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Ruthenium-Catalyzed Epoxidation of Unfunctionalized Olefins with tert-Butyl Hydroperoxide.

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Abstract: A number of unfunctionalized aromatic and aliphatic olefins was tested in ruthenium-catalyzed epoxidation with *tert*-butyl hydroperoxide as the external oxidant. The effect of reaction without ligands and with two different type of ligands was investigated. Olefins containing terminal double bonds afforded low epoxide selectivities, whereas secondary and tertiary olefins afforded up to 80 % selectivity for the epoxide. A mechanism for the ruthenium-catalyzed epoxidation with *tert*-butyl hydroperoxide is proposed.

Metal-catalyzed epoxidations of unfunctionalized olefins constitute an important tool in organic synthesis. There is also a considerable interest in the development of effective catalytic systems for the enantioselective metal-catalyzed epoxidation of prochiral olefins[1]. The major advances in this field have been achieved with chiral porphyrins[2] and chiral manganese(III) Schiff base complexes, the latter developed by Jacobsen[3,4] and Katsuki[5].

Ruthenium is a transition metal that is extremely versatile for oxidation reactions, based on its ability to form compounds in eleven different oxidation states, ranging from Ru^{-2} to Ru^{+8}. Ruthenium-catalyzed epoxidations[6] have been described with sodium periodate[7,8], iodosylbenzene[9], pyridine *N*-oxides[10], hypochlorite[9k,11], hydrogen peroxide[12], *tert*-butyl hydroperoxide[13], aldehyde/O_2[14] and even dioxygen[15,16]. Ruthenium-catalyzed enantioselective epoxidations have also been reported[17,18,19] but are not yet competitive with the above mentioned methods with porphyrins or Schiff base complexes.

In the absence of ligands, RuO_4, in a stoichiometric amount or as catalyst in combination with an oxidant, leads to oxidative cleavage of double bonds with aromatic olefins to afford aldehydes or ketones and to allylic oxidation with aliphatic olefins. Balavoine and coworkers[7] were the first to reason that the small amounts of epoxide, that were sometimes observed as byproducts in these reactions, could probably be enhanced by employing an electron donating ligand to moderate the oxidizing power of RuO_4. This indeed proved to be the case: reaction of olefins with sodium periodate ($NaIO_4$) or sodium hypochlorite (NaOCl), in the presence of catalytic amounts of $RuCl_3$

and bipyridyl or substituted phenanthrolines, afforded the corresponding epoxide as the major product[7]. The reaction was stereospecific for both *cis*- and *trans*-alkenes, consistent with a heterolytic mechanism. Interestingly, the epoxidation of styrene with *tert*-butyl hydroperoxide (TBHP) in the presence of catalytic amounts of $Ru(PPh_3)_3Cl_2$ had been described more than 10 years earlier by Turner and Lyons[14]. This is the only example where ruthenium-catalyzed epoxidation is mentioned with TBHP, affording 25 % styrene oxide. Since TBHP is much more interesting than $NaIO_4$, from an industrial point of view, we have investigated the possibilities of using TBHP in ruthenium-catalyzed epoxidation reactions. Here, we report our results on the use of TBHP in ruthenium-catalyzed epoxidations of unfunctionalized olefins without and with the ligand bipyridyl (bpy, **1**) and the chiral ligand (4*S*,5*S*)-(+)-4-hydroxymethyl)-5-phenyl-2-(2-pyridinyl)-4,5-dihydro[2,1-*d*]oxazole (pymox, **2**)[20] (Figure 1).

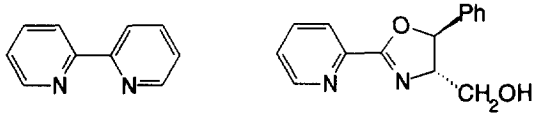

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Figure 1. The structure of bpy (1) and pymox (2).

