

Ruthenium-Promoted Radical Processes Toward Fine Chemistry

Lionel Delaude · Albert Demonceau · Alfred F. Noels (✉)

Center for Education and Research on Macromolecules (CERM), Institut de Chimie (B6a),
University of Liège, Sart-Tilman par 4000 Liège, Belgium
af.noels@ulg.ac.be

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Abstract Ruthenium holds a prominent position among the many transition metals used in radical chemistry. The dichlorotris(triphenylphosphine) complex $[\text{RuCl}_2(\text{PPh}_3)_3]$ was the first active ruthenium-based catalyst investigated for atom-transfer radical addition processes and has found numerous applications in organic synthesis. Other catalytic systems that have been devised since include (1) neutral or cationic Grubbs-type complexes bearing an alkylidene fragment and either phosphine, *N*-heterocyclic carbene, or Schiff base ligands, (2) half-sandwich ruthenium complexes bearing a cyclopentadienyl, a pentamethylcyclopentadienyl, or an indenyl ligand, and (3) ruthenium complexes bearing anionic carborane–phosphine and dicarbollide ligands. Their activities are discussed and the predictive value of cyclic voltammetry in radical chemistry is questioned. A related example of a ruthenium-catalyzed C–H hydroxylation reaction is also reported.

Keywords Atom-transfer reaction · Catalysis · Kharasch addition · Olefin

1

Introduction

Free-radical reactions are particularly useful to accomplish transformations that are not possible or that are difficult to achieve using ionic pathways. In this respect, the development over the last 15 years of new synthetic methods leading to well-defined and controlled radical reactions has weakened the pessimistic old notion of free-radical processes being difficult to control, owing to the intervention of highly reactive intermediates that usually undergo fast reactions with low selectivity. Recent advances in catalysis directed toward the formation of carbon–carbon bonds via free-radical mediated reactions have added a whole new dimension to the repertoire of synthetic methods available for controlling the precise assembly of small organic molecules and of polymer chains. Numerous radical reactions are now both chemoselective and regioselective, and even stereoselectivity can be achieved with a good understanding of the radical intermediate structures.

Radicals being neutral species tend to react together. Indeed, the most common side reactions in free-radical processes involve the formation of adducts between two radicals, via combination or disproportionation. These unwanted termination steps usually occur much faster than the desired reactions between radicals and substrates. Thus, the key to control in both radical addition and polymerization procedures consists in lowering the concentration of transient radical species. This will minimize the side reactions between radical species, yet the kinetics of the useful reactions will also be affected.

Many different metal-based promoters are available to initiate free-radical reactions. Of particular synthetic importance are organotin compounds, although radicals derived from other group 14 elements, notably silicon, are also attracting significant interest [1]. Yet, transition metals offer a useful alternative to their main-group counterparts for controlled radical transformations, and they have found widespread use in fine chemistry. Among the transition metals employed for generating carbon-centered radicals, manganese, chromium, cobalt, and especially copper have been the most widely studied [2, 3]. Ruthenium-catalyzed radical reactions have also recently emerged as particularly promising and worthy of interest, but their potential in organic synthesis and in polymer chemistry remains largely unexplored so far.

2

Metal-Catalyzed Atom-Transfer Reactions

2.1

Historical Background

Atom-transfer reactions encompass a broad range of radical addition processes in which carbon–heteroatom bonds are added across alkenes, alkynes, or other

unsaturated functionalities. The first example of an atom-transfer radical addition (ATRA) involving C–C bond formation and yielding a monomeric product was reported by Kharasch and coworkers in the mid-1940s. Typically, carbon tetrachloride was added to 1-octene in the presence of a radical initiator to afford the anti-Markovnikov addition product [4–7]. Classical initiators such as benzoyl peroxide, azobis(isobutyronitrile), or UV light were employed, and the process took the name of its discoverer in the everyday chemical language. The Kharasch addition reaction was born and has been used in organic synthesis ever since, although its original embodiment suffered from major drawbacks that limited its applicability. These downsides came from competing telomerization and polymerization reactions, which lowered the yields and lengthened the purification procedure.

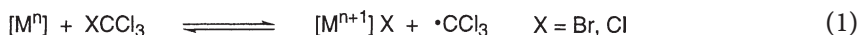
By the mid-1950s, it was recognized that transition metals were also capable of mediating the free-radical addition of polyhalogenoalkanes onto alkenes while limiting the unwanted side reactions. Minisci [8] was among the first investigators to report that carbon tetrachloride could add to olefins to afford only the corresponding monoadducts in the presence of iron or copper salts. In a number of cases, however, the occurrence of competitive oligomerization and telomerization processes still remains a problem that has not been satisfactorily addressed up to the present day. Although Kharasch additions *stricto sensu* refer to reactions promoted by organic radicals or light – and not by metal complexes – transition-metal-promoted reactions of this type are also commonly designated using the same patronymic nowadays.

2.2

Mechanistic Indications

Although detailed kinetic studies on Kharasch and related additions are sparse, there is agreement that two different (but related to some extent) types of mechanism might be operative in these reactions.

