_3 [28]. This mild oxidation of cyclohexane (Scheme 3.3) proceeds in aqueous MeCN, under atmospheric pressure, at rt or with a slight heating (50°C), and in the presence of an acid cocatalyst (typically HNO_3). Among the tested multicopper(II) compounds, the activity in terms of total yields (moles of oxidation products per 100 moles of substrate) follows the trend: **6** (39%) > **4** (37%) > **3** (31%) > **9** (29%) > **10** (17%) > **8** (16%) > **1** (15%).

As indicated earlier, the multicopper(II) catalytic systems require the presence of an acid cocatalyst (promoter). Nitric acid was used (typically 10 equiv relative to Cu compound) as a reference cocatalyst and the activity of Cu compounds depends significantly on the amount of this acid [7, 9, 11, 24]. For the compounds **3** [11], **6** [16], and **10** [24], the effects of other acid cocatalysts were studied. In the case of the dicopper complex $[\text{Cu}_2(\mu\text{-Hbdea})_2(\text{N}_3)_2]$ (**3**), the promoting effect of various acid cocatalysts in the C_6H_{12} oxidation by H_2O_2 follows the trend $\text{CF}_3\text{COOH} > \text{HNO}_3 \geq \text{HCl} > \text{H}_2\text{SO}_4 \gg \text{CH}_3\text{COOH}$ [11]. The type of acid cocatalyst is also a relevant factor that affects the reaction rate [16] in the cyclohexane oxidation catalyzed by $[\text{Cu}_4(\mu_4\text{-O})(\mu_3\text{-tea})_4(\mu_3\text{-BOH})_4][\text{BF}_4]_2$ (**6**), wherein all strong acids exhibit a noticeable promoting effect. However, the reaction is very fast only in the presence of HCl, being one order faster than those promoted by the other acids (HNO_3 , CF_3COOH , and H_2SO_4), resulting thus in the high turnover frequencies (TOFs) of circa 600 h^{-1} [16]. Another remarkable promoting behavior of HCl over HNO_3 was observed in the C_6H_{12} oxidation catalyzed by $[\text{Cu}_6(\mu\text{-H}_2\text{tea})_6\{\text{Fe}(\mu\text{-CN})_6\}]_n(\text{NO}_3)_{2n} \cdot 6n\text{H}_2\text{O}$ (**10**) [24]. The role of the acid cocatalyst presumably consists in (i) promoting proton transfer steps, (ii) activation of catalyst by unsaturation of the Cu(II) centers on ligand protonation, (iii) enhancement of oxidative properties of the catalyst and H_2O_2 , (iv) facilitation of the formation of peroxo complexes, and (v) preventing the decomposition of H_2O_2 to water and oxygen [7, 11, 16].

Besides the type and the amount of cocatalyst, the efficiency of Cu-catalyzed oxidations significantly depends on other factors, such as the amounts of oxidant (typically two- to fivefold molar excess relatively to substrate), catalyst (typically 1–3 mol% vs C_6H_{12}), and solvent (MeCN/ H_2O), reaction temperature, and time. To optimize the cyclohexane oxidation, the effects of these parameters were studied in detail for compounds **1** [7], **3** [11], **4** [7], **6** [7, 16], **8** [7], and **9** [9]. The mild oxidation of C_6H_{12} undergoes in aqueous acetonitrile medium, where water usually appears with aq. H_2O_2 and/or the catalyst solution. The use of the mixed MeCN/ H_2O solvent is essential to solubilize both substrate and catalyst, as the oxidation of cyclohexane does not occur to a considerable extent only in water as a sole solvent [7]. Another feature of the catalysts $[\text{Cu}_4(\mu_4\text{-O})(\mu_3\text{-tea})_4(\mu_3\text{-BOH})_4][\text{BF}_4]_2$ (**6**) and $[\text{Cu}_2(\mu_3\text{-H}_2\text{tea})_2(\mu_4\text{-pma})\{\text{Na}_2(\text{H}_2\text{O})_4\}]_n \cdot 10n\text{H}_2\text{O}$ (**9**) consists in the possibility of their recycling [7, 9], because they can maintain almost full activity even after five (**6**) or three (**9**) reaction cycles in the cyclohexane oxidation.

The complexes **4** and **6** can also be applied for the oxidation of inert gaseous alkanes, methane, and ethane, although less effectively than in the case of cyclohexane [6]. Thus, methanol (TON = 47, 2.2% yield) and ethanol (TON = 23, 2.1% yield) are obtained in the oxidation of CH_4 and C_2H_6 , respectively, using the **6**/ HNO_3 / H_2O_2 system [6]. Besides, bond-, regio-, and stereoselectivity studies were carried out [16, 17] with the most versatile catalyst **6** in the oxidation by H_2O_2 of methylcyclohexane (MCH), *cis*- and *trans*-1,2-dimethylcyclohexanes (*cis*- and *trans*-DMCH), *n*-heptane, and *n*-octane. The observed selectivity parameters suggest the involvement of hydroxyl radicals as active oxidizing species [16]. The radical type of mechanism was also supported by studying the effects of various C- and O-centered radical traps [CBrCl₃, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), and diphenylamine], which strongly decrease the yields of main products in cyclohexane oxidation [7].

A simplified mechanistic pathway (Scheme 3.4) in Cu-catalyzed alkane oxidations by H_2O_2 involves the H-abstraction from alkane (RH) presumably by the hydroxyl radical HO^\bullet , generated through the Cu-assisted decomposition of H_2O_2 (reactions 1, 2), furnishing the alkyl radical R^\bullet (reaction 3) [1a, 16, 28, 29]. Then R^\bullet rapidly reacts with O_2 to form



Scheme 3.4 Simplified mechanism for the Cu-catalyzed oxidation of alkanes (RH) by H_2O_2 to alkyl hydroperoxides (ROOH), alcohols (ROH), and ketones ($\text{R}'=\text{O}$). Multicopper catalyst precursor and derived species are schematically depicted as LCu^{II} and LCu^{I} . Adapted from Reference 16.

the organoperoxy radical ROO^\bullet (reaction 4). The ROO^\bullet can be reduced by a LCu(I) species to the corresponding anion that is further converted into the main primary alkyl hydroperoxide product, ROOH (reactions 5, 6). This undergoes the Cu-assisted homolytic decomposition giving the alkoxy RO^\bullet and alkylperoxy ROO^\bullet radicals (reactions 7, 8). The RO^\bullet radicals are converted to the alcohol (ROH) by H-abstraction from the alkane (reaction 9), whereas the peroxy radicals dismutate (reaction 10) to yield both the alcohol and the ketone ($\text{R}' = \text{O}$) [2a, 16, 28, 30].

3.5 APPLICATION IN ALKANE HYDROCARBOXYLATION

The direct carboxylation of alkanes by CO to give carboxylic acids is a very attractive transformation [12–15, 18–22], as aliphatic carboxylic acids are important commodity chemicals [27]. However, their industrial synthetic methods still represent a number of limitations [20, 27], such as the use of relatively expensive olefins and aldehydes as starting materials, the requirement of harsh reaction conditions, multistage transformations, and expensive metal catalysts.

We have recently developed a new and cleaner method for the direct and highly efficient hydrocarboxylation of various C_n alkanes into the corresponding C_{n+1} carboxylic acids [18, 31]. It consists in reacting an alkane with CO, H_2O , and $\text{K}_2\text{S}_2\text{O}_8$, and in the presence of Cu-catalyst (Scheme 3.5). In contrast to prior alkane carboxylation methods [32, 33], this protocol does not require absolute trifluoroacetic acid as a solvent, and undergoes efficiently at mild temperatures ($50\text{--}60^\circ\text{C}$) and in aqueous acid-solvent-free medium ($\text{H}_2\text{O}/\text{MeCN}$ mixed solvent), wherein water also plays a main role as a reagent, apart from being a component of the solvent system [18].

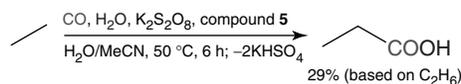
Interestingly, these hydrocarboxylation reactions also occur to some extent in metal-free systems, but the reaction efficiency can be improved significantly by the use of metal catalysts or promoters [18]. Among the variety of different transition metal catalysts, multicopper(II) compounds were usually the most active ones [18, 20], leading to product yields that are circa two to five times superior to those in the metal-free systems. The water-soluble tetracopper(II) complex $[\text{Cu}_4(\mu_4\text{-O})(\mu_3\text{-tea})_4(\mu_3\text{-BOH})_4][\text{BF}_4]_2$ (**6**) was formerly used as a model catalyst in the hydrocarboxylations of $\text{C}_2\text{--C}_6$ alkanes [18, 31]. Since then, the reactions have been optimized further [19–21] and extended to other alkanes and multicopper catalysts, namely including the dimer **2** [22], the trimer **5** [13], the tetramer **7** [14], and the polymers **11** [12], **12** [12], **13** [14], and **15** [15] (Table 3.1). Interestingly, in contrast to alkane oxidation, the hydrocarboxylation reactions do not require an acid cocatalyst.

Although the hydrocarboxylation of methane to acetic acid has so far been unsuccessful [18, 19], other quite inert gaseous $\text{C}_2\text{--C}_4$ alkanes can be transformed into the corresponding C_{n+1} carboxylic acids, when using the compounds **5**, **6**, **7**, and **11–13** as catalysts or catalyst precursors. Owing to the presence of only primary carbon atoms, C_2H_6 is the least reactive alkane, the selective transformation of which to propanoic acid occurs with reasonable efficiency (up to 29% yield based on substrate) in the presence of **5** [13] (Scheme 3.6).

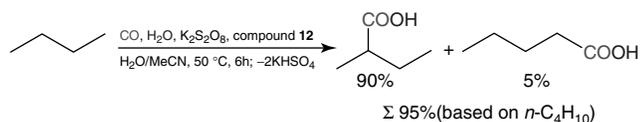
Similarly, propane can be transformed into a mixture of 2-methylpropanoic and butanoic acids, whereas n -butane gives 2-methylbutanoic and pentanoic acids [12, 18, 19]. Although the yields of linear carboxylic acids typically do not exceed 5–9%, the presence of significantly more reactive secondary carbon atoms in these alkanes facilitates their efficient conversion into the branched acids (main products). In these hydrocarboxylation reactions, the hydrosoluble compounds **7** and **11–13** are highly active, exhibiting comparable product yields because of the presence of resembling tetracopper(II) $\{\text{Cu}_4(\mu\text{-Hbes})(\mu\text{-COO})\}^-$ cores [12, 14]. The maximum total yields of carboxylic acids attain values of 78% and 95% (Scheme 3.7) when using catalyst precursor **12** in the reactions of C_3H_8 and $n\text{-C}_4\text{H}_{10}$, respectively [12].



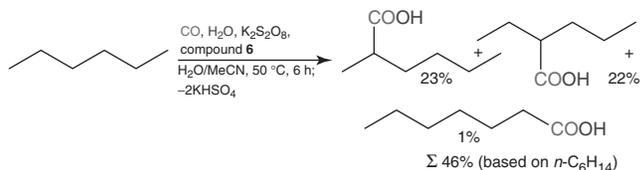
Scheme 3.5 General scheme for the hydrocarboxylation of C_n alkanes to C_{n+1} carboxylic acids. Adapted from Reference 18.



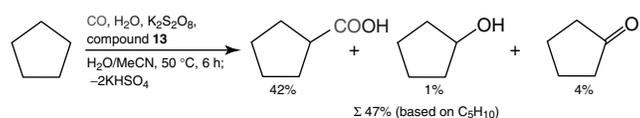
Scheme 3.6 Hydrocarboxylation of ethane to propanoic acid.



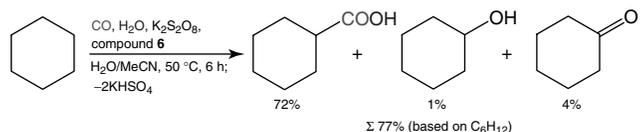
Scheme 3.7 Hydrocarboxylation of *n*-butane to 2-methylbutanoic and propanoic acids.



