Adamantane Selective Hydroxylation by 2,6-Dichloropyridine *N*-Oxide and Organoruthenium(II) Polyoxometalates as Catalyst Precursors

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Dedicated to Prof. Roger Sheldon on the occasion of his 60th birthday.

Abstract: Organoruthenium polyoxometalates with general formula $[\{Ru(C_6Me_6)\}_3M_5O_{18}]$, M=Mo, W, serve as catalyst precursors, together with 2,6-dichloropyridine *N*-oxide, to effect the hydroxylation of adamantane with conversion up to 94%, and C^3-H/C^2-H selectivity >100. Under analogous conditions, hydroxylation of *cis*-decalin occurred with complete stereoretention. Control experiments and kinetic evidence suggest the *in-situ* formation of a high valent Ru-oxo species as the competent oxidant.

Keywords: C-H activation; 2,6-dichloropyridine *N*-oxide; hydrocarbon hydroxylation; oxidation; polyoxometalates; ruthenium

Among the metal-mediated oxidations, ruthenium catalysts have shown some unmatched performances in terms of dioxygen activation, selectivity, and turnover rate.[1–3] Outstanding results have been obtained in many diverse transformations, including alcohol[4] and ether oxidation,[5] epoxidation,[6] and hydroxylation of unactivated alkanes.[3] Considering the catalyst design, a twofold issue to be addressed relates to the electronic tuning of the catalytic centre and the inertness of the metal coordination sphere under oxidising conditions. A promising perspective is to provide the active ruthenium centre with a totally inorganic ligand system derived from polyoxometalates (POM).[7]

With this aim, two different routes have been pursued: (i) ruthenium incorporation within the polyoxoanion framework, leading to ruthenium-substituted polyoxometalates;[8] (ii) functionalisation of the polyoxoanion surface leading to ruthenium-supported polyoxometalates.[9] The latter approach has been used for the synthesis of new organometallic species providing the ruthenium centre with a hybrid set of ligands comprising both organic residues and polyoxometalates.[10]

We now present preliminary results obtained in the oxyfunctionalisation of adamantane with 2,6-dichloropyridine *N*-oxide and organoruthenium(II) polyoxometalates with general formula $[\{Ru(C_6Me_6)\}_3M_5O_{18}]$, M=Mo, W. These complexes are lacunary Lindqvist-type polyoxoanions supporting three ruthenium centres (Figure 1).[9]

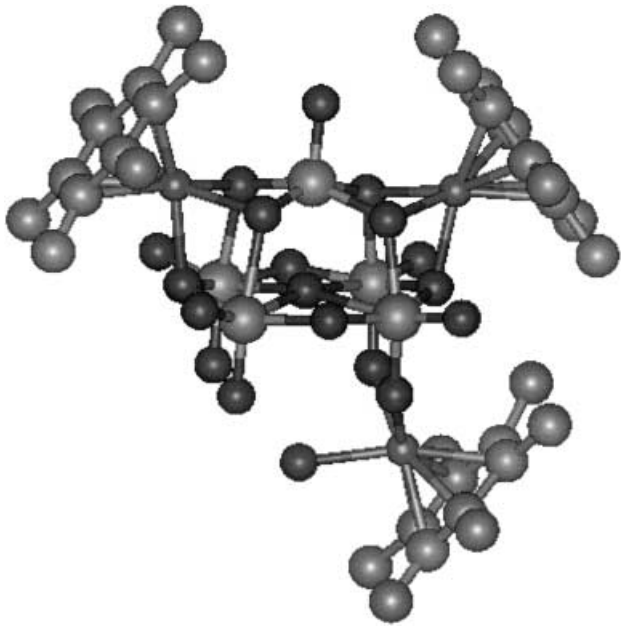

Figure 1. Structure of organoruthenium polyoxometalates $[\{Ru^{II}(C_6Me_6)\}_3M_5O_{18}]$ M=Mo, W.