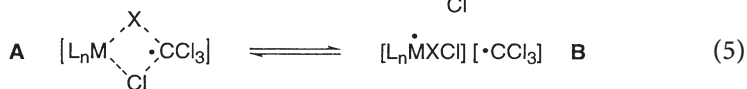
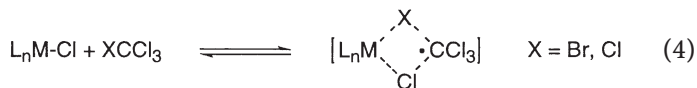
The first type of mechanism involves a redox chain process. As shown in Eqs. (1–3), it begins with the abstraction of a halogen atom from a polyhaloalkane reagent by the metal complex. This generates a radical species that further adds to an olefin. A chain-transfer reaction ensues and yields back the reduced metal species, hence the acronym ATRA, for the sequence.



Since metal halides have a much larger chain-transfer constant than $XCCl_3$ (X is Cl or Br), halogen transfer from the oxidized metal is favored over a propa-

gation step. This strongly limits or suppresses the competitive telomerization processes. Only reactions that are rapid than the halogen-atom transfer can occur between the addition and the chain-transfer steps. Moreover, the C–C bond-forming step in ATRA is a discrete step in the productive radical chain. Hence, ATRA reactions tolerate olefins that give slow addition steps. The olefin addition has only to be faster than radical–radical coupling or radical–solvent reactions. Of course, the carbon–heteroatom bond formed in the product must be stronger than the one broken in the initial reactant, and the abstraction of the transferred group needs to be fast (which usually is the case) in order to minimize oligomerization reactions. The selectivity toward a 1:1 addition therefore stems from the controlled chain termination, and the olefin seems to play no role in the rate-determining step of the redox chain mechanism. A similar situation is encountered in some atom-transfer radical polymerization (ATRP) reactions.

The second type of mechanism proceeds via a nonchain pathway and the organic radical results from a single electron transfer (SET) as illustrated in Eqs. (4–6). The species resulting from the SET interaction is a radical that apparently remains caged in the coordination sphere of the metal center (A or B). Olefin coordination to species A or B remains a matter of debate and, possibly, depends upon the nature of the metal complex.



2.3

Specificity of Ruthenium-Based Systems

The ability of ruthenium to assume a wide range of oxidation states and coordination geometries provides unique opportunities for catalysis. Indeed, a wide range of mechanistically very different processes are catalyzed by ruthenium complexes [9]. The development of highly efficient ruthenium-based catalysts is also driven by their tolerance toward functional groups, their easy access, and their versatility. Ruthenium holds a prominent position among the many transition metals (Cr, Mn, Fe, Ni, Pd, Cu, etc.) used in radical chemistry, both for synthetic applications [10, 11] and for polymer chemistry [12–14]. In particular, the dichlorotrakis(triphenylphosphine) complex $[RuCl_2(PPh_3)_3]$ (**1**) was the first active ruthenium-based catalyst precursor for ATRA [15]. The same complex was later used as a promoter for the controlled polymerization of methyl methacrylate (MMA), but in this case further activation by a Lewis acid such as aluminum triisopropoxide was required [16–18].

3 The $[\text{RuCl}_2(\text{PPh}_3)_3]$ Catalytic System

3.1 General Considerations

The Kharasch addition reactions promoted by $[\text{RuCl}_2(\text{PPh}_3)_3]$ are believed to proceed through a redox chain mechanism (Eqs. 1–3) [16]. Their kinetics show a first-order dependence both on the ruthenium complex and on CCl_4 . Whereas no clear-cut evidence for alkene coordination to the metal was found with catalyst precursor **1** (which readily loses one phosphine ligand), olefin coordination cannot be excluded because there is a saturation kinetic rate dependence on the alkene. This observation led to the proposal of a reversible step involving olefin coordination to the metal center [16, 19, 20]. Recent work with other ruthenium-based catalysts further supports olefin coordination (see later).

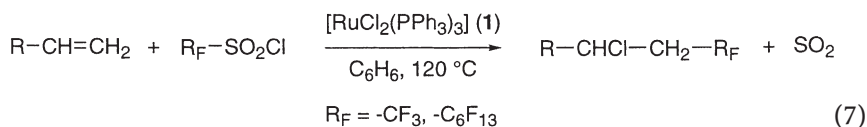
The effect of ring size on the reactivity of C_5 – C_{10} *cis*-cycloalkenes in addition reactions with CCl_4 was investigated with a number of metal complexes, including **1**, and relative reactivities were expressed in terms of rate constants compared with those of the corresponding normal alkenes [21]. There were only small differences in the relative reactivities of cycloalkenes when the addition was promoted by a conventional initiator (benzoyl peroxide) or catalyzed by a metal complex (Cu-, Mo-, Co-, Fe-, and Ru-based catalysts were used in the study). The relative rate constants followed the trend observed for alicyclic systems in addition reactions with a number of free radicals, and the relative reactivities of *cis*-cycloalkenes decreased according to the sequence $\text{C}_8 > \text{C}_5 > \text{C}_7 > \text{C}_6 > \text{C}_{10}$. The addition reactions were mainly controlled by *I*-strain in the cycloalkene molecules. A strong catalyst influence on the stereoselectivity of the addition was observed, however, with cyclohexene. The *cis*-to-*trans* isomer ratio of the adduct was significantly affected by the ruthenium catalyst when compared with reactions promoted by benzoyl peroxide. Cu-, Mo-, Co-, and Fe-based catalysts also had the same effect, but to a somewhat lesser extent. Here also, a nonchain mechanism involving the coordination of reactants was proposed for the metal-catalyzed reaction, especially in the ruthenium case. Other variations of the mechanism might account for the reaction products as well. For instance, the experimental data did not allow a process involving an oxidative addition of the polyhalogenated molecule to ruthenium(II) and one implying some other interactions between the $\cdot\text{CCl}_3$ radical and the metal center to be distinguished. As a matter of fact, many oxidative additions are known to proceed via radical intermediates [22].