Scheme 3.8 Hydrocarboxylation of *n*-hexane to 2-methylhexanoic, 2-ethylpentanoic, and heptanoic acids.



Scheme 3.9 Hydrocarboxylation of cyclopentane to cyclopentanecarboxylic acid (major product). Cyclopentanol and cyclopentanone are formed as by-products of oxidation.

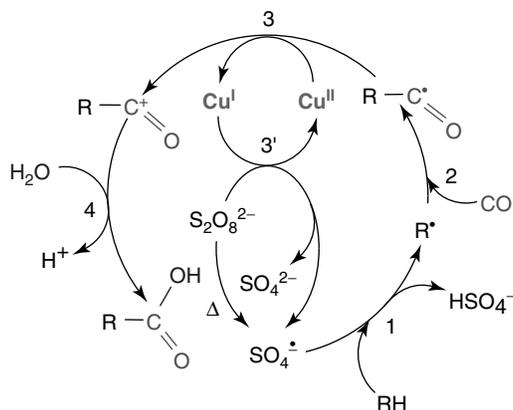


Scheme 3.10 Hydrocarboxylation of cyclohexane to cyclohexanecarboxylic acid (major product). Cyclohexanol and cyclohexanone are formed as by-products of oxidation.

Multicopper(II) catalytic systems are also efficient in the hydrocarboxylation of linear C_5 – C_9 alkanes [14, 15, 18, 21, 22], generating a mixture of isomeric monocarboxylic acids. Branched acids are the major products derived from the hydrocarboxylation at different secondary C(2), C(3), C(4), or C(5) carbon atoms of the alkane chain, while the corresponding fatty acids are formed in minor amounts (<2% yield). *n*-Pentane and *n*-hexane (Scheme 3.8) are more reactive substrates, giving 39% and 46% total product yields when using catalysts **2** and **6**, respectively [14, 21]. The hydrocarboxylation reactions of higher alkanes are less efficient [14, 21, 22], leading to the maximum total product yields of 26% (n - C_7H_{16}), 22% (n - C_8H_{18}), and 18% (n - C_9H_{20}), when using catalyst precursors **13**, **2**, and **6**, respectively.

Cyclic C_5 – C_8 alkanes also undergo hydrocarboxylation to give the corresponding cycloalkanecarboxylic acids [13–15, 18, 20, 22]. The formation of only one carboxylic acid product is observed because of the presence of a single type of carbon atoms in these cycloalkanes. Cyclopentane and cyclohexane were the most reactive cycloalkane substrates [13, 14, 20]. Their transformations (Schemes 3.9 and 3.10) result in cyclopentanecarboxylic and cyclohexanecarboxylic acids in up to 42% (with **13**) and 72% (with **6**) yields, respectively [14, 18]. The hydrocarboxylation reactions of cycloheptane and cyclooctane are less efficient [14, 15], with the highest yields of cycloheptanecarboxylic (29%) and cyclooctanecarboxylic (14%) acids achieved in the presence of **7** and **15**, respectively. In contrast to linear alkanes, the reactions involving cycloalkanes as substrates [13–15, 18, 20, 22] also generate the oxidation products (cyclic ketones and alcohols).

Given the high activity of the tetracopper(II) complex **6**, the hydrocarboxylations of ethane, propane, *n*-butane, *n*-pentane, cyclopentane, *n*-hexane, and cyclohexane were optimized to a variety of reaction parameters, including solvent composition, temperature, time, CO pressure, and relative amounts of substrate, oxidant, and catalyst [18–21]. The solvent composition is a reaction parameter of crucial importance [18, 19], as the hydrocarboxylation reactions practically do not occur in either only H_2O or only MeCN, or in the absence of both of them. Acetonitrile solubilizes the organic species, while water



Scheme 3.11 Simplified mechanism for the Cu-catalyzed hydrocarboxylation of alkanes (RH) to carboxylic acids (RCOOH). Adapted from Reference 14.

dissolves the catalyst and peroxodisulfate oxidant, also providing the main source of the hydroxyl group for the carboxylic acid. The optimal solvent compositions for linear and cyclic alkanes typically consist of 1 : 2 or 1 : 1 H₂O/MeCN volumetric ratios, respectively [18–21]. The use of K₂S₂O₈ is also indispensable, as it acts as both a radical initiator and an oxidant, and the hydrocarboxylation reactions do not occur in its absence or on its substitution for O₂, H₂O₂, or *t*-BuOOH [14, 18, 19]. An important feature consists in the fact that K₂S₂O₈ is almost quantitatively transformed during the reaction to give KHSO₄ [18, 20], which can be easily crystallized, separated by filtration, and potentially reconverted to peroxodisulfate via established electrochemical processes [18–20].

A simplified mechanistic pathway (Scheme 3.11) was proposed [14, 15, 18] for the Cu-catalyzed hydrocarboxylation of various alkanes (RH) on the basis of experimental data, including the analysis of various selectivity parameters [14, 18–21], tests with radical traps [18–20] and ¹⁸O-labeled H₂O [18], DFT calculations, and other studies [18, 33]. It includes the following steps [12–15, 18–22]: (1) generation of the alkyl radicals R• from an alkane [formed via H-abstraction by sulfate radical SO₄^{•-} derived from K₂S₂O₈], (2) carbonylation of R• by CO to form the acyl radicals RCO•, (3) oxidation of RCO• by copper(II) species to the acyl cations RCO⁺ (with concomitant formation of Cu(I) species), (3') the regeneration of the Cu(II) species on oxidation of Cu(I) by K₂S₂O₈, and (4) the hydrolysis of RCO⁺ to furnish the carboxylic acid products. The step (4) was also confirmed [18] on the basis of experiments with ¹⁸O-labeled H₂O in the hydrocarboxylation of C₆H₁₂, and theoretical calculations on ethane hydrocarboxylation. The active role of sulfate radical SO₄^{•-} was supported by various selectivity tests, while the involvement of alkyl radicals was also proved by performing carboxylation reactions in the presence of the carbon-centered radical trap CBrCl₃ [18–20].

The described alkane hydrocarboxylations show a number of important features. In particular, very high product yields (up to 95% based on alkane) can be attained [12–15, 18–22], especially considering the exceptional inertness of saturated hydrocarbons and the fact that such reactions involve C–H bond cleavage, C–C bond formation, and proceed in an acid-solvent-free H₂O/MeCN medium 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.

3.6 CONCLUDING REMARKS

This chapter showed that various multicopper(II) complexes and coordination polymers bearing different di-, tri-, and tetracopper aminoalcoholate cores can be easily generated by aqueous medium self-assembly method, using simple and commercially available chemicals. Apart from representing a number of important features (e.g., solubility in water and structural diversity), these multicopper(II) compounds act as highly efficient catalysts or catalyst precursors for the oxidation and hydrocarboxylation of various alkanes, under mild conditions. Although the described single-pot protocols for the Cu-catalyzed transformation of alkanes to alcohols, ketones, or carboxylic acids are characterized by a variety of advantages (i.e., high yields, mild reaction conditions, use of aqueous medium, and good substrate versatility and selectivity), further exploration and optimization of both alkane oxidation and hydrocarboxylation reactions to overcome some limitations

of the current systems should be continued. These consist of searching for other cheaper and cleaner oxidants and solvents, carbonylating agents, recyclable catalysts, and more favorable reaction conditions.

Although a rational design of highly efficient and versatile metal complex catalysts still remains a difficult task, the analysis of multicopper compounds that have already shown recognized applications in the oxidation and hydrocarboxylation of alkanes helps to identify some favorable requirements for a desirable homogeneous copper catalyst. These 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 multicopper 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. We believe that future research in the field of Cu-catalyzed oxidative functionalization of alkanes should envisage the development of both synthetic and catalytic directions, by widening the type of multicopper(II) catalysts, alkane substrates, and the respective catalytic transformations.

ABBREVIATIONS

aq.	Aqueous
Bis–Tris	See H ₅ bts
<i>cis</i> -DMCH	<i>cis</i> -1,2-Dimethylcyclohexane
CyOOH	Cyclohexyl hydroperoxide
DFT	Density functional theory
equiv	Equivalents
GC	Gas chromatography
H ₂ bdea	<i>N</i> -Butyldiethanolamine
H ₂ edea	<i>N</i> -Ethyldiethanolamine
H ₂ tpa	Terephthalic acid
H ₃ bes	<i>N, N</i> -Bis(2-hydroxyethyl)-2-aminoethanesulfonic acid
H ₃ tea	Triethanolamine
H ₄ pma	Pyromellitic acid
H ₅ bts	Bis–Tris (bis(2-hydroxyethyl)amino-tris(hydroxymethyl)methane)
Hba	Benzoic acid
Hmhba	3-Hydroxybenzoic acid
Hphba	4-Hydroxybenzoic acid
MCH	Methylcyclohexane
pMMO	Particulate methane monooxygenase
poba	4-Oxybenzoate(2–)
rt	Room temperature (20–25 °C)
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TOF	Catalyst turnover frequency (moles of products per mol of catalyst per hour)
TON	Catalyst turnover number (moles of products per mol of catalyst)
<i>trans</i> -DMCH	<i>trans</i> -1,2-Dimethylcyclohexane.

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ACTIVATION OF C–O AND C–F BONDS BY PINCER–IRIDIUM COMPLEXES

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4.1 INTRODUCTION

Pincer-ligated metal complexes have displayed extraordinarily rich chemistry and have found widespread use in catalysis. Pincer complexes of numerous transition metals have been synthesized, but the most well-studied probably involve Ru, Rh, Ir, and Pd [1–7]. Our group has largely focused on pincer–iridium complexes, which have shown a strong tendency toward the activation of C–H bonds. These complexes have been found to effect the oxidative addition of a variety of C–H bonds including those with sp^2 - and sp -hybridized carbon [8–10]. Most notable, however, has been the activation of $C(sp^3)$ –H bonds, leading to alkane dehydrogenation [6, 7].

The first pincer–iridium-based alkane dehydrogenation catalyst, $(PCP)IrH_2$ ($PCP = \kappa^3-C_6H_3-2, 6-[CH_2P(t-Bu)_2]_2$) (**1-H₂**), was reported by Kaska and Jensen [11] in the mid-1990s, and is active for the transfer dehydrogenation of *n*-alkanes and cycloalkanes, a reaction that we have developed and studied mechanistically [12–17]. The initial success of $(PCP)Ir$ in transfer dehydrogenation was followed by the development of a series of (pincer)Ir catalysts with varied steric and electronic properties [18–20]. We subsequently combined the high activity for C–H bond activation of (pincer)Ir complexes with Schrock-type olefin metathesis catalysts to afford a novel tandem process for alkane metathesis, relying on (pincer)Ir to dehydrogenate *n*-alkanes to olefins, followed by olefin metathesis to generate two new olefins, and then subsequent hydrogenation of these olefins by $(pincer)IrH_2$ to yield two new alkanes [21–23]. We have also found that certain pincer–iridium complexes are capable of taking *n*-alkanes to arenes through multiple dehydrogenations and subsequent electrocyclization (dehydroaromatization) [20]. Taken together, these three processes (dehydrogenation, alkane metathesis, and dehydroaromatization) hold great potential for converting low value *n*-alkanes into valuable fuels, feedstock, and commodity chemicals; these reports have been reviewed [6, 24].