Results and Discussion

Both H_2O_2 and TBHP are susceptible to facile ruthenium-catalyzed decomposition. The mechanism for the decomposition is shown below (Scheme 1). The formation of a tBuO• radical is initiated by a one-electron reduction of TBHP by ruthenium.

$$tBuOOH + Ru^{n+} \longrightarrow tBuO\bullet + Ru^{(n+1)+}$$

$$tBuO\bullet + tBuOOH \longrightarrow tBuO_2\bullet + tBuOH$$

$$2\,tBuO_2\bullet \longrightarrow 2\,tBuO\bullet + O_2 \longrightarrow tBuOOtBu + O_2$$

Scheme 1. Ruthenium-initiated decomposition of TBHP.

When $RuCl_3$ is added to a 70 % TBHP solution in water, spontaneous gas evolution (O_2) is observed and within seconds all the TBHP is decomposed to afford the theoretical amount (40 ml) of oxygen. The rate of decomposition is substantially decreased if the reaction is performed in a water-free environment. Therefore, to suppress the decomposition of TBHP, a 2.7 M TBHP solution

in 1,2-dichloroethane[21] was used and the reactions were performed under water-free conditions, using $Ru(dmso)_4Cl_2$[22] as the source of ruthenium. Some experiments were performed to quantify the rate and amount of decomposition, by measuring the amount of molecular oxygen evolved from the reaction mixture, using different ligands or complexes and temperatures. They showed that reaction at 0°C gave a substantially lower rate of decomposition than reaction at 20°C. After a short period, probably because initially there is some free ruthenium in the solution, the decomposition of TBHP with *in situ* generated complexes ceased (Figure 2). When an olefin (*trans*-ß-methylstyrene) was added the total decomposition drops dramatically to 15 ml of O_2 (of 40 ml theoretical) for $Ru(dmso)_4Cl_2$/bpy and 10 ml for $Ru(dmso)_4Cl_2$/pymox. This suggests that the olefin participates in the complex formation.

A number of olefins was tested with $Ru(dmso)_4Cl_2$, $Ru(dmso)_4Cl_2$/bpy (**1**) and $Ru(dmso)_4Cl_2$/pymox (**2**). The results are shown in Table 1. The blank reaction (reaction without ruthenium) afforded only low conversions in all cases (8 % maximum for *trans*-ß-methylstyrene). In contrast to the reaction with $NaIO_4$, where reaction without ligand afforded benzaldehyde as the only product[7,8], here reaction without ligand afforded substantial amounts of epoxide *e.g.* 79 % conversion and 42 % selectivity for *trans*-stilbene.

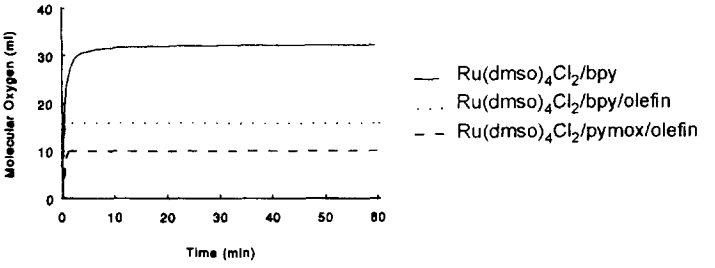


Figure 2. Graph of evolution of O_2 (40 ml at complete decomposition) from reaction of TBHP with bpy, bpy/olefin and pymox/olefin at 20°C.

During the reaction, the dimethyl sulfoxide (dmso) ligands are oxidized (dimethyl sulfone was found in the GC-MS chromatogram of the crude product). When ligands were used, the epoxide selectivity reached from 65 % to 76 % for *trans*-stilbene and 78 % for *cis*-stilbene. The reaction with preformed $Ru(bpy)_2Cl_2$ was much slower than with the *in situ* generated complex. With *trans*-stilbene the epoxidation was stereospecific, while with *cis*-stilbene a *cis/trans* mixture of 70:30 was observed, indicating some contribution of one-electron transfer. It should be noted that, because the amount of decomposition of TBHP may vary, 2-4 equivalents of TBHP were used, sufficient for the completion

of each reaction. For the epoxidation of *trans*-stilbene using pymox (**2**) as the ligand, an e.e. of 5 % was observed, again suggesting some contribution from one-electron transfer since the epoxidation with $NaIO_4$ (which proceeds only via a two-electron transfer) afforded 13 % e.e.[23].