Besides promoting the Kharasch addition reaction of polyhalogenated alkanes to MMA, the $[\text{RuCl}_2(\text{PPh}_3)_3]$ complex (**1**) also initiates the controlled polymerization of MMA, provided that the XCCl_3 concentration is kept low. Thus, the switch between the polymerization and the 1:1 Kharasch addition reaction depends solely on the relative concentration of the polyhaloalkane (“the initiator” in polymerization reactions) to the metal catalyst. Using near-to-

equimolar proportions of XCCl_3 and complex **1** leads to controlled polymerization, whereas using a large excess of XCCl_3 relative to the metal promotes the Kharasch addition. Not all the ruthenium-based catalysts, however, behave in the same way.

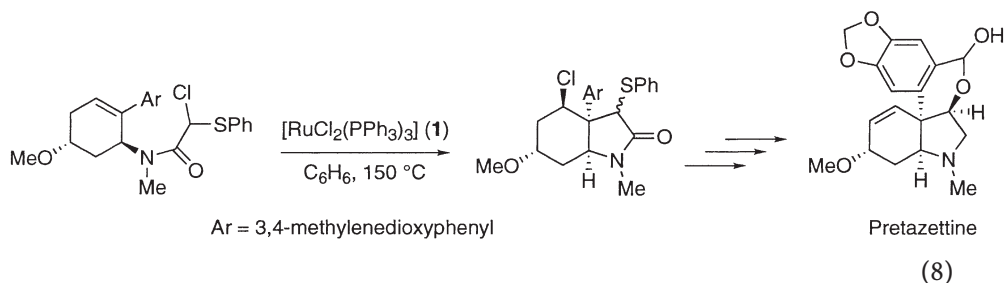
3.2 Applications in Organic Synthesis

The synthesis of polyhalogenated alkanes, lactams, lactones, etc., which are versatile intermediates in the synthesis of natural products and of bioactive molecules, has held the attention of chemists for many years. The Ru(II)-catalyzed addition of polychloroacetic acid to terminal olefins affords the corresponding adducts in high yields. Similarly, dichloroacetic and trichloroacetic esters add to a variety of olefins to give the corresponding chloroesters and lactones. Several applications along these lines can be found in Ref. [10]. The same methodology also provides ready access to perfluorinated alkanes as complex **1** catalyzes the reaction of alkenes with perfluoroalkanesulfonyl chlorides at 120 °C. Yields are more than satisfactory (up to 87%) with alkenes and vinylarenes, but poor with cycloolefins [23]. From a mechanistical point of view, the reactions are interesting because the sulfonyl radicals formed by the interaction of the sulfonyl chloride and the ruthenium catalyst release SO_2 to form perfluoroalkyl radicals (Eq. 7).

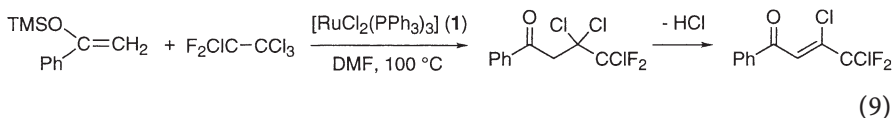


Addition of CCl_4 to chloroethene and 1,1-dichloroethene occurred selectively under the influence of a catalytic amount of complex **1** and afforded the 1:1 anti-Markovnikov adducts in 86% and 89% yield, respectively. No reaction was observed with chlorotrifluoroethene [24].

A key intermediate in the synthesis of pretazettine (Eq. 8), an alkaloid that contains a *cis*-3a-arylhydroindole ring system and shows antiviral and anti-cancer properties, has been synthesized by chlorine-atom transfer cyclization of a chloroacetamide in a highly stereocontrolled manner [25].



Complex 1 also catalyzes the regioselective radical addition of perhalogenoethanes to silyl enol ethers. The primary addition–desilylation products undergo the facile β -elimination of a chloride to afford α,β -unsaturated ketones [26, 27]. For example, $\text{CF}_2\text{ClCCl}_3$ adds to the trimethylsilyl enol ether of acetophenone to yield β -chloro- β -(chlorodifluoromethyl)- α,β -acetophenone in 80% yield (Eq. 9).