This ability of $(PCP)Ir$ to oxidatively add covalent bonds has been found to extend to O–H [25, 26], N–H [27–29], and C–I [30] bonds. We have also found that the Ir–H bond resulting from alkynyl C–H addition could add across an acetylene triple bond to give a vinyl–alkynyl iridium complex that undergoes C–C elimination to give the corresponding enyne [10]. This led us to study C–C elimination from a range of complexes $(PCP)IrRR'$ [30]. Some of this chemistry is illustrated in Fig. 4.1. We were interested in extending this work to the elimination of other C–X bonds, including X = O. Density functional theory (DFT) calculations suggested, however, that such reactions might be thermodynamically favorable in the direction of oxidative addition; this made such studies all the more intriguing. Herein, we describe our efforts toward oxidative addition of C–O [31, 32] bonds by $(PCP)Ir$, subsequently extended to C–F [33] bonds, and in both cases extended to 1,2-H–X elimination. Quite surprisingly, these transformations all occur via the addition of $C(sp^3)$ –H bonds.

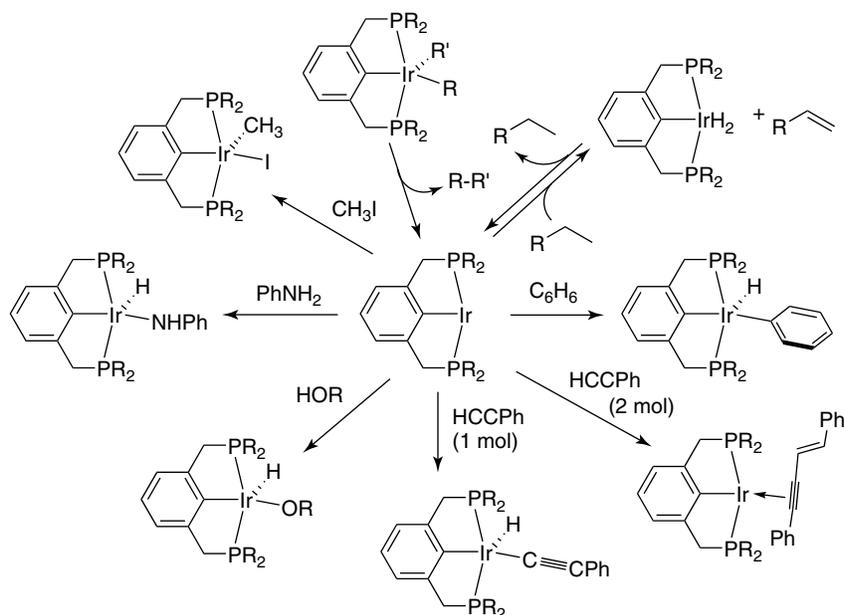
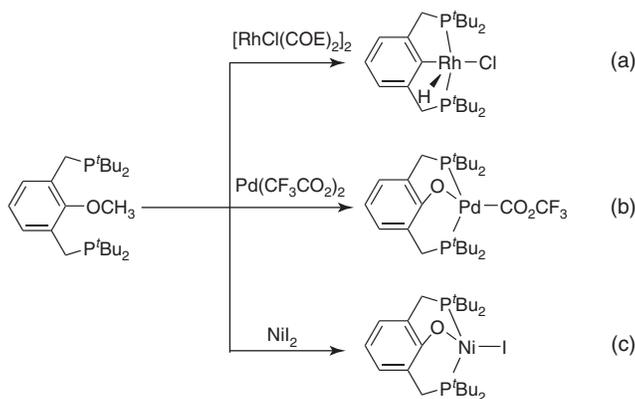


Figure 4.1 Some reactions of (PCP)Ir complexes.

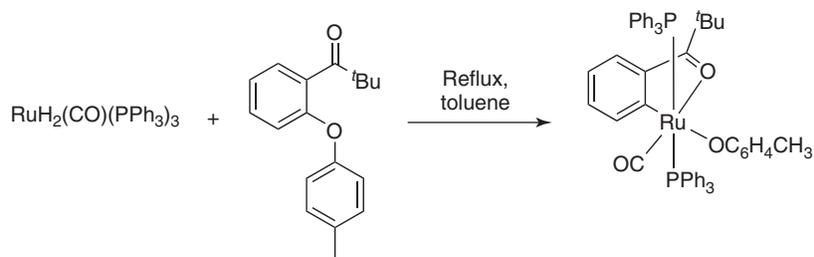


Scheme 4.1

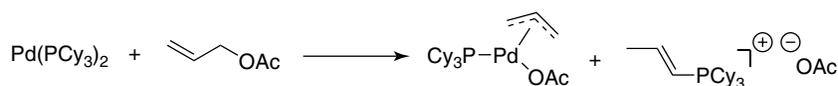
4.2 CLEAVAGE AND OXIDATIVE ADDITION OF C–O BONDS

4.2.1 Introduction

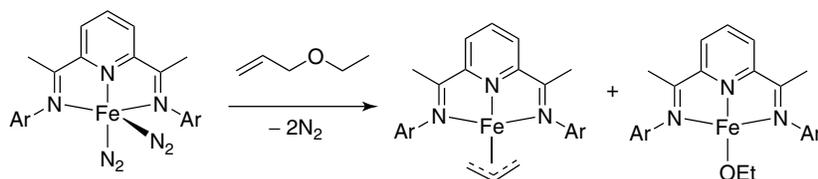
The oxidative addition to metal centers of unactivated C–O bonds, and particularly C(sp³)–O bonds, is not common. Before this work, there was only one well-characterized example of intermolecular oxidative addition of a C(sp³)–O ether bond (discussed below) [34, 35]. In the late 1990s, Milstein and coworkers [36, 37] reported several examples of intramolecular cleavage of C(sp³)–O and C(sp²)–O bonds of an analogous (PCP) ligand, where the phosphine moieties coordinate to the metal complex and serve to direct activation of the C–O bond on the aryl ring of the ligand. Interestingly, the authors found that they could control the selectivity of C(sp³)–O versus C(sp²)–O cleavage based on the metal complex employed; nucleophilic Rh(I) complexes yielded aryl C–O bond cleavage to afford (PCP)Rh complexes (Scheme 4.1a), while electrophilic Pd(II) or Ni(II) complexes afforded alkyl C–O bond cleavage giving rise to phenoxy-ligated metal complexes (Scheme 4.1b and c) [38]. Further, Kakuichi [39] later observed direct aryl C–O oxidative addition to Ru directed by a pendant ketone (Scheme 4.2).



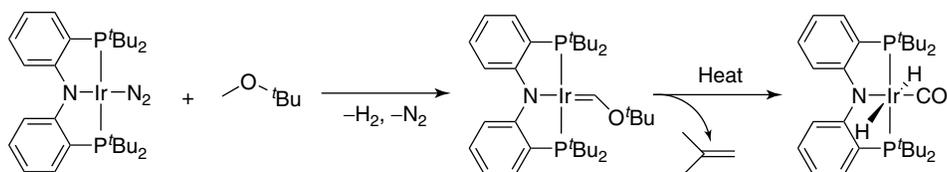
Scheme 4.2



Scheme 4.3



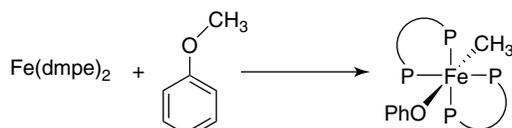
Scheme 4.4



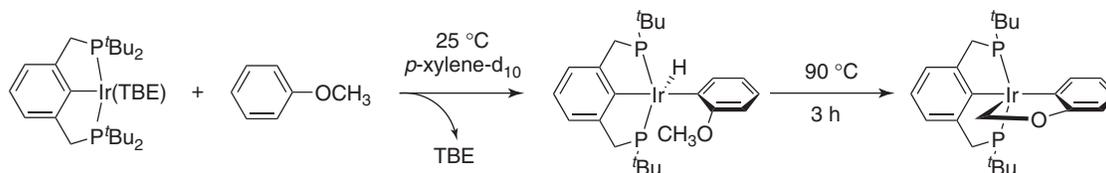
Scheme 4.5

Examples of intermolecular cleavage of “activated” C–O bonds are well preceded, for example, involving allylic C–O bonds. Early work by Yamamoto [40, 41] revealed cleavage of allylic C–O bonds in acetates and ethers, likely proceeding via a π -allyl mechanism (Scheme 4.3). More recently, Chirik [42] reported the activation and cleavage of allylic ethers and acyl/ester C–O bonds by bis(imido)pyridine iron complexes (Scheme 4.4). Carmona and Paneque [43–45] have reported the extraordinary rearrangement reactions of methyl aryl ethers by a tris(pyrazolyl)borate iridium complex involving cleavage of the methyl–oxygen bond. Grubbs and Ozerov [46] have investigated the reactions of (PNP)Ir and anthrphos-based (PCP)Ir complexes with methyl *t*-butyl and methyl benzyl ether, resulting in methoxy C–H activation and the formation of alkoxy carbene complexes (Scheme 4.5) found to be active for multiple-bond metatheses with various electrophilic heterocumulenes (e.g., CO₂, CS₂, and AdN₃). Remarkably, the formation of a carbonyl ligand results from the cleavage of every bond to the original ether methoxy carbon *except* the C–O bond [47, 48]. To our knowledge, however, the only example before this work of “simple” intermolecular oxidative addition of an unactivated C(sp³)–O bond was reported by Ittel and Tolman [34, 35] who observed cleavage of the C–O bond of anisole by the highly nucleophilic Fe(dmpe)₂ (Scheme 4.6).

During the course of this work, Ozerov et al. and Jones et al. [48, 49] reported C(sp³)–O bond addition in the reactions of benzyl methyl ether with an Ir complex and methyl benzoate with a Pt complex, respectively.



Scheme 4.6



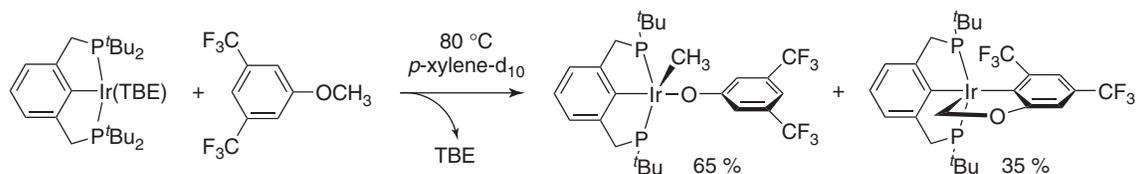
Scheme 4.7

4.2.2 Cleavage and Oxidative Addition of Aryl Alkyl Ether C(sp³)–O Bonds

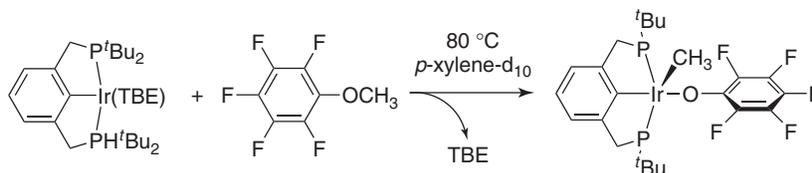
Our exploration of the reactivity of (PCP)Ir toward C–O bonds began with anisole. At room temperature, we observed immediate formation of product resulting from oxidative addition of the aryl C–H bond *ortho* to the methoxy substituent, which was spectroscopically analogous to (but significantly more thermodynamically stable than) the previously reported (PCP)Ir(Ph)(H) complex [8]. In an effort to effect subsequent C–O bond activation, (PCP)Ir(H)(*o*-C₆H₄OCH₃) was heated for 3 h at 90 °C, but this yielded exclusively the cyclometalated product arising from activation of the methoxy C(sp³)–H bond (Scheme 4.7).

In order to disfavor aryl C–H addition, and hopefully thereby allow C–O addition to proceed, we investigated anisole derivatives in which the *ortho*-C–H bonds were either replaced with *ortho*-methyl groups or sterically blocked by *meta*-methyl groups. Unfortunately, reactions with either 2,6-dimethylanisole or 3,5-dimethylanisole resulted in complex mixtures that showed no indication of the desired C–O activation products.

