ORGANIC LETTERS

2005
Vol. 7, No. 6
987−990

Convenient Method for Epoxidation of Alkenes Using Aqueous Hydrogen Peroxide

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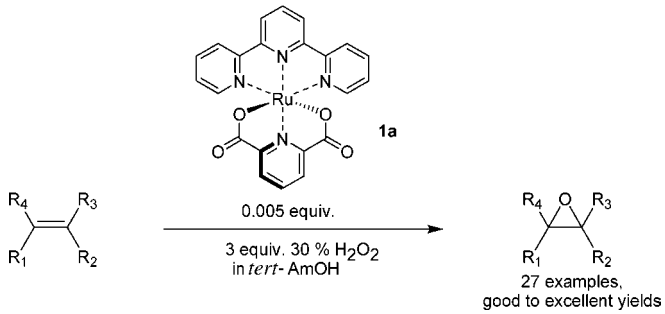
Received November 22, 2004

ABSTRACT



The complex [Ru(tpy)(pydic)] (1a) is an active catalyst for epoxidation of alkenes by aqueous 30% hydrogen peroxide in tertiary alcohols. The protocol is simple to operate and gives the corresponding epoxides in good to excellent yields. Chiral enantiopure [Ru(tpy*)(pydic)] complexes have been synthesized and successfully applied in this procedure.

Oxidation reactions of olefins to give epoxides are of major importance for organic synthesis. Nowadays, especially asymmetric epoxidation reactions[1] and the use of environmentally benign oxidants[2] are the focus of methodological developments. Apart from molecular oxygen,[3] hydrogen peroxide is an ecologically sustainable, "green" oxidant.[4] It can reach up to 47% atom efficiency in epoxidation reactions and generates only water as a byproduct. Moreover, it is economical and readily available.[5]

Traditionally, epoxides are synthesized by reaction of olefins with peroxoacids generated from hydrogen peroxide and acids or acid derivatives.[6] A drawback of this convenient

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10.1021/ol047604i CCC: $30.25
Published on Web 02/17/2005

method is the limited use for acid-labile olefins or epoxides and the generation of significant amounts of waste (salts). To control the selectivity of epoxidation reactions and to overcome the aforementioned problems, transition metal-catalyzed oxidations using hydrogen peroxide have been developed.[7] Among them, probably the most general method to epoxidize alkenes in neutral conditions is the well-known methyltrioxorhenium (MTO) system.[8] Nevertheless, from a practical point of view, the development of more active and productive catalysts for stereoselective and racemic oxidation reactions using H_2O_2 is an important and challenging goal in oxidation chemistry.

Recently, we became interested in the use of ruthenium catalysts[9] for olefin epoxidations.[10] For example, we were able to make optically active ruthenium (pyridine-bisoxazoline)(2,6-pyridinedicarboxylate) complexes [Ru(pybox)(pydic)][9c] (**2**) to become more practical oxidation catalysts by adding a defined amount of water to the reaction mixture.[11] This also led to the development of novel enantioselective epoxidation protocols applying alkyl peroxides[12] and hydrogen peroxide[13] as oxidants in the presence of ruthenium pybox and pyboxazine complexes.

Figure 1 shows 3 of over 50 ruthenium complexes we have synthesized and applied in asymmetric epoxidations. Despite the advantages of these catalytic systems such as (enantio)-selectivity, generality, and tunability, we looked for more active and robust complexes that would diminish the catalyst loading (5 mol %), which is typically needed for the [Ru(pybox)(pydic)] protocol, and allow at the same time for epoxidation of a broader substrate range. Here, we report for the first time a general epoxidation protocol that uses [Ru(terpyridine)(2,6-pyridinedicarboxylate)] (**1a**) and is carried out under mild neutral conditions in an environmentally benign tertiary alcohol with 30% aqueous hydrogen peroxide as the oxidant as well as the initial attempt for its asymmetric version.

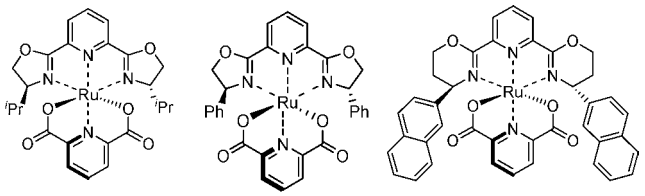

Figure 1.