4 Engineering of New Ruthenium Catalytic Systems

The previous examples have established ruthenium-catalyzed atom-transfer reactions as a valuable addition to the list of synthetic methods available in fine chemistry. The potential of these systems is obvious, but sometimes their applicability is limited by rather poor catalytic activity and/or selectivity, particularly when it comes to the chemoselectivity of the addition and the concurrent formation of telomers. Hence, the need to extend the range of possible substrates and to perform the reactions under milder conditions led to the search for new catalytic systems with improved performances. Yet, the application of ruthenium catalysis to radical reactions remains a relatively unexplored and new field.

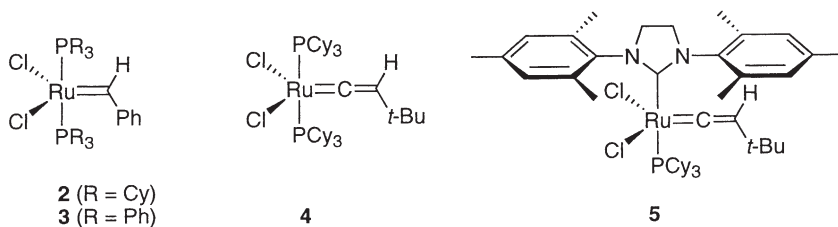
Astonishingly, all the reactions described up to 1999 use $[\text{RuCl}_2(\text{PPh}_3)_3]$ (1) as a catalyst precursor, with almost no ligand variation. It is nevertheless evident that the coordination sphere of the ruthenium atom plays a crucial role in tuning the activity of the catalyst for the activation and deactivation steps in the ATRA mechanism. Bulky ligands are expected to reduce the rate of activation by restricting the access to the metal center. Depending on their electronic properties, ligands also modulate the redox potential of the Ru(II)/Ru(III) couple. For instance, basic, strong σ -donating ligands should ease the oxidation step, whereas good π -acceptor ligands are more likely to stabilize the lower oxidation state of the metal center. Developments along these lines have led to new families of ruthenium complexes with quite often improved performances in radical reactions. These new catalyst precursors can be classified among the three following families:

1. Neutral or cationic Grubbs-type complexes bearing an alkylidene fragment and either phosphine, *N*-heterocyclic carbene (NHC), or Schiff base ligands.
2. Half-sandwich ruthenium complexes bearing a cyclopentadienyl (Cp), a pentamethylcyclopentadienyl (Cp*), or an indenyl ligand.
3. Ruthenium complexes bearing anionic carborane–phosphine and dicarbollide ligands.

4.1

Grubbs and Related Complexes as Catalysts for Radical Reactions

Two groups independently reported in 1999 that Grubbs' popular olefin metathesis catalyst [$\text{Cl}_2\text{Ru}(\text{=CHPh})(\text{PCy}_3)_2$] (**2**), where Cy is cyclohexyl, and related complexes were efficient promoters for Kharasch additions of CHCl_3 and CCl_4 across double bonds [28, 29]. Furthermore, the same ruthenium alkylidene complexes also catalyze the controlled ATRP of various monomers [28, 30]. Under the same experimental conditions, complex **2** displays a greater activity in ATRP and affords lesser telomerization than complex **1**. An excess of free phosphine ligand has an inhibitory effect on the Kharasch reactivity, and the presence of radical scavengers severely limits the formation of the addition product without significantly affecting the metathesis activity. This latter result supports the intervention of free radicals in the addition reaction. Furthermore, it has been shown that the Grubbs benzylidene catalyst **2** generates persistent radical anions upon treatment with π -acceptor quinones, and also with dienes and even monoenes. There is evidence that the observed electron paramagnetic resonance signals arise from charge transfer [31, 32]. Thus, charge-transfer complexes with halogenated initiators could enhance the free-radical activity of the ruthenium alkylidene complexes and be responsible for their efficacy.

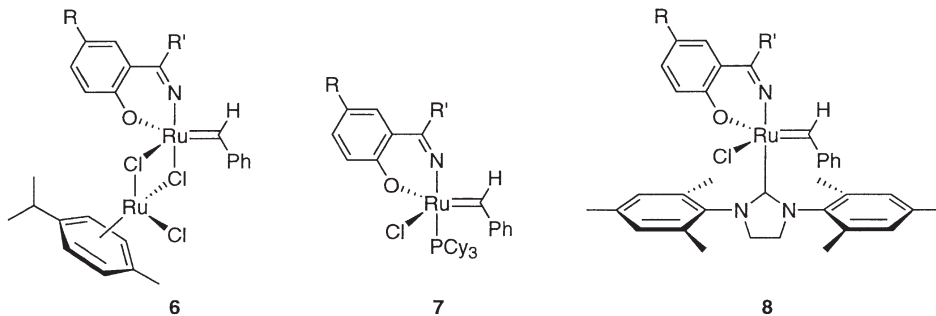


Within the series of [$\text{Cl}_2\text{Ru}(\text{=CHPh})(\text{PR}_3)_2$] complexes tested, the highest ATRA activity for the reaction of CCl_4 with vinyl substrates was obtained with the triphenylphosphine derivative [$\text{Cl}_2\text{Ru}(\text{=CHPh})(\text{PPh}_3)_2$] (**3**). Quantitative yields of monoadducts were obtained with styrene and MMA, and up to 61% conversion was achieved with 1-octene at a catalyst loading of 2.5 mol % [28]. The corresponding tricyclohexylphosphine complex **2** afforded less active catalytic systems. The reaction worked well with 1,1-disubstituted olefins but could not be extended to their 1,2-disubstituted counterparts. In all cases, yields were significantly lower when chloroform served as reagent instead of carbon tetrachloride [28, 29].