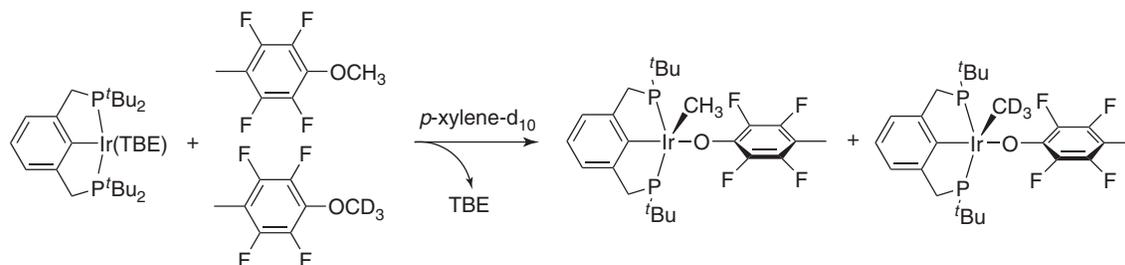
We considered that electron-withdrawing groups could be used to favor C–O addition as well as blocking C–H addition. Indeed, addition of 3,5-bis(trifluoromethyl)anisole to a solution of (PCP)Ir(TBE) resulted in formation of the C–O cleavage product, (PCP)Ir(CH₃)[*O*-3,5-C₆H₃(CF₃)₂] (65%) as well as *ortho*-cyclometalated product (35%) (Scheme 4.8). Pentafluoroanisole gave quantitative conversion at room temperature to the C–O addition product, (PCP)Ir(CH₃)(OC₆F₅) (Scheme 4.9) [31]. These results were only the second example of *intermolecular* oxidative addition of an unactivated ether C(sp³)–O bond (three decades after the first such report, noted earlier, by Ittel and Tolman [34, 35].).



Scheme 4.8



Scheme 4.9



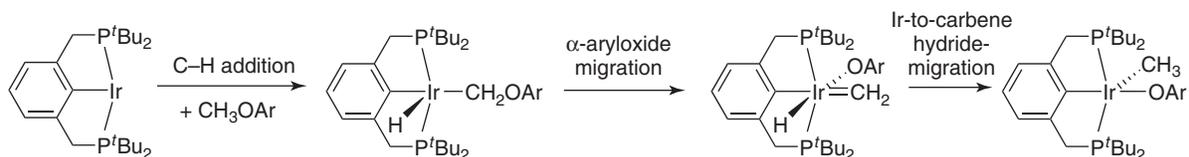
Scheme 4.10

Studies by Goldberg and Williams [50–52] have demonstrated that reductive elimination of C–O bonds (the reverse of oxidative addition) from Pt(IV) metal centers proceeds by dissociation of a hydroxide or phenoxide anion, which subsequently attacks the alkyl group to form an alcohol or ether. In view of the high nucleophilicity of $\text{Fe}(\text{dmpe})_2$, and the trans disposition of the added methyl and phenoxy groups, it seems quite likely that the mechanism proposed by Goldberg and Williams applies to the Ittel and Tolman system as well, with the metal complex attacking the anisole methyl group in an $\text{S}_{\text{N}}2$ manner. Such a mechanism would seem unlikely in the case of $(\text{PCP})\text{Ir}$, however, as its chemistry is dominated by the addition of nucleophiles or covalent bonds, rather than by any nucleophilicity of the complex. Accordingly, a kinetic isotope effect (KIE) competition experiment was conducted comparing the relative reactivity of 4-methoxy-2,3,5,6-tetrafluorotoluene and its CD_3 -deuterated analog (Scheme 4.10). A significant primary, normal KIE, $k_{\text{OCH}_3}/k_{\text{OCD}_3} = 4.3(3)$, was found at 25°C . This KIE is inconsistent with either a direct C–O oxidative addition mechanism or a nucleophilic attack on the methyl group, but instead indicates that cleavage of a C–H bond is involved in, or occurs before, the rate-determining step.

DFT calculations indicate that direct oxidative addition of the C–O bond of $\text{MeO}(p\text{-C}_6\text{F}_4\text{Me})$, via a three-centered transition state (TS), would have a prohibitively high activation barrier, with a computed TS free energy of 33.4 kcal/mol relative to free ether and $(\text{PCP})\text{Ir}$, using M06 functionals [32]. Relative to the precursor $(\text{PCP})\text{Ir}(\text{TBV})(\text{H})$, or a calculated resting state of $(\text{PCP})\text{Ir}(\text{MeOAr})$, the overall barriers would be circa 5 kcal/mol greater.

An alternative mechanism, proceeding through the initial addition of a methoxy C–H bond, shown in Fig. 4.2, is calculated to have an activation barrier that is nearly 18 kcal/mol lower than direct C–O oxidative addition ($\Delta G^\ddagger = 33.4$ kcal/mol). Addition of the $\text{C}(\text{sp}^3)\text{--H}$ bond adjacent to oxygen forms a five-coordinate Ir(III) intermediate, which undergoes α -aryloxy elimination to afford a methylidene complex. 1,2-Migration of the hydride from Ir to the methylidene ligand affords the observed C–O oxidative addition product. Figure 4.3 shows the Gibbs free energy profile for this mechanism.

The α -aryloxy migration is calculated to have a slightly lower barrier than the hydride-to-methylidene migration, but the difference is probably too small to be significant when comparing such different species. The calculations, however, predict a significant difference in the KIE depending on which of these steps is rate-determining. If the rate-determining step is hydride transfer (as suggested by the slightly higher barrier for this step than for α -aryloxy migration), the overall KIE is calculated to be 7.2, which is significantly greater than the experimental value. If α -aryloxy migration is rate-determining, however, the calculated KIE is 4.16, in excellent agreement with experiment. This value may be decomposed as the product of (i) the equilibrium isotope effect (EIE) for the pre-equilibrium of free ether plus $(\text{PCP})\text{Ir}$ precursor (e.g., $(\text{PCP})\text{Ir}(\text{TBV})\text{H}$) with the aryloxymethyl hydride/deuteride, calculated to be 3.13; and (ii) the secondary KIE for α -aryloxy migration, calculated as 1.33. The EIE of 3.13 is slightly higher than typical C–H(D) addition EIEs [53, 54]; this may be attributable to low Ir–H(D) bending frequencies in the addition product resulting from the shallow energy surface for deformation of the ligand arrangement in the equatorial plane of the five-coordinate d^6 complex [55]. The value of 1.33 (1.15 per C–H/D

Figure 4.2 Mechanism for the net oxidative addition of methyl aryl ether $\text{C}(\text{sp}^3)\text{--O}$ bonds via initial C–H activation.

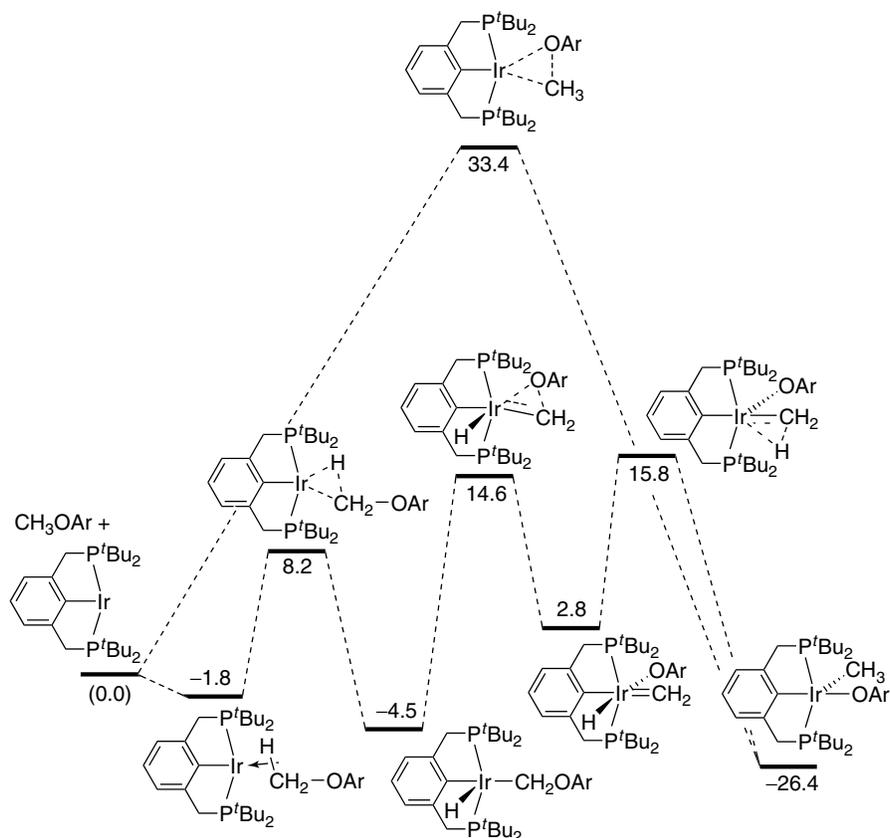
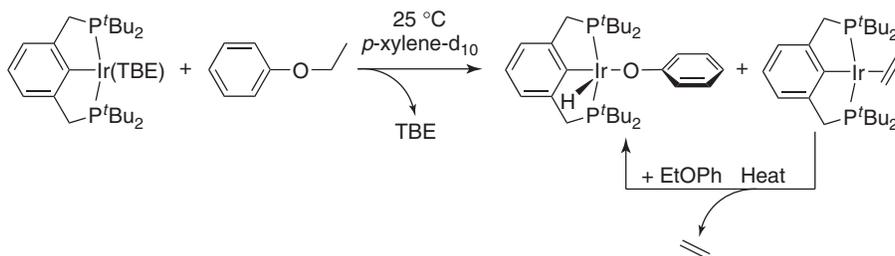


Figure 4.3 Calculated Gibbs free energies (in kcal/mol; relative to free (PCP)Ir and ether) for the reaction of (PCP)Ir with CH₃OAr, Ar = *p*-C₆F₄Me.

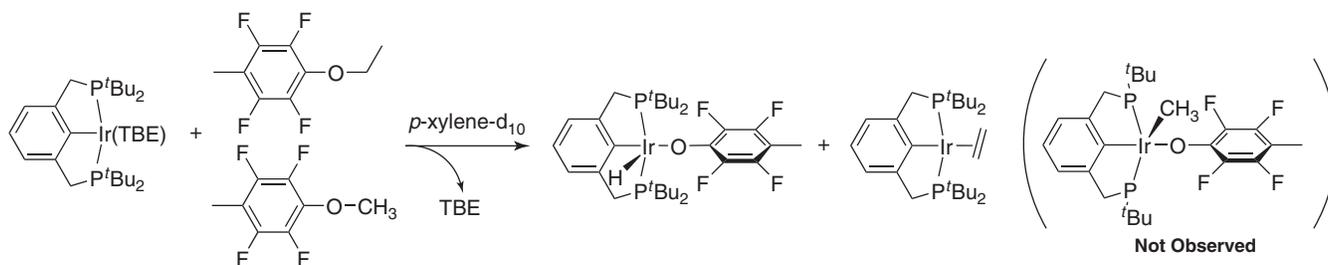
bond) may seem high for a secondary KIE, but it is fully consistent with the KIE reported for related S_N1 reactions of organic species with oxygenate-leaving groups, for which values above 1.2 per H/D atom are common [56–63].

4.2.3 1,2-H–OAr Eliminations of Ethers with Higher Alkyl Groups

Alkyl aryl ethers with a β-C(sp³)–H bond were also found to undergo C–O bond cleavage on reaction with (PCP)Ir, but of a distinctly different type than observed for methyl aryl ethers. Thus, ethoxybenzene reacts with (PCP)Ir at room temperature to give a 1 : 1 mixture of (PCP)Ir(H)(OPh) and (PCP)Ir(ethylene), which on heating at 125 °C eventually gives pure (PCP)Ir(H)(OPh) and free ethylene (Scheme 4.11). The net reaction is thus a 1,2-dehydroaryloxylation. As was found with methyl aryl ethers, enhanced reactivity is observed when the fluorinated analog, 4-ethoxy-2,3,5,6-tetrafluorotoluene,



Scheme 4.11



was employed, giving the analogous aryloxy hydride and ethylene products at room temperature, followed by full conversion to give exclusively the aryloxy hydride at 80 °C.

