Urea-Hydrogen Peroxide/Hexafluoro-2-propanol: An Efficient System for a Catalytic Epoxidation Reaction without a Metal

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Keywords: Epoxidation / Urea-hydrogen peroxide / Fluoroalcohol / Fluoroketones / Catalysis

Hexafluoro-2-propanol (HFIP) exhibits a unique ability to release and activate H_2O_2 from the urea-hydrogen peroxide adduct (UHP). This UHP/HFIP system was investigated in epoxidation of olefins, using various fluoroketones as catalysts. With reactive olefins, no catalyst was required. With monosubstituted olefins, epoxides were obtained in high yields by using catalytic amounts (3–5%) of perfluorodecan-2-one.

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The search for safe and easily accessible sources of primary oxidants is of great interest in chemistry. With this in mind, the urea-hydrogen peroxide adduct (UHP) has been reported as a safe source of anhydrous hydrogen peroxide.[1] UHP is a white crystalline solid, formed by strong hydrogen bonding between urea and hydrogen peroxide in a 1:1 proportion (Figure 1);[2,3] it is easily handled, without the need for special precautions. UHP is commercially available, cheap, and can be stored for months at +4 °C without any change in the oxygen content. However, such a high stability could be considered, to be a drawback to its potential chemical reactivity towards substrates.

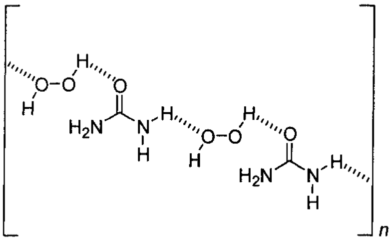

Figure 1. Structure of UHP

Although its preparation was first described in 1941,[2] the use of UHP as oxidizing agent in chemical synthesis was first reported by Heaney at the beginning of the last decade, in particular for the epoxidation of olefins and for Baeyer−Villiger reactions.[1] In these reactions the oxidizing species was a peroxyacid, generated in situ from UHP and an anhydride, the most efficient of which were acetic and trifluoroacetic anhydrides.[1,4] An excess of reagents was required for complete reaction (1.5−10 equiv. of anhydride and 3−10 equiv. of UHP). Such an excess can lower selectivity, and is incompatible with the use of acid-sensitive compounds. Much effort has been focused on the optimisation of the use of UHP in oxidation reactions, and great improvements have been achieved through the use of various metal complexes as catalysts.[5] For instance, very good results for epoxidation have been obtained using methyltrioxorhenium (MTO) in chloroform or in dichloromethane.[6]

Results and Discussion

Due to the cost and/or toxicity of most of the reported metal catalysts, a metal-free epoxidation process is still of great value. The use of a fluorinated alcohol as solvent was proposed to be a good alternative. In 1998, we reported an easy and efficient selective oxidation of sulfides into sulfoxides with 30% aq. H_2O_2, in hexafluoro2-propanol (HFIP) or trifluoroethanol (TFE).[7] A strong hydrogen bond between the oxygen of H_2O_2 and the acidic hydrogen of HFIP ($pK = 9.3$, $\alpha = 1.96$) or TFE ($pK = 12.8$, $\alpha = 1.51$)[8,9] was put forward to explain the activation of H_2O_2.[7b] Later reports, in particular by Neumann, showed that uncatalysed epoxidation of reactive olefins could be effected with 60% aq. H_2O_2 in refluxing TFE, or at room temperature in HFIP.[10,11] The existence of hydrogen bonding between H_2O_2 and HFIP has been proved by NMR experiments.[10] These results prompted us to investigate the effect of fluorinated alcohols on the activation of H_2O_2 from UHP.

As a preliminary study, epoxidation of the highly reactive cyclooctene was performed using UHP (3 equiv.) in different solvents (Table 1).

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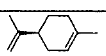
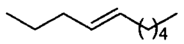
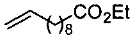
Table 1. The effect of solvent on the uncatalysed epoxidation of cyclooctene with UHP[a]

Entry	Oxidant	Solvent	Time [h]	Conversion [%][b]
1	30% H_2O_2	HFIP	24	79
2	UHP	HFIP[c]	10	100[d]
3	UHP	TFE	24	4
4	UHP	MeOH[c]	24	0
5	UHP	CH_2Cl_2	24	0
6	UHP	MeCN	24	0
7	UHP	EtOAc	24	0

[a] Reaction conditions: cyclooctene (1 mmol), UHP or 30% aq. H_2O_2 (3 mmol), HFIP (3 mL), 25 °C. [b] The epoxide was the only product. Measured by GC. [c] UHP is soluble in this solvent. [d] Isolated yield: 91%.