The range of ruthenium alkylidene catalysts active in radical chemistry was further enlarged to the readily accessible vinylidene complexes **4** and **5** [33]. Catalyst precursors **4** and **5** were tested for the ATRA of polyhalogenated alkanes with various olefins. Substitution of one phosphine in **4** by an NHC improves its catalytic efficiency. This is a surprising result given that **3** is more ac-

tive than **2**, and that NHCs are significantly more basic ligands than alkyl phosphines [34]. It confirms once again that catalyst-tailoring requires a suitable adjustment between the catalyst, monomer, initiator, and atom (or group of atoms) being transferred. The monocationic complexes generated in situ by treating **4** and **5** with silver tetrafluoroborate are less efficient catalysts for ATRA than their neutral parents, although they are more active in ATRP. Since olefin coordination is favored in cationic complexes, this observation may indicate that polymerization reactions with these ruthenium complexes proceed through olefin coordination.

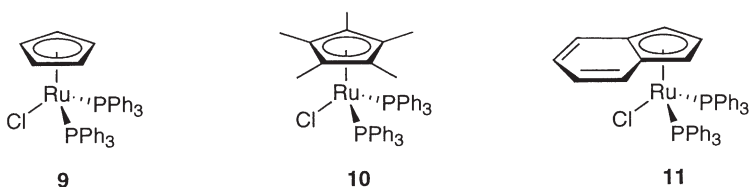
The robust homobimetallic ruthenium complexes **6** also efficiently catalyze the addition of carbon tetrachloride across a variety of C=C double bonds [35]. The influence of various *R* and *R'* substituents on the outcome of the reaction was investigated. Steric bulkiness is needed in the Schiff base moiety to attain reasonable catalytic activity. Electron-withdrawing *R* groups have a detrimental effect. The best combination of steric crowding and electronic balance in the complexes tested is reached when *R*=H and *R'* is the 2,6-dimethyl-4-bromophenyl group. This particular complex stands among the best catalyst precursors for Kharasch additions of carbon tetrachloride to olefins, including acrylonitrile (66% yield at 85 °C). Substitution of the [(*p*-cymene)RuCl₂] fragment by PCy₃ or by an NHC ligand yields new ruthenium complexes of the type **7** or **8** which show about the same catalytic efficiency as **6** [36]. The latter family of complexes exhibits poor ATRP activity, although styrene can be polymerized to some extent. These results sharply contrast with those obtained with [(arene)RuCl₂L] complexes (*L* is phosphine or NHC), whose activity can be tuned to promote either ATRA or ATRP depending on the exact nature of the ligand. Thus, aliphatic phosphines (typically tricyclohexylphosphine) lead to very good ATRP catalysts, while the presence of aromatic rings (as in triphenylphosphine) allows Kharasch additions to be performed with fairly good selectivity (A.F. Noels, A. Démonceau, unpublished results). Ruthenium-*p*-cymene complexes bearing NHC ligands are liable to even larger variations in the carbene structure, thereby providing a wide range of options for catalyst fine-tuning and engineering in atom-transfer radical reactions [37].



4.2

Cp-, Cp*- and Indenyl-Ru(II) Complexes as Catalysts for Radical Reactions

The catalytic activity of half-sandwich ruthenium complexes **9**, **10**, and **11** was investigated in the Kharasch addition of carbon tetrachloride against a set of four representative olefins, viz. *n*-butyl acrylate, MMA, styrene, and 1-decene. Not surprisingly, the outcome of the reaction depended very strongly on the olefin used [38]. Complexes **10** and **11** outperformed **9** in all cases, except with MMA, for which monoadduct production was almost quantitative with all three catalysts within 2 h at 85 °C. With styrene, longer reaction times (5 h) were required to achieve high yields, respectively 95% with **10** and 80% with **11**. *n*-Butyl acrylate, an easily polymerizable substrate, underwent clean addition of CCl₄, yielding 85% of 1,3,3,3-tetrachloropropylbenzene in 4 h with **10**. No telomer formation was observed under these conditions. In all cases 1-decene, a model for the nonfunctionalized α -olefins, was less prone to react. A modest 45% yield of addition product was nevertheless obtained with the indenyl-substituted complex **11** after 24 h at 60 °C.