The observation that the C–O cleavage reaction of ethyl aryl ethers occurs without the need to block *ortho* C–H activation suggests that the 1,2-dehydroaryloxylation is a more facile reaction than the ether C–O oxidative addition. Accordingly a competition experiment, in which a mixture of 4-methoxy-2,3,5,6-tetrafluorotoluene and 4-ethoxy-2,3,5,6-tetrafluorotoluene was added to (PCP)Ir(TBE), resulted in exclusive formation of (PCP)Ir(H)(OAr) and (PCP)Ir(ethylene) (the products obtained from C–O cleavage of the ethyl ether), and no evidence of any reaction of the methyl ether (Scheme 4.12).

DFT calculations were employed to gain insight into the mechanism of the 1,2-dehydroaryloxylation. One possible pathway could involve initial direct C–O oxidative addition followed by β -hydride elimination; however, the earlier observations that direct C–O oxidative addition does not occur for methyl aryl ethers along with the observation that 4-ethoxy-2,3,5,6-tetrafluorotoluene reacts faster than 4-methoxy-2,3,5,6-tetrafluorotoluene (i.e., the substrate with the β -C–H bond reacts faster than the substrate with the α -C–H bond) would argue against such a mechanism. Accordingly, the barriers to direct C–O addition for 4-ethoxy-2,3,5,6-tetrafluorotoluene and ethoxybenzene were calculated to be prohibitively high, 35.0 and 40.8 kcal/mol, respectively. In contrast, the barriers for addition of the β -C–H bond followed by β -aryloxy elimination and loss of ethylene (Fig. 4.4) were found to be considerably lower (Fig. 4.5).

4.2.4 Oxidative Addition of Ester C(sp³)–O Bonds

The C(sp³)–O cleavage reactions observed for ethers were found to extend to other alkyl oxygenates, specifically esters and tosylates. In contrast with the methyl ether reaction, however, the reaction of methyl acetate proved more forthcoming with respect to mechanistic clues in the form of reaction intermediates. Methyl acetate (8.3 mmol) was observed to rapidly react with *in situ*-generated (PCP)Ir(TBV)(H) (8.3 mmol) at room temperature to yield (PCP)Ir(H)(κ^2 -CH₂-OAc), the product of carbomethoxy C(sp³)–H bond oxidative addition and coordination of the carbonyl oxygen (Scheme 4.13). Heating this species at 80 °C for 5 h affords a very surprising product, characterized spectroscopically and crystallographically (Fig. 4.6a), which apparently results from insertion of the iridium-bound methylidene group into the PCP *ipso*-C–Ir bond. Further heating to 125 °C for 6 h yields a mixture of the net product of oxidative addition of the methyl acetate methoxy C–O bond, (PCP)Ir(CH₃)(κ^2 -OAc), and the cyclometalated-pincer product, (κ^4 -PCP)Ir(κ^2 -OAc) (Fig. 4.6b), which appears to result from decomposition of (PCP)Ir(CH₃)(κ^2 -OAc) with the loss of methane.

DFT calculations were employed to study the mechanism of methyl ester C–O addition. A low barrier [8.4 kcal/mol relative to free (PCP)Ir and methyl acetate] was calculated for C–H addition to give (PCP)Ir(H)(κ^2 -CH₂OAc), the species that was observed to form at room temperature. This intermediate has two potential coordination isomers: one where

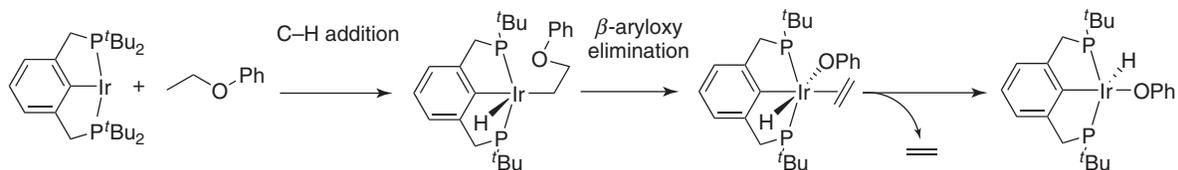


Figure 4.4 Mechanism of 1,2-dehydroaryloxylation of ethyl aryl ethers.

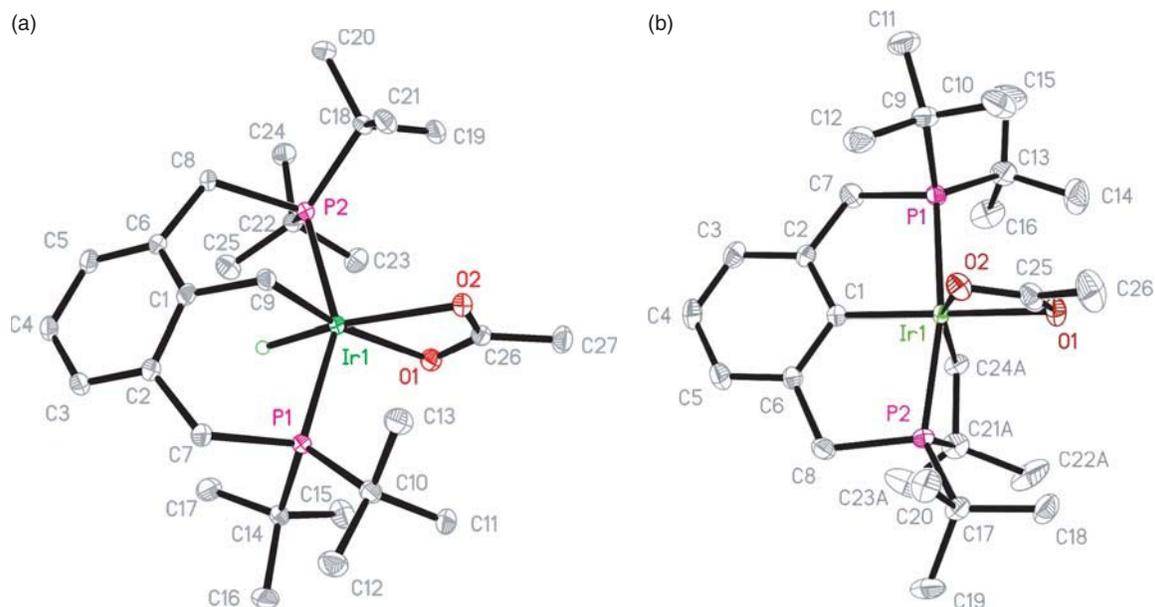


Figure 4.6 X-ray structures of (a) $(\text{PCP} - \text{CH}_2)\text{Ir}(\text{H})(\kappa^2\text{-O}_2\text{CMe})$ and (b) cyclometalated $(\text{PCP})\text{Ir}(\text{acetate})$, $[\kappa^4\text{-C}_6\text{H}_3\text{-2}-(\text{CH}_2\text{P}'\text{Bu}_2)\text{-6}-(\text{CH}_2\text{P}'\text{Bu}(\text{CMe}_2\text{CH}_2))]\text{Ir}(\kappa^2\text{-O}_2\text{CMe})$. (See insert for color representation of the figure.)

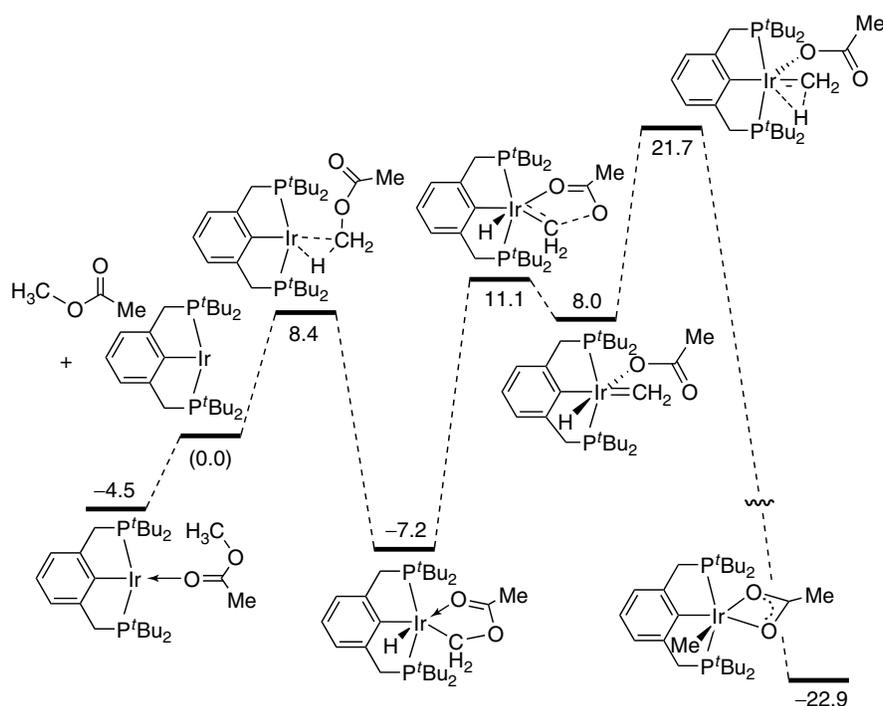


Figure 4.7 Calculated Gibbs free energies (in kcal/mol; relative to free $(\text{PCP})\text{Ir}$ and ester) for the reaction of $(\text{PCP})\text{Ir}$ with methyl acetate occurring via a *cis* methylene hydride intermediate (a hypothetical pathway, *not* proposed).

the iridium-bound methylene group is *cis* to the hydride (isolated experimentally) (Fig. 4.7), and one of slightly higher energy (by ca. 5 kcal/mol) with the methylene unit *trans* to the hydride (Fig. 4.8). For the experimentally observed C–H-*cis* isomer, a relatively low barrier (18.3 kcal/mol) was calculated for α -acetate migration, in analogy with the pathway proposed for C–O addition of the methyl aryl ether methoxy group. This migration is calculated to proceed via a