Olefins with a terminal double bond were not effective substrates in epoxidation reactions with TBHP. Styrene, α-methylstyrene and also 1-octene gave poor results. In the case of styrene, this is a result of instability of styrene oxide, which reacted further to give the chlorohydrin. Although the necessary HCl could be derived from the catalyst, this could not account for the amount of chlorohydrin formed. The only other possible explanation is that HCl is formed from the solvent, CH_2Cl_2, presumably via initial hydrogen abstraction by a tert-butoxy radical. Both *trans*-ß-methylstyrene and indene afforded good selectivities in the presence of bpy and pymox. With indene the reaction rate is also strongly enhanced when the ligand is applied (from 24 to 5 hours reaction time). Some aliphatic olefins were also tested. Again, 1-octene with a terminal double bond hardly gave any conversion. The other olefins, cyclooctene and *cis*-2-heptene afforded 61 % and 64 %, respectively with pymox as ligand. However, no enantioselectivity was observed in these cases.

Mechanism of ruthenium-catalyzed epoxidation

tert-Butyl hydroperoxide (TBHP) can act as either a one- or a two-electron oxidant. Quite surprisingly, the oxidation of olefins with TBHP catalyzed by $Ru(dmso)_4Cl_2$ in the absence of added ligands afforded substantial amounts of the epoxide (9 - 42 %, Table 1).

Separate experiments were carried out using cyclobutanol as a mechanistic probe[24]. Oxidation of cyclobutanol with TBHP, in the presence of $Ru(dmso)_4Cl_2$, led to the formation of both cyclobutanone and ring-opened products, mainly butyraldehyde and butyric acid (identified by gc-ms). The latter are indicative of a homolytic mechanism. Similarly, when the oxidation of $Ru(dmso)_4Cl_2$ was performed in the presence of the radical inhibitor Ionol (2,6-di-*tert*-butyl-4-methylphenol) no oxidation products were observed, consistent with a homolytic pathway. Moreover, the low e.e. observed with TBHP (5 % *vs.* 13 % with $NaIO_4$[8]) in the Ru/pymox-catalyzed epoxidation of *trans*-stilbene suggests a substantial contribution from one-electron transfer.

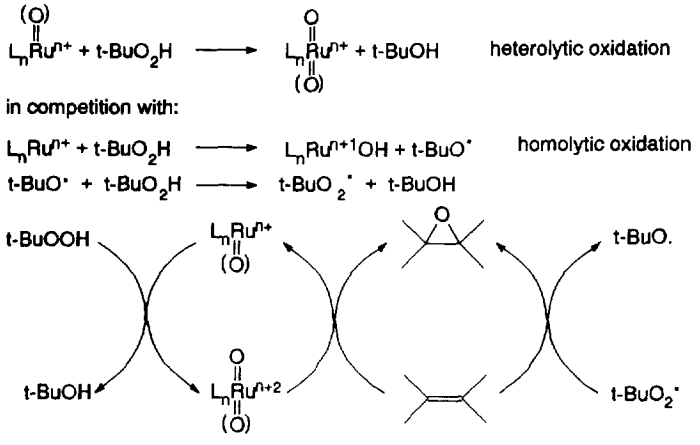
We propose the mechanism outlined in Scheme 2 to account for the observed results. Initial reaction of a ruthenium(II) complex with TBHP can involve the formation of oxoruthenium(IV) and/or dioxoruthenium(VI) complexes via a heterolytic mechanism or the formation of a *tert*-butoxy radical via one-electron transfer. In the latter case the *tert*-butoxy radical reacts with TBHP to afford a *tert*-butylperoxy radical. Subsequent epoxide formation results from reaction of either a (di)oxoruthenium complex or a *tert*-butylperoxy radical with the olefin substrate.

Table 1. Epoxidations of unfunctionalized olefins with TBHP at 0°C.