Complex **1a** was introduced by Nishiyama *et al.* for epoxidation of alkenes.[9c] The original protocol in dichloromethane used 5 mol % **1a** with oxidants such as $PhI(OAc)_2$, oxygen/^{t}BuCHO, and ^{t}BuOOH. Unfortunately, the catalyst showed only low activity (the reaction took 72 h to complete) and no general substrate variations were demonstrated.

In our recent work on catalytic asymmetric epoxidations,[13] we were able to employ *tert*-amyl alcohol as the solvent and 30% aqueous hydrogen peroxide as the oxidant. In a prototypical reaction, β-methyl styrene was used as the substrate. To our delight, complex **1a** showed, under the same conditions and in comparison to **2**−**4**, a significantly increased reactivity and stability.

Even at 0.01 mol % catalyst loading with 0.1 mol % of both terpyridine (tpy) and pyridine-2,6-dicarboxylic acid (H_2-pydic), conversions of 93 and 88% were observed, which corresponds to a TON of 8800. At a ruthenium content of as low as 0.001 mol %, there was still an observable activity (Table 1).

Table 1. Influence of Catalyst Loading[a]

entry	catalyst loading (mol %)	conversion[b] (%)	yield[b] (%)	TON
1	1	100	96	96
2	0.1	100	95	950
3	0.01	22	18	1800
4	**0.01**	**93**[c]	**88**[c]	**8800**
5	0.001	14[c]	8[c]	8000

[a] Reaction conditions: In a 25 mL Schlenk tube, the catalyst **1a** was stirred at room temperature in *tert*-amyl alcohol (9 mL) for 10 min. β-Methyl styrene (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added. To this reaction mixture was added a solution of hydrogen peroxide (170 μL, 1.5 mmol) in *tert*-amyl alcohol (830 μL) over a period of 12 h via a syringe pump. [b] Determined by comparison with authentic samples on GC-FID. [c] At the outset, 0.1 mol % tpy and 0.1 mol % H_2pydic were added.

The continuous addition of H_2O_2 by a syringe pump was proven to be a reliable method to avoid nonproductive decomposition of the oxidant. Interestingly, also an addition of all the oxidant at once gave good results in most cases,

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especially with electron-rich substrates such as β-methyl styrene or 1-phenylcyclohexene. Nevertheless, we persisted with the continuous addition to allow for a more general method. From the data in Table 1, the beneficial effect of additional ligands suggests that the development of an *in situ*-type reaction is possible. Thus, by simply adding some ruthenium source and the ligands separately, the additional preparation of **1a** can be avoided. In Table 2, the feasibility

Table 2. Epoxidation Using an *in situ* Catalyst System[a]

entry	tpy (mol %)	H_2pydic (mol %)	conversion[b] (%)	yield[b] (%)	selectivity (%)
1[c]			25		
2[c]	0.5		5	<2	<40
3[c]		0.5	29	21	72
4[c]	0.5	0.5	40	37	93
5[d]			32		
6[d]	0.5		12	<2	<20
7[d]		0.5	42	24	57
8[d]	0.5	0.5	45	35	78

[a] Reaction conditions: In a 25 mL Schlenk tube, the ruthenium source, tpy, and pydic were stirred at room temperature in *tert*-amyl alcohol (9 mL) for 10 min. β-Methyl styrene (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added. To this reaction mixture was added a solution of hydrogen peroxide (170 μL, 1.5 mmol) in *tert*-amyl alcohol (830 μL) over a period of 12 h *via* a syringe pump. [b] Determined by comparison with authentic samples on GC-FID. [c] Performed with 0.0025 mmol $RuCl_3 \cdot nH_2O$ as the Ru source. [d] Performed with 0.00125 mmol $[Ru(p\text{-cymene})Cl_2]_2$ as the Ru source.