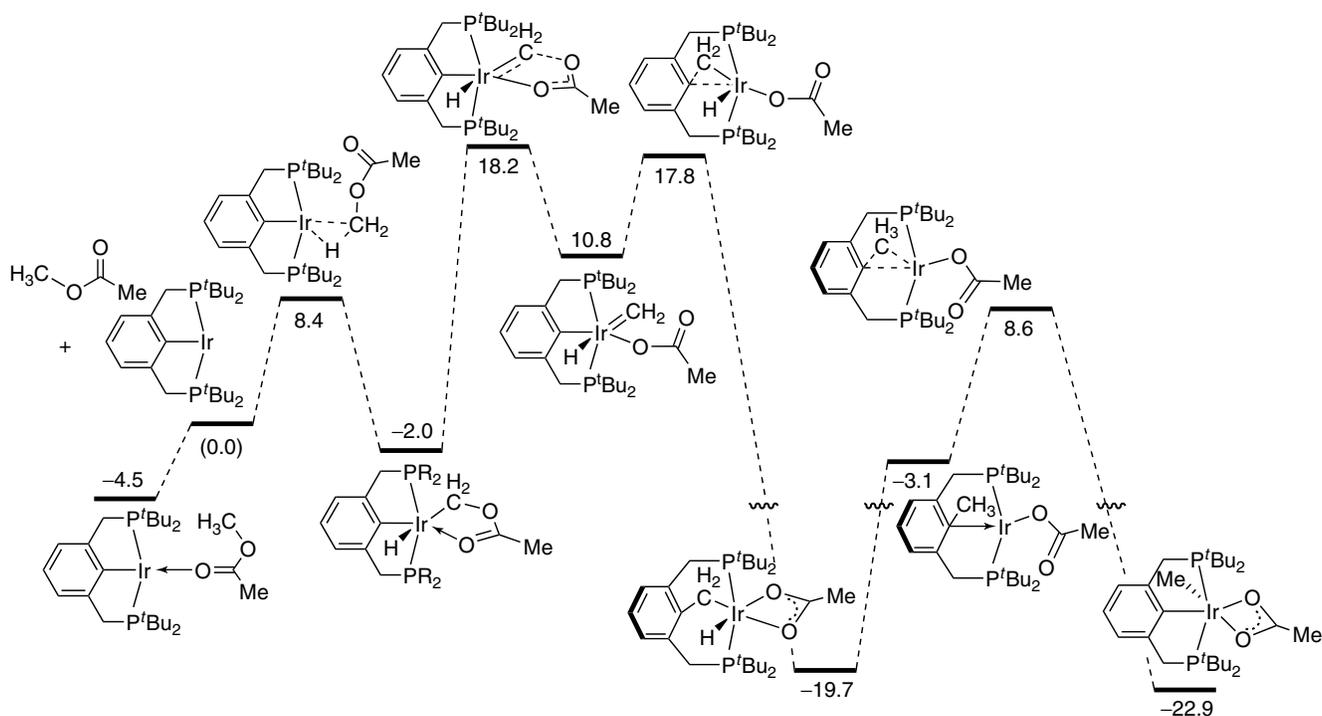
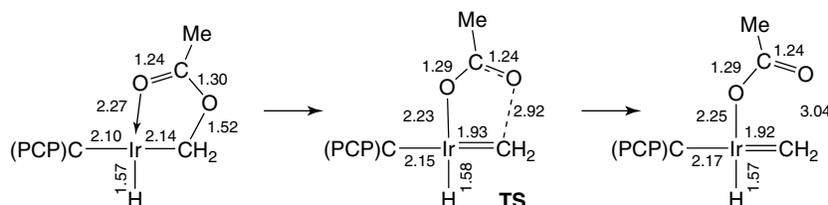


Figure 4.8 Calculated Gibbs free energies (in kcal/mol; relative to free (PCP)Ir and ester) for the reaction of (PCP)Ir with methyl acetate occurring via a *trans* methylene hydride intermediate (proposed pathway).



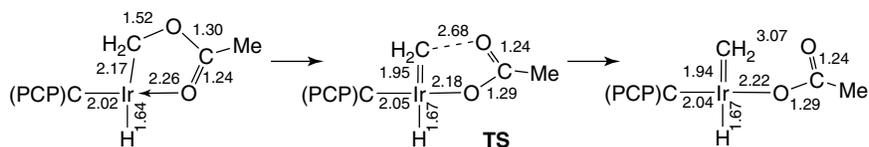
Scheme 4.14 Acetate migration by *cis*-(PCP)Ir(H)(κ^2 -CH₂OAc).

five-membered TS in which the dative bond with the carbonyl oxygen gives rise to a covalent iridium–acetate bond (Scheme 4.14). The resulting species *cis*-(PCP)Ir(H)(CH₂)(OAc) can then undergo iridium-to-methylidene hydride migration, which would give the observed C–O oxidative addition product. However, the barrier for this reaction, 28.9 kcal/mol (relative to C–H–*cis*(PCP)Ir(H)(κ^2 -CH₂OAc)) is fairly high; moreover, this pathway does not account for the experimental observation and isolation of (PCP-CH₂)Ir(H)(OAc).

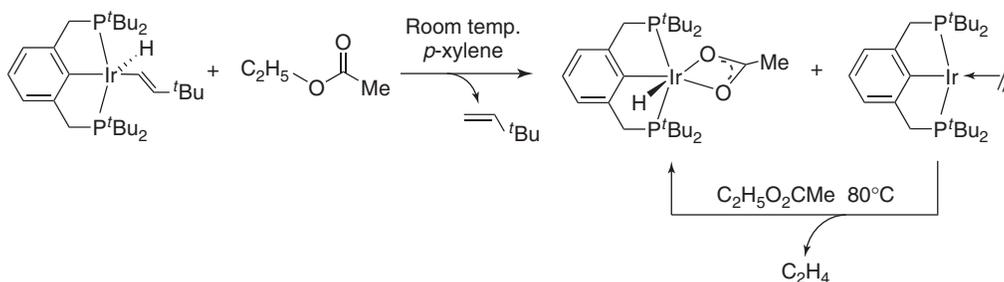
A low barrier is calculated for the conversion of *cis*-(PCP)Ir(H)(CH₂)(OAc) to the coordination isomer *trans*-(PCP)Ir(H)(CH₂)(OAc), which is circa 5 kcal/mol higher than the *cis* isomer. The *trans* isomer can then undergo α -acetate migration, as in the case of the *cis* isomer, with an analogous five-membered TS (Scheme 4.15).

The product of this migration, in which the methylidene and hydride are in a mutually *trans* disposition, is geometrically incapable of undergoing iridium-to-methylidene hydride migration. However, it can very readily (7.0 kcal/mol barrier) undergo an aryl *ipso*-carbon-to methylidene migration (Fig. 4.8); this gives the isolated (PCP-CH²)Ir(H)(OAc) intermediate. As is well preceded in the work by Milstein et al. [64, 65], such species may undergo C(PCP-CH₂)-H elimination followed by C–C cleavage; this results, in this case, in the formation of (PCP)Ir(CH₃)(κ^2 -OAc), the C–O oxidative addition product.

As with aryl ether substrates, we also investigated alkyl esters with alkyl groups higher than methyl. As with the higher alkyl ethers, such species undergo 1,2-H–O elimination instead of C–O oxidative addition. Ethyl acetate, for example,



Scheme 4.15 Acetate migration by *trans*-(PCP)Ir(H)(κ^2 -CH₂OAc).



Scheme 4.16 Transition state for β -acetate migration in the reaction of ethyl acetate.

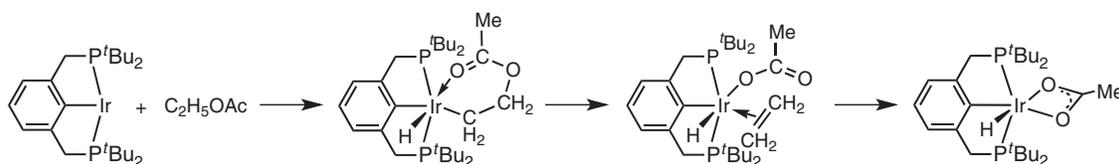
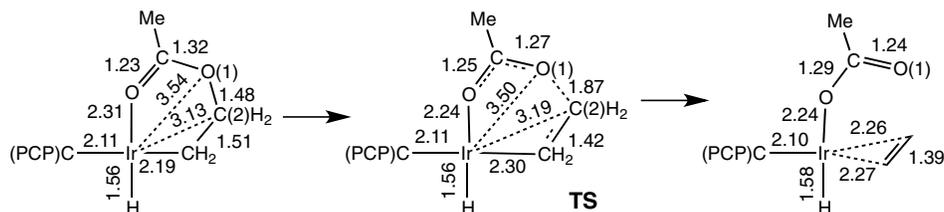


Figure 4.9 Mechanism for 1,2-H–OAc elimination from ethyl acetate.



Scheme 4.17 Transition state for β -acetate migration in the reaction of ethyl acetate.

readily reacts with (PCP)Ir(TBV)(H) at room temperature to afford a mixture of (PCP)Ir(H)(OAc) and (PCP)Ir(ethylene) [subsequent heating results in the loss of ethylene and quantitative conversion to (PCP)Ir(H)(OAc)] (Scheme 4.16), while isopropylacetate rapidly reacts to give (PCP)Ir(H)(OAc) and free propylene.

DFT calculations are consistent with a pathway for the H–OAc eliminations initiated by addition of the β -C–H bond, proceeding by the mechanism shown in Fig. 4.9. In the case of ethyl acetate, this yields the cyclometalated intermediate (PCP)Ir(κ^2 -CH₂CH₂OAc). This complex then undergoes β -acetate migration, cleaving the C–O bond to form the resulting ethylene-bound intermediate, (PCP)Ir(H)(OAc)(ethylene). The TS structure for the β -acetate migration (Scheme 4.17) is unusual, containing a six-membered ring in which the C–O bond is cleaved without any direct participation from the iridium center.

This TS has a free energy of 12 kcal/mol relative to free reactants, slightly higher in energy than the preceding TS for C–H activation (Fig. 4.10). The resulting ethylene complex can then lose ethylene to yield the product, (PCP)Ir(H)(κ^2 -OAc), while the free ethylene then reacts with (PCP)Ir(TBV)(H) to form the observed byproduct, (PCP)Ir(ethylene). A TS corresponding to the loss of ethylene from (PCP)Ir(H)(OAc)(ethylene) was not found, but olefin loss is calculated to be 4.5 kcal/mol

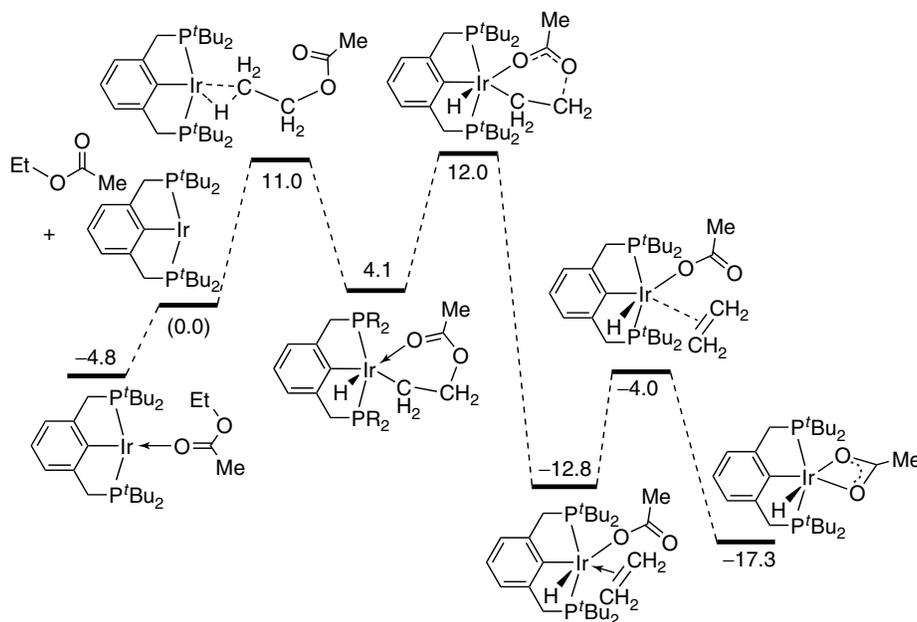


Figure 4.10 Calculated Gibbs free energies (in kcal/mol; relative to free (PCP)Ir and ethyl acetate) for the cleavage of the C–O bond of ethyl acetate by (PCP)Ir.

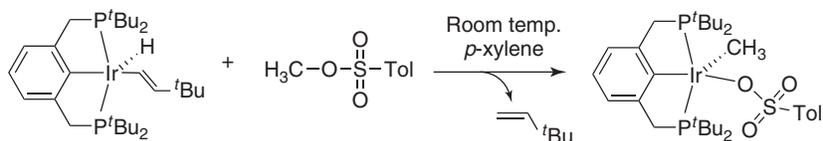
exergonic (entropically favored), and certainly the barrier to an exergonic ligand loss is expected to be much less than the circa 25 kcal/mol barrier to the acetate-migration back reaction.