Olefin	Catalyst	Conversion (%)	Selectivity[a] (%)	TBHP (eq.)	Time (h)
trans-stilbene	-	4	12	2	72
	$Ru(dmso)_4Cl_2$	79[b]	42	2	24
	$Ru(dmso)_4Cl_2$/bpy	80	76	3	5
	$Ru(bpy)_2Cl_2$	54	61	2	24
	$Ru(dmso)_4Cl_2$/pymox	99	65	3	30
cis-stilbene	-	3	73[c]	2	68
	$Ru(dmso)_4Cl_2$/pymox	99	78[c]	4	30
styrene	-	0	-	4	66
	$Ru(dmso)_4Cl_2$	31	17[d]	4	48
	$Ru(dmso)_4Cl_2$/pymox	99	n.d.[d]	4	30
α-methylstyrene	-	0	-	4	66
	$Ru(dmso)_4Cl_2$	41	9	4	48
	$Ru(dmso)_4Cl_2$/pymox	98	5	4	72
trans-ß-methylstyrene	-	8	13	3	20
	$Ru(dmso)_4Cl_2$	97	27	3	2
	$Ru(dmso)_4Cl_2$/bpy	98	57	3	2
	$Ru(dmso)_4Cl_2$/pymox	99	56	3	3
indene	-	0	-	2	24
	$Ru(dmso)_4Cl_2$	98	26	2	24
	$Ru(dmso)_4Cl_2$/bpy	97	77	2	5
	$Ru(dmso)_4Cl_2$/pymox	96	80	2	6
cyclooctene	-	5	n.d.	4	67
	$Ru(dmso)_4Cl_2$/pymox	99	61	4	72
1-octene	-	trace	-	4	72
	$Ru(dmso)_4Cl_2$/pymox	trace	-	4	72
cis-2-heptene	-	1	n.d.	4	43
	$Ru(dmso)_4Cl_2$	15	22	4	48
	$Ru(dmso)_4Cl_2$/pymox	95	64	4	40

(a) Selectivity of epoxide *vs.* aldehyde/allylic oxidation products. (b) reaction at 6°C. (c) *cis*/*trans*-ratio 70:30. (d) Styrene oxide proved to be unstable under the reaction conditions. GCMS showed that the chlorohydrin of styrene oxide was the main product.

In the presence of bpy or pymox the reaction is both faster and more selective, *i.e.* ligand-accelerated catalysis is observed[25]. The higher selectivities suggest that in the presence of these ligands more reaction occurs via the putative oxoruthenium intermediates. A puzzling feature of these reactions is the observation that the reaction with preformed $Ru(bpy)_2Cl_2$ was much slower than the *in situ* generated complex. It suggests that prior coordination of the olefin to the ruthenium is a prerequisite for effective epoxidation. Moreover, it implies that stoichiometric epoxidations with preformed oxoruthenium complexes are not a good measure of what is happening in ruthenium-catalyzed epoxidations.



Scheme 2. Proposed mechanism for ruthenium-catalyzed epoxidations with TBHP as the primary oxidant.

In conclusion, ruthenium-catalyzed epoxidations of olefins with TBHP are complex processes involving both homolytic and heterolytic pathways. The mechanistic details of the oxygen transfer step are currently under further investigation.

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Experimental

General procedure for epoxidation of olefins with TBHP.

24 mg (0.05 mmol) of $Ru(dmso)_4Cl_2$ (and 3 equivalents of ligand) were dissolved in 25 ml of CH_2Cl_2 and stirred with a magnetic stirrer for 1 h at 600 rpm. Then, 0.54 g (3 mmol) of *trans*-stilbene was added and the reaction mixture was cooled to 0^0C. 2-4 eq. Of a 2.67 M TBHP solution in $ClCH_2CH_2Cl$ was added with a Dosimat at a rate, similar to the reaction rate. The reaction was monitored by GC and ^{1}H-NMR and compared to authentic samples of the products.

Decomposition of TBHP.

In a closed reaction vessel 24 mg of complex (and ligand) in 12 ml CH_2Cl_2 was stirred and 1 ml of 4.4 M TBHP solution in $ClCH_2CH_2Cl$ was added. The amount of oxygen evolving was measured by leading it into a column of water.

UV-Vis experiments with $Ru(bpy)_2Cl_2$ and TBHP.

To a solution of 26.0 mg of $Ru(bpy)_2Cl_2$ in 100 ml of CH_2Cl_2 were added 2 equivalents of TBHP and this mixture was allowed to stir for 2 days. The oxidation was monitored by UV-Vis. After complete oxidation *trans*-stilbene was added. No change of the UV-spectrum was observed.

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