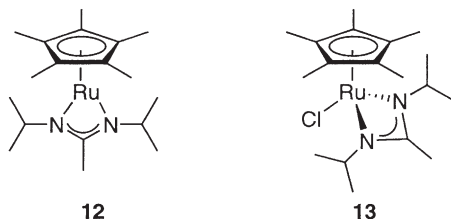


The high efficiency of Ru-Cp/Cp* catalyst precursors **10** and **11** was preserved when the reaction of styrene and MMA was carried out at 40 °C or even lower temperatures. Indeed, a 90% yield of the styrene-carbon tetrachloride adduct is obtained at room temperature with complex **10** [38]. Hence, it is one of the most efficient catalytic systems reported so far for this reaction. Addition of free triphenylphosphine to the reaction medium strongly depresses the catalytic activity. The same negative trend is observed when the original PPh₃ ligand in **10** is replaced by either tris(4-methoxyphenyl)phosphine or tris(4-trifluoromethylphenyl)phosphine [39]. In fact, the reactivity order correlates well with the ruthenium phosphine bond energy order, i.e., with the relative ease of formation of coordinatively unsaturated 16-electron species through PAR₃ ligand disengagement. A mechanism in which the catalytically active species is generated by release of a phosphine ligand has also been postulated for the Kharasch reaction mediated by **1** [16].

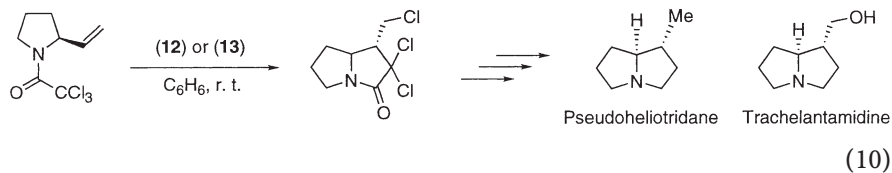
Addition of carbon tetrachloride to complexes **9**–**11** in toluene-*d*₈ promotes the decomposition of all three molecules into unidentified paramagnetic ruthenium species [38]. The relative rates of decomposition are very different from each other, however, and ³¹P NMR permitted the correlation of the highest catalytic activity with the highest reactivity toward carbon tetrachloride. All the kinetics data were interpreted in terms of a two-step mechanism, in which

phosphine ligand disengagement occurs prior to the activation of the halogenated compound by the ruthenium center.

The family of Ru(II)-Cp* ATRA catalysts was recently extended to novel ruthenium amidinate complexes **12** and **13** [40]. Complex **12** displays two successive one-electron oxidation waves in cyclic voltammetry, assigned to Ru(II)/Ru(III) and Ru(III)/Ru(IV) oxidation steps, respectively. This opens the door to chemical transformations of organic molecules on **12** either by way of one-electron redox processes [i.e., Ru(II) to Ru(III) or Ru(III) to Ru(IV)], or via two-electron processes [i.e., Ru(II) to Ru(IV)].



Both complexes **12** and **13** are active toward atom-transfer cyclization of *N*-allyltrichloroacetamides [40]. Of particular interest is the synthesis of a pyrroizolidine alkaloid skeleton. Much milder conditions are needed when using ruthenium-based catalysts instead of copper derivatives, although a high catalyst loading (30 mol %) is still required. Thus, an *N*-functionalized vinyl pyrrolidine is smoothly converted at room temperature into a bicyclic lactam, in 90% and 85% yield with complexes **12** and **13**, respectively. The product is a precursor of the pyrroizolidine alkaloids trachelantamide and pseudoheliotridane (Eq. 10).

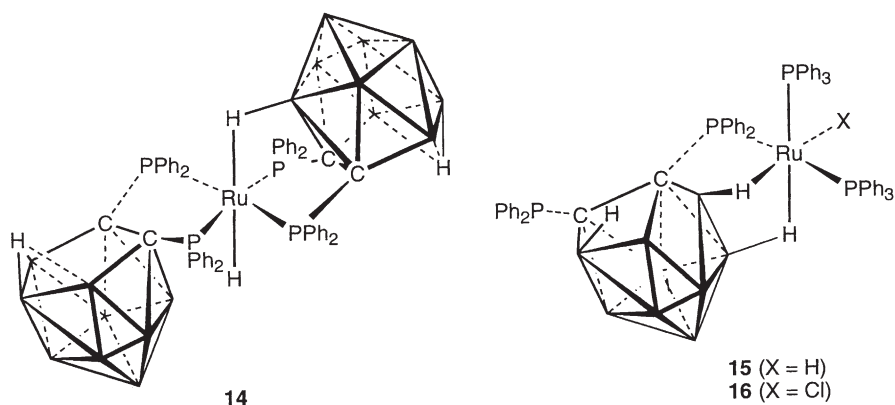


4.3

Ru(II) Complexes with Anionic Carborane Ligands as Catalysts for Radical Reactions