4.2.5 Cleavage and Oxidative Addition of Tosylate C–O Bonds

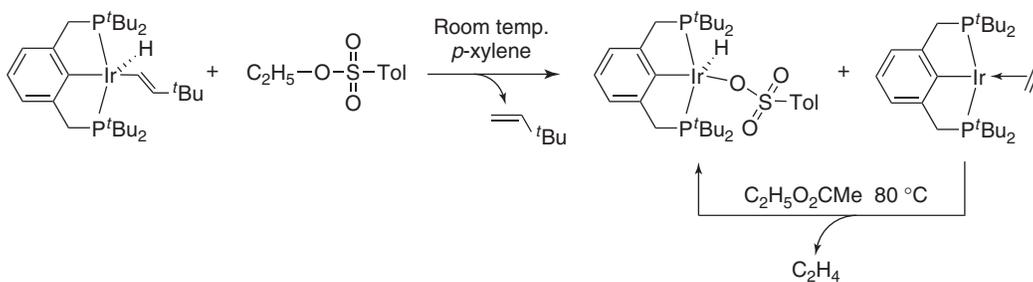
Methyl tosylate has also been found to react with (PCP)Ir to undergo C(sp³)–O oxidative addition. (PCP)Ir(TBV)(H) reacts rapidly at room temperature with methyl tosylate (1.1 equiv) to give the C–O oxidative addition product, (PCP)Ir(Me)(OTs), in quantitative yield (Scheme 4.18). KIE experiments involving competition between a 10-fold excess each of CH₃OTs and CD₃OTs yielded a KIE, $k_{\text{CH}_3}/k_{\text{CD}_3} = 2.4(2)$, that again indicates that C–H activation is involved during or before the rate-determining step.

Also in analogy with the ether and ester chemistry, ethyl tosylate reacts with (PCP)Ir(TBV)(H) at room temperature to quickly yield an equimolar mixture of (PCP)Ir(H)(OTs) and (PCP)Ir(ethylene), which on heating to 80 °C for several hours results in the loss of ethylene and full conversion to (PCP)Ir(H)(OTs) (Scheme 4.19).

DFT calculations indicate that the C–OTs addition proceeds analogously to the ether C–O additions (Fig. 4.11). Initial oxidative addition of the MeOTs methoxy C–H bond, calculated to be exergonic by 5.8 kcal/mol, is followed by α -migration of the OTs group with a barrier of 21.5 kcal/mol and a TS that is 15.7 kcal/mol above the free reactants. The TS for the subsequent Ir-to-methylidene hydride migration, to yield the observed C–O oxidative addition product, was calculated to have an essentially identical free energy (15.8 kcal/mol). Thus, the DFT calculations alone cannot reliably predict the identity of the rate-determining TS. However, these two TSs would each give rise to a very different overall OCH₃ / OCD₃ KIE for the C–O addition, depending on which is rate-determining. If α -OTs migration is rate-determining, the KIE is calculated to be



Scheme 4.18



Scheme 4.19

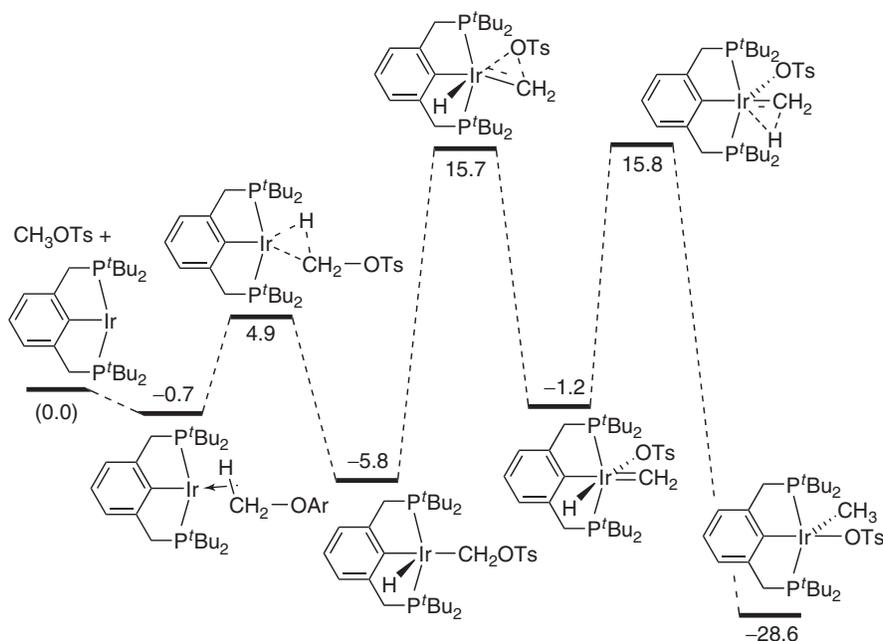


Figure 4.11 Calculated Gibbs free energies (in kcal/mol; relative to free (PCP)Ir and methyl tosylate) for the reaction of (PCP)Ir with methyl tosylate.

2.9, whereas a rate-determining step involving H-migration is predicted to yield a significantly greater KIE of 6.7. Comparing these values to our experimentally determined KIE of 2.4, we clearly see much better agreement with rate-determining α -OTs migration.

4.3 CLEAVAGE AND OXIDATIVE ADDITION OF C–F BONDS

Having made headway into facile C–O bond cleavage via initial C–H bond activation, we next sought to extend the same strategy to the activation of C–F bonds. Although oxidative addition of C–Cl, C–Br, and C–I bonds to metal centers is well studied [66], there is no precedent for oxidative addition of unactivated C(sp³)–F bonds. Thus, C(sp³)–F oxidative addition is even less well preceded than C(sp³)–O oxidative addition; perhaps, this is not surprising in the light of the greater bond dissociation energies of C(sp³)–F bonds (e.g., the C–F BDE of fluoromethane is 110 kcal/mol while the anisole C(sp³)–O BDE is only 65 kcal/mol) [67]. Note, however, there are numerous reported examples of C–F oxidative addition (and reductive elimination), generally involving fluorine bound to sp²-hybridized vinyl or aryl carbon atoms (Fig. 4.12) [68–81].

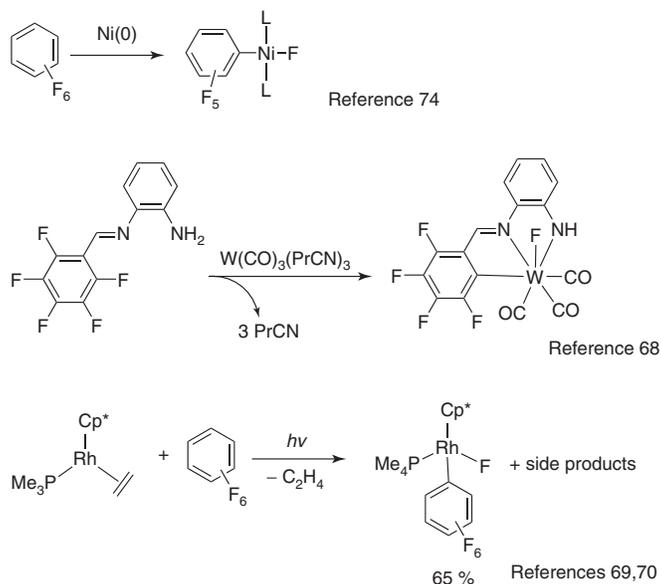
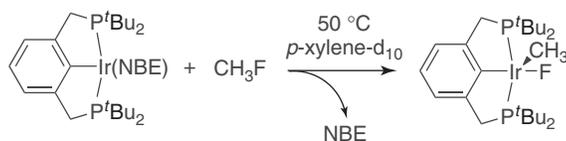
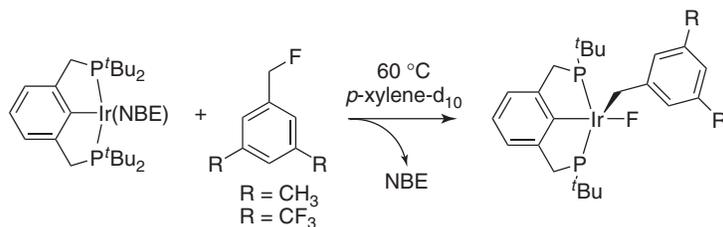


Figure 4.12 Some notable examples of oxidative addition of C_{sp^2} -F bonds to transition metal centers.



Scheme 4.20



Scheme 4.21

Nevertheless, the $C(sp^3)$ -OR cleavage chemistry indicated that the tendency toward oxidative addition correlated with the electron-withdrawing ability of the R group. This suggested that $C(sp^3)$ -F addition would be even more favorable than any of the $C(sp^3)$ -OR additions. Indeed, $(PCP)Ir(NBE)$ was found to react readily with fluoromethane at $50\text{ }^\circ\text{C}$ to yield a single major species, the oxidative addition product $(PCP)Ir(CH_3)(F)$ (Scheme 4.20) [33]. Likewise, benzyl fluoride derivatives [containing either methyl or trifluoromethyl substituents *meta* to the $-CH_2F$ group to prevent $C(sp^2)$ -H activation] also react readily at $60\text{ }^\circ\text{C}$ to afford $(PCP)Ir(F)(CH_2Ar)$ complexes (Scheme 4.21). In the case of the trifluoromethyl-substituted substrate, a clean conversion to the product in 95% yield is observed, while the methyl substituted substrate exhibits a lower yield (70%) with significant amounts of unidentified side products.

As in the case of the C–O addition reactions, a KIE was measured to probe the reaction pathway. $(PCP)Ir$ was reacted with a fivefold excess of 3,5-bis(trifluoromethyl)benzyl fluoride and its deuterated (CD_2F) analog at $60\text{ }^\circ\text{C}$ (Fig. 4.13). The KIE (k_{CH_2F}/k_{CD_2F}) was determined to be 2.7, indicating that the C–F addition proceeds via C–H addition. Analogously to the C–O additions, we propose that the reaction proceeds via the initial C–H activation to yield the five-coordinate

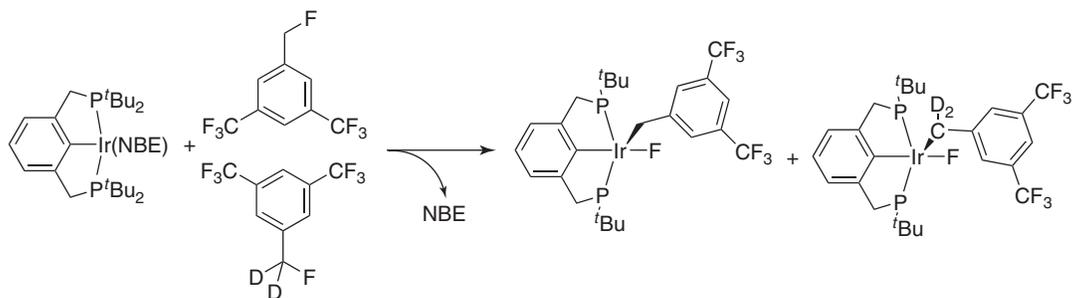


Figure 4.13 Competition kinetic isotope effect experiment for the addition of 3,5-bis(trifluoromethyl)benzyl fluoride and its deuterated analog to (PCP)Ir(NBE).

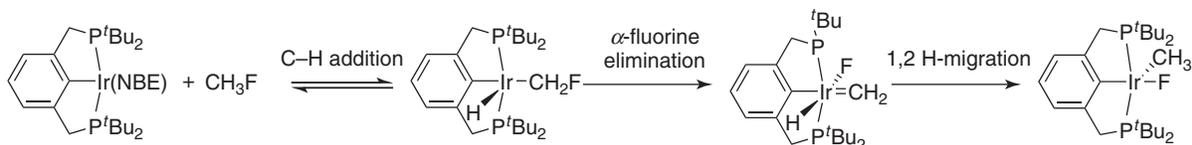


Figure 4.14 Mechanism for the net oxidative addition of $\text{CH}_3\text{-F}$ to (PCP)Ir.