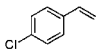
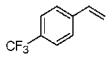
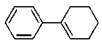
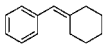
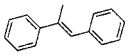
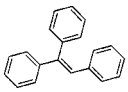
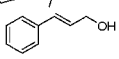
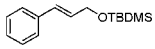
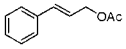
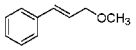
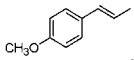
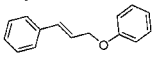
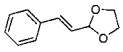
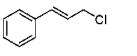
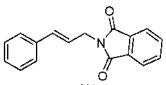
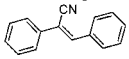
of such a concept is demonstrated using two readily available ruthenium sources, $RuCl_3 \cdot nH_2O$ and $[Ru(p\text{-cymene})Cl_2]_2$, along with tpy and H_2pydic at 0.5 mol % each (Table 2, compare Table 1, entry 3).

No epoxide was observed without any added ligand and with only terpyridine. H_2pydic as the sole ligand showed some reactivity; however, the selectivity toward the desired product was lower than that in the case when both ligands were applied. The differences between the two ruthenium sources were insignificant. These results suggest that both ligands are necessary for obtaining a high epoxide selectivity. H_2pydic is mainly responsible for the reactivity and tpy for the selectivity.

Since the yields in the *in situ* systems are somewhat lower compared to that obtained by the application of the pre-made **1a**, we used the protocol described in Table 1 as the standard procedure.

As shown in Table 3, a large number of different alkenes were epoxidized in good to excellent yields. All substitution patterns of aromatic olefins such as monosubstituted, 1,1-disubstituted, 1,2-*cis*/*trans*-substituted, 1,1,2-trisubstituted, and finally tetrasubstituted alkenes gave the corresponding epoxides. The compatibility of this protocol with functional groups such as −OH-, −OR-, −OTBDMS-, halogen-, acetal-, and nitrogen-containing compounds is noteworthy (Table 3). In cases of less reactive substrates (entries 15 and 26), neither increasing the concentration of **1a** to 1 mol % nor conducting the reaction at 50 °C resulted in higher

Table 3. Epoxidation of Various Alkenes with H_2O_2[a]

Entry	Alkene	Conv[b] (%)	Yield[b] (%)
1		100	84
2		100	71
3		100	83
4		100	86
5		100	>99
6		90	89
7		100	>99
8		100	>99
9		100	80
10		100	88
11		100	>99
12		100	91
13		100	86[d]
14		100	95
15		66[c,e]	66[c,e]
16		100	86
17		100	96
18		100	97
19		100	>99
20		100	98
21		100	96
22		100	99
23		100	92
24		100	62[d]
25		100	94
26		> 90	81[d]
27		92[c]	87[c]

[a] Reaction conditions: In a 25 mL Schlenk tube, the catalyst **1a** (0.0025 mmol) was stirred at room temperature in *tert*-amyl alcohol (9 mL) for 10 min. Alkene (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added. To this reaction mixture was added a solution of hydrogen peroxide (170 μL, 1.5 mmol) in *tert*-amyl alcohol (830 μL) over a period of 12 h *via* a syringe pump. [b] Determined by comparing with authentic samples on GC-FID. [c] Performed with 0.05 mmol $[Ru(^tBu_3\text{-tpy})(pydic)]$ **1b** as the catalyst. [d] Isolated yield. [e] Determined by ^1H NMR.

epoxide yields (>50%). We thought that this may be due to the insufficient solubility of **1a** at higher concentration (1 mol %) and the increased decomposition of the hydrogen peroxide at elevated temperature. A solution to this problem was found in the application of a more soluble ruthenium terpyridine complex [Ru(^{t}Bu$_3$-tpy)(pydic)] **1b**. It is interesting to note that the reaction conditions could be easily scaled up to 10 mmol in a 10-fold substrate concentration smoothly.[14]

Of all epoxidation procedures using hydrogen peroxide in neutral conditions known in the literature, our protocol compares best to the MTO-system. Advantageously, our system runs in environmentally benign solvents and the catalyst is more easily prepared compared to methyltrioxorhenium.