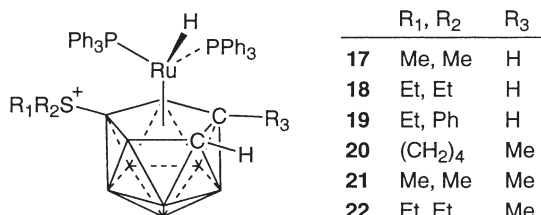
Mechanistic investigations in the field of ruthenium-catalyzed radical chemistry led to the idea that coordinatively unsaturated metal complexes generated through ligand release from a given precursor might be key intermediates in the catalytic process. It was therefore anticipated that stable, well-defined 14-electron complexes could provide direct access to the catalytic species. Ruthenium carborane complexes in which B-H→Ru agostic bonds are favored meet these criteria. Indeed, boron clusters provide structural and bonding possibil-

ities distinct of conventional organic ligands [41]. Thus, the catalytic activity of three 14-electron ruthenium(II) complexes, **14**, **15**, and **16**, with one or two *nido*-diphosphinocarborane anions was investigated for the addition of carbon tetrachloride onto a set of five representative olefins [42]. The idea behind the catalyst design was borne out to some extent. Yet, the outcome of the reactions dramatically depended both on the complex used and on the substrate. Even if the yields were satisfactory with some olefins and compared favorably with those obtained with $[\text{RuCl}_2(\text{PPh}_3)_3]$ (**1**), the addition products were always accompanied by oligomers or telomers. Hence, the ruthenium carborane complexes, being less selective, cannot compete with the best catalyst precursors, for example **10**, described so far.



The dicarbollide dianion $[\text{7,8-C}_2\text{B}_9\text{H}_{11}]^{2-}$ stands among the best studied η^5 -boron ligands. The C_2B_3 coordinating motif of this cluster is related to the widely used monoanionic (Cp) ligand, although behind the apparent similarity of the two ring systems, some remarkable differences remain. Among the singularities brought about by the $[\text{7,8-C}_2\text{B}_9\text{H}_{11}]^{2-}$ ligand prevails its ability to stabilize higher oxidation states than Cp. Moreover, the out-of-plane disposition of the open-face substituents could be beneficial to catalysis, particularly in ATRA reactions. Substitution of one open-face hydrogen by an SR_2 group leads to carbollide monoanions $[\text{X-R}_2\text{S-7,8-C}_2\text{B}_9\text{H}_{11}]^-$. The stability of such ligands in coordination complexes and the negative charge dissipation on the bond between substituents of the C_2B_3 open-face ring are well-known. Overall, the monoionic and dianionic boron clusters could behave as an electron pool connected to the metal center and fulfill the catalyst electronic requirements. Ruthenium carbollide complexes **17–22** indeed meet the expectations, and some of them emerge as the most efficient ATRA catalysts described so far for the addition of carbon tetrachloride to styrene and MMA. In particular, structure **19** affords quantitative yields of Kharasch addition products while displaying turnover numbers (TON) of 4,200 and 9,000 with MMA and styrene, respectively, and initial turnover frequencies (TOF) of 1,880 and 1,500 h^{-1} at

40 °C. These values are significantly higher than those recorded with **10** (TON=1,600–1,700, TOF=400 h⁻¹ for MMA) [43]. The TON for **19** even surpasses that obtained with the pincer N,C,N-chelating aryldiaminonickel complex reported as the most efficient ATRA catalyst to date (TON=1,731 and TOF=400 h⁻¹ for MMA at 25 °C) [44, 45].



5

Cyclic Voltammetry as a Probe for Catalyst Efficiency

One expects easy and reversible Ru(II)/Ru(III) redox processes to be crucial for achieving high catalytic efficiency in atom-transfer radical reactions. Electron-transfer properties of some of the most active ruthenium complexes reported so far for controlled radical reactions were determined by cyclic voltammetry in dichloromethane. The investigations commented on hereafter concern the series of closely related complexes described in the preceding sections. They were initiated following the recent disclosure of electrochemical analyses performed with copper-based ATRP catalysts [46, 47]. All potentials are referenced to Fc/Fc⁺ (where Fc is ferrocene) and the oxidative response is assigned to the Ru(II)–Ru(III) oxidation. The process is reversible with a peak-to-peak separation (ΔE_p) of about 80–90 mV. Interestingly, the oxidation potentials (E_{ox}) for complexes **17**–**20**, the most active catalyst precursors so far, are close to each other and are centered around –270 mV, whereas E_{ox} values of about –370 mV are observed for the slightly less efficient catalyst precursors **21** and **22**. The oxidation potentials range from –100 to +150 mV for species **9**, **10**, and **11** (+133, –83, and –10 mV, respectively), the former complex (**9**) being by far the less efficient catalyst of the series [43].

A more positive E_{ox} value denotes a more stabilized Ru(II) state, and a more negative E_{ox} value a more stabilized Ru(III) state. The fact that the highest catalytic activities correlate to E_{ox} values lying between the edges suggests that neither Ru(II) nor Ru(III) species should be too stabilized within the same ligand framework to display a good turnover. Accordingly, a complex displaying a relatively high oxidation potential should possess a rather inert divalent metal in its coordination sphere and is not expected to display an outstanding activity in ATR reactions. This observation is fostered when comparing the efficacy of the [(arene)RuCl₂(PR₃)] family of complexes with their arene-tethered analogues [η^1 : η^6 -(phosphinoarene)RuCl₂]. Both series of complexes undergo a

one-electron reversible oxidation, which occurs at a significantly higher oxidation potential for the strapped complexes [48, 49]. Even though some of the former ruthenium arene complexes are outstanding ATRP catalysts but poor ATRA catalysts (depending on the nature of the phosphine ligand), none of the tethered complexes show any significant activity in radical reactions (A.F. Noels, A. Demonceau, unpublished results).