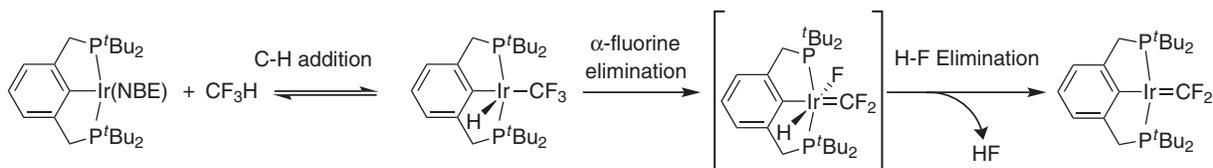


Figure 4.15 Mechanism for the reaction of (PCP)Ir(NBE) and CHF_3 to yield the difluorocarbene complex, (PCP)Ir CF_2 .

Ir(III) intermediate, (PCP)Ir(H)(CH₂F), followed by α -F elimination to yield a methylenidene intermediate, and then hydride migration from iridium to the carbene to afford the overall oxidative addition product (Fig. 4.14).

In an effort to observe the proposed intermediates (or analogs thereof), we investigated the reaction of trifluoromethane [33] with the hope that additional fluoro groups might stabilize either of the two intermediates shown in Fig. 4.14 [82–84]. Indeed, at moderately low temperature (-10°C), an intermediate species was observed that is apparently the C–H addition intermediate (Fig. 4.15), most characteristically evidenced by a broad hydride triplet at -45.5 ppm (this high upfield shift is consistent with a square pyramidal complex where the hydride is *trans* to a vacant coordination site). On warming to room temperature, conversion of this intermediate to a major new product characterized as the four-coordinate square planar difluorocarbene, (PCP)Ir(CF₂), occurred, along with a minor product corresponding to (PCP)Ir(CO) and an additional unidentified product. The four-coordinate carbene product would result from HF elimination from the putative six-coordinate (PCP)Ir(CF₂)(H)(F) complexes (Fig. 4.15). The reaction of four-coordinate metal difluorocarbene complexes with adventitious water has been previously shown to yield corresponding metal carbonyls [83–85]. The unidentified product revealed spectroscopic features strongly indicative of metal bifluoride complexes presumably resulting from reaction with free H–F [86].

The pathway leading to net C–F oxidative addition via initial C–H activation is supported by DFT calculations (Fig. 4.16). Direct oxidative addition of the C–F bond of fluoromethane was calculated to have an activation barrier of 31.1 kcal/mol relative to free fluoromethane and (PCP)Ir [or 37.5 kcal/mol relative to (PCP)Ir(NBE)], corresponding to the three-centered TS for C–F cleavage. In contrast, the pathway leading to net C–F oxidative addition through C–H activation has a calculated barrier of 16.5 kcal/mol relative to free fluoromethane and (PCP)Ir, or 22.9 kcal/mol relative to (PCP)Ir(NBE), with α -elimination of fluorine being the rate-determining step. This calculated value of ΔG^\ddagger is fully consistent with the experimentally determined (approximate) reaction rate.

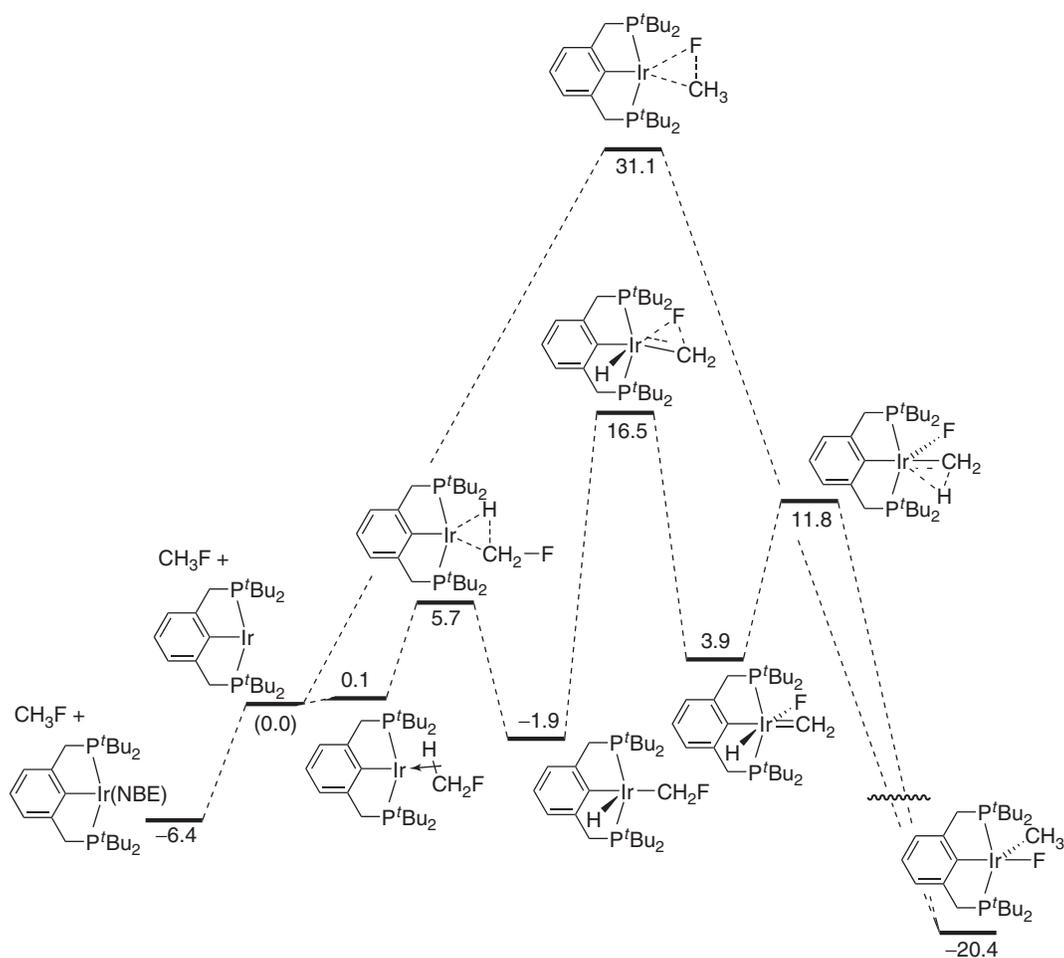
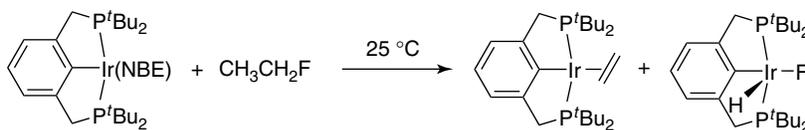
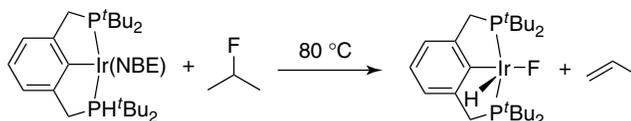


Figure 4.16 Calculated Gibbs free energies (in kcal/mol; relative to free (PCP)Ir and CH_3F) for the reaction of (PCP)Ir and CH_3F .



Scheme 4.22



Scheme 4.23

As discussed earlier, alkyl oxygenates with β -C–H bonds undergo 1,2-H–O elimination as opposed to C–O addition. The analogous behavior is observed with alkyl fluorides. Thus, the reaction of (PCP)Ir(NBE) with fluoroethane results in rapid formation of an equimolar mixture of (PCP)Ir(H)(F) and (PCP)Ir(ethylene) (Scheme 4.22). Reaction of (PCP)Ir(NBE) with 2-fluoropropane, followed by heating to 80 °C, resulted in quantitative conversion to (PCP)Ir(H)(F) (Scheme 4.23).

The mechanism for the reaction of alkyl fluorides bearing a β -hydrogen atom, in analogy with the oxygenates, likely proceeds via initial C–H oxidative addition to give (PCP)Ir(H)(fluoroalkyl), which then undergoes β -F elimination to yield

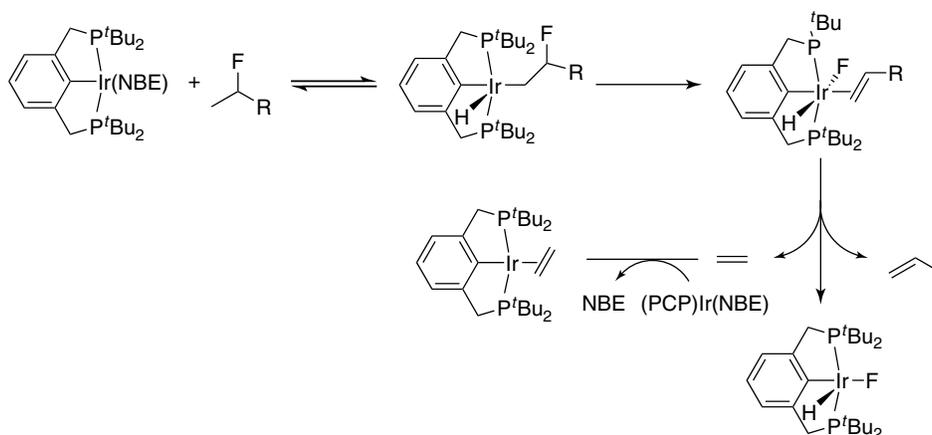


Figure 4.17 Mechanism for the reaction of (PCP)Ir(NBE) with fluoroethane and 2-fluoropropane.

(PCP)Ir(H)(F)(olefin) (Fig. 4.17). Presumably, ethylene is lost from this six-coordinate species to afford the hydrido fluoride product; the free ethylene then displaces NBE from (PCP)Ir(NBE) to form the (PCP)Ir(ethylene). For 2-fluoropropane, the same general mechanism applies, but the propylene formed from β -fluorine elimination binds less strongly than ethylene to (PCP)Ir, thus eventually allowing quantitative conversion to (PCP)Ir(H)(F).

4.4 SUMMARY

We have found that typically unreactive $C(sp^3)-O$ and $C(sp^3)-F$ bonds, including those of methyl aryl ethers (with electron-poor aryl groups), methyl esters, methyl tosylate, and methyl or benzyl fluoride, can undergo relatively unprecedented oxidative additions of the $C(sp^3)-X$ bond to the 14-electron fragment (PCP)Ir ($X = OR$, including OAr, OAc, or OTs, or $X = F$). Perhaps even more surprisingly, the reactions are found to proceed not via direct oxidative addition of the $C-X$ bond (which is computationally predicted to have a prohibitively high energy barrier), but rather through the initial activation of a $C-H$ bond positioned α to the O or F atom. In the case of alkyl oxygenates or fluorides in which the alkyl groups have H atoms in the β -position, reaction with (PCP)Ir also results in $C-X$ bond cleavage, but of a very different type, namely, 1,2-dehydro-oxygenation or 1,2-dehydrofluorination. In this case, the reaction appears to proceed via oxidative addition of a $\beta-C-H$ bond, followed by $\beta-C-X$ migration, to give (PCP)IrHX and olefin.

While $C-H$ addition has been an intensively studied field of chemistry for several decades now, this has almost invariably been with an eye toward “functionalizing the $C-H$ bond” in some manner. This work indicates that $C-H$ addition can represent a route toward activating a different bond in the molecule, in this case a $C-X$ bond located either α or β to the $C-H$ bond that undergoes addition.

By the principle of microscopic reversibility, these reaction mechanisms suggest new routes for the formation of $C(sp^3)-X$ bonds. Perhaps most intriguing, the mechanism elucidated for $C-X$ oxidative addition implies that its microscopic reverse, $C-X$ reductive elimination, must occur, for these systems, via an initial $\alpha-H$ migration from alkyl group to the metal center to generate the key alkylidene intermediate. The generality of this with respect to systems beyond (PCP)Ir(alkyl)X remains to be determined, but given that reductive elimination from late metal systems often proceeds via five-coordinate d^6 complexes, this mechanism may well be more broadly applicable. Likewise, the mechanism of the 1,2-H-X elimination reactions may offer insight applicable to the design of potential catalysts for 1,2-H-X addition reactions.

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