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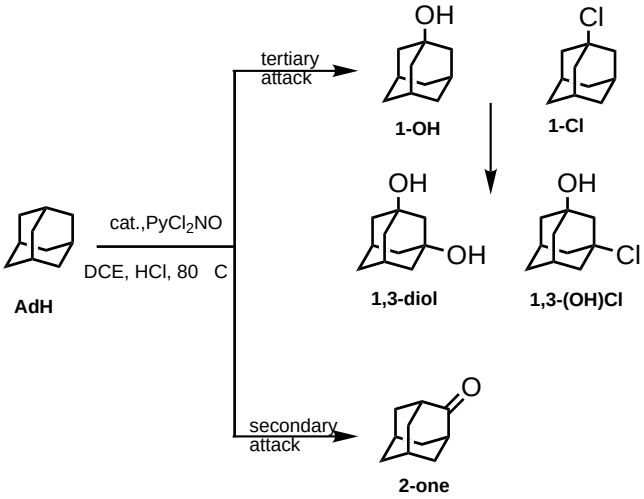
For comparison purposes we have also investigated the catalytic behaviour of two organometallic precursors used for the synthesis of POM derivatives, i.e., $[Ru(C_6Me_6)Cl_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$. No reaction was observed with the ruthenium incorporated polyoxotungstate $[Ru(DMSO)PW_{11}O_{39}]^{5-}$.[8]

In our study, to prevent the incursion of radical oxidation pathways, likely occurring when peroxidic oxidants are used with transition metal catalysts, a heteroaromatic *N*-oxide was chosen as oxygen donor.[1,11] Furthermore, 2,6-dichloropyridine *N*-oxide is simply generated by reaction of the parent pyridine with hydrogen peroxide in acidic media, thus a global catalytic process may be envisaged where the pyridine by-product is recycled and the primary oxidant is ultimately H_2O_2.[12]

The hydroxylation of aliphatic hydrocarbons is certainly one of the most interesting oxidations from both a synthetic and mechanistic point of view.[11] A typical substrate widely used for studying these oxidative processes is adamantane (AdH). Owing to its peculiar nature it is a very useful probe to evaluate both the efficiency of a catalytic system and its selectivity on the basis of the product distribution. The careful analysis of the selectivity, apart from the substantial meaning connected with the synthetic aspect of the oxidation, is also essential in mechanistic studies aimed at obtaining information on the nature of the active species.

Adamantane hydroxylation was performed in acidic 1,2-dichloroethane at 80 °C in the presence of 2,6-dichloropyridine *N*-oxide (1 – 3 equivalents) and the organoruthenium complex (2 – 8 mol % based on ruthenium). In the absence of ruthenium no attack to the substrate is detected. Scheme 1 illustrates the reaction conditions and classifies the observed products highlighting the regioselectivity.

As reported in Table 1, addition of acid promotes the oxidation rate with no appreciable influence on the product distribution (entry 1). The oxidation catalysed by $[\{Ru(C_6Me_6)\}_3Mo_5O_{18}]$ (catalyst A) has been taken as reference to investigate both the effect of 2,6-dichloropyridine *N*-oxide concentration (entries 2 – 6) and the catalyst loading (entries 2, 7, and 8). Substrate conversion up to 94% was obtained by using an excess of the oxygen donor while lowering the catalyst results in a



Scheme 1. Reaction conditions and observed products.

Table 1. Adamantane hydroxylation by organoruthenium catalysts and 2,6-dichloropyridine *N*-oxide.[a]

#	Catalyst[b] [mol %]	Sub./O.D.[c]	Conv.[d] [%]	Product Distribution[e] [%]	TOF[f] [TON h^{-1}]
1[g]	A [4]	1:1	56	1-OH [81] 1-Cl [8.5] 2-one [3] 1,3-diol [7]	n.d.
2	A [4]	1:1	59	1-OH [85] 1-Cl [6] 2-one [2.5] 1,3-diol [6.5]	13
3	A [4]	1:0.75	52	1-OH [84] 1-Cl [7] 2-one [3] 1,3-diol [6]	8
4	A [4]	1:1.5	85	1-OH [72] 1-Cl [8.5] 2-one [2.5] 1,3-diol [15.5] 1,3-(OH)Cl [1.5]	17
5	A [4]	1:2	86	1-OH [69] 1-Cl [12] 2-one [3] 1,3-diol [14] 1,3-(OH)Cl [2]	18
6	A [4]	1:3	94	1-OH [54] 1-Cl [20] 2-one [3] 1,3-diol [18] 1,3-(OH)Cl [5]	15
7	A [2]	1:1	62	1-OH [85] 1-Cl [6.5] 2-one [2.5] 1,3-diol [6.5]	30
8	A [8]	1:1	64	1-OH [82] 1-Cl [7] 2-one [2.5] 1,3-diol [7.5]	6
9	B [4]	1:1	51	1-OH [84] 1-Cl [8] 2-one [3] 1,3-diol [5.5]	9
10	C [4]	1:1	60	1-OH [87] 1-Cl [3.5] 2-one [2] 1,3-diol [7.5]	5
11[h]	D [4]	1:1	55	1-OH [82] 1-Cl [9] 2-one [2.5] 1,3-diol [6.5]	40