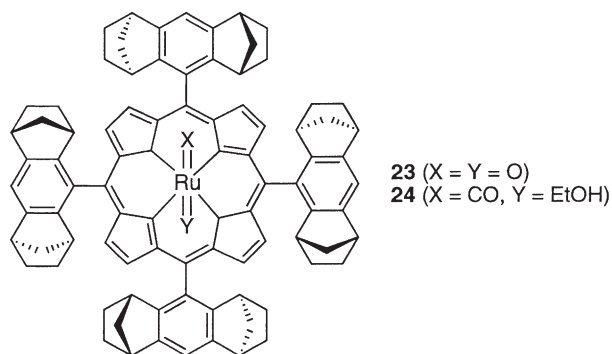
The predictive value of cyclic voltammetry data in radical chemistry seems, however, rather limited. An adequate redox potential of the metal complex is required for obtaining efficient catalysts, and comparison of the values recorded within a family of closely related species can allow meaningful forecasts, but other parameters need to be considered. Atom-transfer processes give rise to an expansion of the metal coordination sphere, and the Ru(II)/Ru(III) equilibrium is affected not only by the redox couple, but also by the energetics of the X–Ruⁿ⁺¹ bond. Steric hindrance, ligand oxidation, and a host of other parameters also play a crucial role in the overall process. The fact that electrochemical measurements are carried out on catalyst precursors, and not necessarily on the genuine active species, using an experimental setting quite different from the actual reaction conditions in terms of temperature and solvent (a supporting electrolyte, usually a tetrabutylammonium salt, is required) may also influence the results.

6 Ruthenium Porphyrin Complexes as Catalysts for C–H Hydroxylation

Applications of controlled radical reactions – including oxidation – deal almost exclusively with C=C double bonds. Indeed, a multitude of examples have been reported for the selective transformation of this functional group. Contrasting with this situation, only a very limited number of selective (“stereocontrolled”) radical reactions involving *sp*³-hybridized C–H bonds are known. Particularly useful functionalizations along these lines include the hydroxylation and the acyloxylation of alkyl chains. The reason for their limited success is of course due to the high stability of the C–H bond compared with that of the olefinic C=C unit: most electrophilic reagents which readily add to unsaturated substrates are not able to oxidize a C–H bond.

Iron-containing cytochrome P-450 constitutes the most famous example of a selective C–H bond oxidizer. Although the exact nature of the mechanism remains controversial, the reaction most likely proceeds through radical intermediates [2]. The hydroxylation of activated C–H bonds has also been carried out in the presence of synthetic porphyrin complexes. In these biomimetic processes, ruthenium plays a relatively minor role when compared with iron. Zhang et al. [50], however, recently reported the enantioselective hydroxylation of benzylic C–H bonds using ruthenium complexes supported by a *D*₄-symmetric porphyrin bearing a crafted chiral cavity. Thus, complex **23** reacts in a stoichiometric manner with ethylbenzene to give phenethyl alcohol with a

45% ee. The same hydroxylation proceeds catalytically (72% ee) using **24** as the catalyst and 2,6-dichloropyridine *N*-oxide as a terminal oxidant. Other acyclic alkylarenes are converted into alcohols with rather good enantioselectivity, but the reaction of cyclic substrates takes place only with modest selectivity. In all the cases, chemical yields are modest to poor.



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Conclusion and Perspectives

Currently, the number of synthetically useful ruthenium-catalyzed atom-transfer reactions remains rather limited. In view of the versatility and potential utility of these reactions in fine chemistry, it seems likely that further applications and extensions of known reactions will appear in the near future. Suffice it to recall that the recent breakthroughs in the field are due to catalyst engineering and only occurred after 1999. Thus, impressive progress has already been made in a short period of time.

The development of ruthenium complexes for other applications in radical chemistry is still in its infancy, but seems well suited to future expansion, thanks to the versatility of ruthenium as a catalytically active center. Large avenues have not been explored yet and remain open to research. For instance, the development of methodologies for the asymmetric functionalization of C–H bonds remains a challenge. The Kharasch–Sosnovsky reaction [51, 52], in which the allylic carbon of an alkene is acyloxylated, its asymmetric counterpart, and the asymmetric version of the Kharasch reaction itself are practically terra incognita to ruthenium chemistry, and await the discovery of improved catalysts.

Thanks to the development of the Grubbs benzylidene catalyst (**2**) and other related ruthenium complexes, olefin metathesis has experienced spectacular advances over the past 10 years. The various incarnations of the reaction (acyclic diene metathesis, ring-closing metathesis, ring-opening metathesis polymerization, etc.) have now acquired first rank importance in synthesis. Clearly, the emergence of a similar, generic, efficient catalytic system for con-

trolled radical reactions would contribute enormously to their popularity among the community of organic chemists. This will presumably follow from a better understanding of the mechanisms of these highly complex reactions.

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