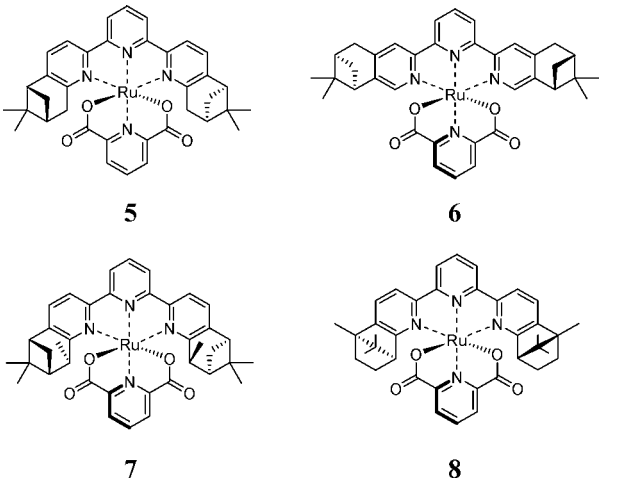


Figure 2.

Due to the excellent performance of **1a** in racemic epoxidations we started to explore an enantioselective procedure by variation of the terpyridine ligand. The ligands were prepared according to a reaction scheme known in the literature.[15] All complexes **5**−**8** were synthesized under similar conditions as **1** and **2** (see Supporting Information). With our model substrate β,β-dimethyl styrene, excellent yields were reached for **5**, **6**, and **8** applied at a comparably low concentration of 0.5 mol %. For **6**, a moderate enantioselectivity of 54% *ee* (Table 4) was achieved.

Table 4. Epoxidation of β,β-Dimethyl Styrene[a]

entry	catalyst	conversion[b] (%)	yield[b] (%)	*ee*[c] (%)
1	**5**	100	93	−15
2	**6**	100	96	+54[d]
3	**7**	53	45	+24[d]
4	**8**	100	96	−29

[a] Reaction conditions: In a 25 mL Schlenk tube, the catalyst was stirred at room temperature in *tert*-amyl alcohol (9 mL) for 10 min. Olefin (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added. To this reaction mixture was added a solution of 30% hydrogen peroxide (170 μL, 1.5 mmol) in *tert*-amyl alcohol (830 μL) over a period of 12 h *via* a syringe pump. [b] Determined by comparison with authentic samples on GC-FID. [c] Determined by HPLC. [d] (*R*)-(+)-1-Phenyl-2-methyl-1-propene oxide was the major enantiomer.

In summary, we have developed a ruthenium-catalyzed epoxidation protocol that runs under mild conditions in an environmetally friendly manner. In general, highly selective epoxidation of aromatic and branched aliphatic alkenes is achieved at low catalyst loading, and moderate enantioselectivity was obtained for the asymmetric protocol. Further work using other ruthenium terpyridine pydic complexes for epoxidation is currently in progress.

Acknowledgment. This work has been supported by the State of Mecklenburg−Western Pommerania and the Bundesministerium für Bildung und Forschung (BMBF). We thank Mrs. C. Mewes, Mrs. H. Baudisch, Mrs. A. Lehmann, and Mrs. S. Buchholz (all IfOK) for their excellent technical and analytical support. Dr. A. Köckritz (ACA) is thanked for general discussions.

Supporting Information Available: Synthesis and characterization of all complexes, experimental procedures, and characterization data for all epoxides. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047604I

(14) 1-Phenyl-2-cyclohexene (9.5 mmol) and [Ru(tpy)(pydic)] (**1a**, 0.05 mmol, 0.5 mol %) were dissolved by stirring in *tert*-amyl alcohol (20 mL). To this mixture was added 30% aqueous hydrogen peroxide (3.04 mL) *via* syringe pump over 12 h. After quenching the reaction (30 mL of 10% aqueous Na_2SO_3 solution), extraction (three times with 20 mL of ethyl acetate), and purification (column chromatography, Merck silica gel 60, hexane to hexane/ethyl acetate 95:5 as the gradient eluent), 1.37 g (83% yield with respect to 1-phenyl-2-cyclohexene) of the epoxide remained.

(15) (a) Ziegler, M.; Monney, V.; Stoeckli-Evans, H.; Von Zelewsky, A.; Sasaki, I.; Dupic, G.; Daran, J. C.; Balavoine, G. G. A. *J. Chem. Soc., Dalton Trans.* **1999**, 667−675. (b) Kwong, H.-L.; Lee, W.-S. *Tetrahedron: Asymmetry* **2000**, *11*, 2299−2308.