[a] In all reactions: adamantane 0.07 mmol, DCE (1 mL), concentrated HCl (2 μL) at 80 °C; products analysed after complete consumption of 2,6-dichloropyridine *N*-oxide (*ca.* 3 h).
[b] A = $[\{Ru(C_6Me_6)\}_3Mo_5O_{18}]$, B = $[\{Ru(C_6Me_6)\}_3W_5O_{18}]$, C = $[Ru(C_6Me_6)Cl_2]_2$, D = $[Ru(p\text{-cymene})Cl_2]_2$. Catalyst loading based on the total ruthenium amount.
[c] Adamantane/2,6-dichloropyridine *N*-oxide (Oxygen Donor) ratio.
[d] Conversion based on the substrate.
[e] For product abbreviations see Scheme 1.
[f] Calculated on the basis of the maximum oxidation rate (zero-order phase of the kinetics).
[g] Reaction performed in the absence of added acid. Reaction time 22 h.
[h] Reaction time 0.5 h.

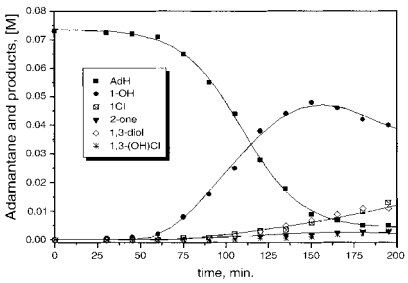


Figure 2. Time course for adamantane hydroxylation by $[\{Ru^{II}(C_6Me_6)\}_3Mo_5O_{18}]$ and 2,6-dichloropyridine *N*-oxide (entry 6 in Table 1).

higher turnover frequency (TOF), so that the overall oxidation rate is not much affected. The kinetic behaviour of the model oxidation (entry 4) has been monitored by quantitative GC analysis of adamantane conversion and product formation over time (Figure 2).

A sigmoidal curve, typical of an auto-catalytic process, was indeed detected in all reactions explored. As it can be seen in Figure 2, the kinetic trace can be dissected in two phases where the first lag phase, corresponding to a marked induction time (t_{ind}), is followed by a fast zero-order phase. From this linear part we extracted a turnover frequency (TOF) as detailed in Table 1. The presence of an induction time likely rules out the starting ruthenium complex as the competent catalyst. Inspection of Table 1 reveals that all the Ru(II) systems promote the oxidation with similar product distribution and turnover frequency. So both POM-based species (catalysts A and B) and organometallic precursors (catalysts C and D) in the presence of 2,6-dichloropyridine *N*-oxide appear to evolve to the same active intermediate which is able to hydroxylate adamantane. The *p*-cymene derivative (catalyst D) promotes the fastest reaction (entry 11). It is evident therefore that the active species derives from the decomposition of the original catalyst introduced in the reaction mixture. In this case, a structure-reactivity correlation based on the polyoxometalate nature becomes pointless, moreover the acceleration obtained with the molybdate complex with respect to the parent tungstate derivative is very modest (entries 2 and 9 in Table 1). However, it should be also pointed out that commercially available $RuCl_3$ or $Ru(acac)_3$ precursors show poor reactivity (10% conversion).

To address the nature of the active oxidant formed in solution, we should consider the selectivity parameter defined as the relative reactivity of tertiary to secondary CH groups calculated per H atom (4 tertiary and 12 secondary in adamantane). The C^3-H/C^2-H factor can be calculated on the basis of the product distribution (see Scheme 1), using Equation (1): where 1,2-dihydroxyadamantane and 1-chloro-3-hydroxyadamantane, are considered as deriving from a double attack to a tertiary C-H, while 2-adamantanone, which derives from a subsequent fast oxidation of 2-hydroxyadamantane, is considered as a single attack to a secondary position.

$$C^3\text{–H}/C^2\text{–H} = \frac{([1-OH]+[1-Cl]+2[1,3-diol]+2[1,3-(OH)Cl])/4}{[2AdO]/12} \quad (1)$$

Values for the selectivity in the oxidation of adamantane with several oxidants are reported in the literature, interestingly, radical oxidations are characterised by low C^3-H/C^2-H values in the range 1 – 25[13] while catalytic systems based on Ru derivatives exhibit C^3-H/C^2-H values $\geq$ 100.[3,14]

In that respect the important point which emerges from the data collected in Table 1 is related to the somewhat high value of the ratio C^3-H/C^2-H observed in all oxidations. Such a number, which does not vary much in the different reaction conditions, is in the range 100 – 130. This evidence speaks against the occurrence of a radical process, and indicates a ruthenium-centred species as the active oxidant.[3,14]

To further substantiate this conclusion, hydroxylation of *cis*-decalin was used as mechanistic probe. The oxidation catalysed by $[\{Ru(C_6Me_6)\}_3Mo_5O_{18}]$ (catalyst A), proceeds up to 18% conversion in 1.5 hours, leading to (*Z*)-9-decalol with complete stereoretention and no trace of isomerisation products [*trans*-decalin, (*E*)-9-decalol]. Once again this behaviour is consistent with the involvement of a high valent oxo-ruthenium complex as reactive species in the system. [1,3,14]

The nature of the competent oxidant can be addressed by considering previously reported spectroscopic and mechanistic evidence acquired on related systems.

The interaction of 2,6-dichloropyridine *N*-oxide with the ruthenium pentafluorophenylporphyrin [Ru(TPFPP)(CO)] was found to produce the extremely reactive Ru^V-oxo intermediate characterised by high selectivity and an unprecedented turnover frequency for adamantane hydroxylation (TON 48,000 h^{-1}). [3a] In the system under investigation, which yields analogous chemo- and stereoselectivities, this kind of rapid catalysis was not observed. The role of the porphyrin ligand could however play a major role on the reactivity of the active species.[3b] On the other hand, selective alkane hydroxylation with non-porphyrin ruthenium catalysts has been generally ascribed to oxo-ruthenium intermediates generated by reaction of low valent precursors with bulk oxidants.[1] Furthermore, the reactivity pathway delineated so far, presents strong analogies with the ruthenium tetraoxide (RuO_4)-mediated oxidations,[14] namely: (i) scarce influence of the precursor ligand system; (ii) C^3-H/C^2-H selectivity around 100; (iii) retention of configuration in decalin oxidations; (iv) production of chloroalkanes (1-Cl/1-OH = 1/10) in the presence of chloride ions. In catalytic

processes, RuO_4 is usually generated *in situ* by reaction of $RuCl_3$ or RuO_2 with $NaIO_4$, HIO_4, NaOCl or $NaBrO_3$.[1,14] These reactions are carried out in a biphasic medium and require a delicate balance of a solvent mixture: usually CCl_4, CH_3CN and water to prevent catalyst deactivation. It is therefore difficult to correlate the catalyst efficiency under so diverse conditions, but for the sake of comparison AdH hydroxylation mediated by RuO_4 has been reported to proceed with *ca*. 60% conversion in 19 h.[14a]

Although precise mechanistic information remains to be acquired in order to address the nature of active oxidant, our results extend the protocol for the use of 2,6-dichloropyridine *N*-oxide as primary oxidant, which represent an attractive alternative to both peroxidic and halogenated oxidants. The fact that its reduction product is recovered unaltered and potentially recycled makes it a valuable tool to activate hydrogen peroxide overcoming the problem of catalase-like induced decomposition and radical reactions. Both aspects are fundamental for lowering the environmental "E" factor of the oxidation process.[15]

Work in progress aims at finding an access to rapid Ru-mediated hydroxylation with polyoxometalate-based systems, thus mimicking the perfluoroporphyrin behaviour with highly robust, environmentally benign catalysts.

Experimental Section

General Oxidation Procedure

Oxidation reactions were carried out (duplicate runs) by dissolving $[AdH] = 0.071$ mol L^{-1} in distilled 1,2-dichloroethane (1 mL) together with 2,6-dichloropyridine *N*-oxide (1–3 equivalents *vs.* AdH), a GC internal standard ($C_{16}H_{34}$), the ruthenium catalyst (2–8% vs. AdH based on ruthenium amount) and 37% aqueous HCl (2 μL). The reaction mixture was then thermostatted at 80° C. Products were identified by GC (HP 5890 series II instrument equipped with a 15 m, 0.5 mm I.D, 0.25 μ AT-1701 capillary column) and GC-MS (HP 5890 series II instrument equipped with HP 5970 Mass selective detector and a 30 m, 0.25 mm I.D, 0.25 μ EC-1 capillary column) analysis. Chemical yields and conversions were determined by quantitative GC analysis with respect to the internal standard.

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