Entries 1 and 2 clearly show the efficiency of UHP in HFIP compared to that of 30% aq. H_2O_2, with a 100% conversion of cyclooctene after 10 h in the case of UHP, compared to an incomplete reaction after 24 h with 30% aq. H_2O_2.[10] While it could be easily argued that the efficiency of anhydrous H_2O_2 is expected to be higher than that of 30% aq. H_2O_2, it is remarkable that the reaction with UHP in HFIP does not require any additive. It is also significant that of all the different solvents used, epoxidation only occurred in HFIP. UHP is not soluble in other commonly used reaction solvents (CH_2Cl_2, MeCN and EtOAc) and in these cases, cyclooctene remained unchanged even after 24 h. In TFE, which is also an efficient solvent for uncatalysed epoxidation of cyclooctene with aqueous H_2O_2,[10] the reaction occurred with only 4% conversion after 24 h (entry 3). This indicates that dissociation of the UHP adduct is an essential factor. Therefore, the insolubility of UHP in TFE can be evoked to explain its lack of reactivity: TFE is less dissociative than HFIP ($Y = 1.80$ and 3.61 respectively).[12,13] Conversely with MeOH, despite the complete dissolution of UHP, cyclooctene remained unchanged (entry 4). MeOH is not a good enough hydrogen-bond donor ($\alpha = 0.93$)[8] to activate H_2O_2 after its release. HFIP has the unique ability to combine the two requirements for efficient epoxidation with UHP: dissociation of the UHP adduct, and activation of hydrogen peroxide.

Table 2. Uncatalysed epoxidation with UHP in HFIP [a]

Entry	Olefin	Time [h]	Conversion [%][b]	Yield [%][c]
1		7	100[d]	88[e]
2		48	100	90
3		48	7	–

[a] Reaction conditions: olefin (1 mmol), UHP (3 mmol), HFIP (3 mL), 25 °C. [b] The epoxide was the only product. Measured by GC. [c] Yield of isolated product. [d] Ratio of monoepoxide/diepoxide was 93:7. [e] Yield of monoepoxide (oxidation of trisubstituted double bond), 1:1 mixture of diastereoisomers.

The epoxidation of other olefins was also investigated (Table 2).

As expected the reaction with limonene was efficient, giving 100% conversion after 7 h (entry 1). With less-reactive olefins, the reaction rate decreased dramatically. A 48 h reaction time was required for the complete epoxidation of an internal aliphatic olefin (*trans*-dec-4-ene, entry 2), and the poorly reactive terminal olefin ethyl 10-undecenoate afforded only a 7% conversion in the same time. Interestingly, when *tert*-butyl methyl ether was added to a solution of UHP in HFIP, the precipitation of a solid, which was proved to be UHP (m.p., IR analysis[3]) was observed. Consequently, the reactions could be worked up safely despite the excess of H_2O_2: simple precipitation of the urea and excess UHP by addition of a small amount of *tert*-butyl methyl ether, followed by filtration through a short pad of silica gel, allowed isolation of the corresponding oxiranes.[14]

In order to improve the reaction, the UHP/HFIP system was investigated in the presence of fluoroketones as catalysts. In the presence of anhydrous H_2O_2, perfluoroketones provide perhydrates which are powerful catalysts for many oxidation reactions.[15,16] The most well-known precursor of such a perhydrate is the commercially available hexafluoroacetone,[17] but other perfluoroketones have been successfully used in epoxidation reactions.[18] Recently, Sheldon reported great improvements in hexafluoroacetone-catalysed epoxidation when performed in HFIP, allowing, for example, the epoxidation of cyclooctene in 6 h with hexafluoroacetone (5 mol %) and 60% aq. H_2O_2 (2 equiv.).[19] The UHP/HFIP/fluoroketone catalyst system was evaluated in the epoxidation of the unreactive ethyl 10-undecenoate. For this purpose, three ketones and an aldehyde of $CF_3C(O)R$ type ($R = H$, $CHCl_2$, and C_8F_{17} [20]) were evaluated as new fluoroketone catalysts and compared to hexafluoroacetone (Table 3).

Table 3. The influence of catalysts on the epoxidation of ethyl 10-undecenoate with UHP in HFIP[a]

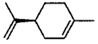
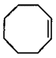
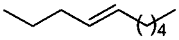
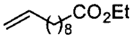
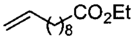
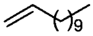
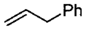
Entry	Catalyst (10 mol %)[b]	Oxidant	Solvent	Conversion [%][c]	
4 h	24 h				
1	–	UHP	HFIP	0	3
2	(**1**) CF_3CHO	UHP	HFIP	2	6
3	(**2**) $CF_3COCHCl_2$	UHP	HFIP	18	59
4	(**3**) CF_3COCF_3	UHP	HFIP	25	77
5	(**4**) $CF_3COC_8F_{17}$	UHP	HFIP	61	100
6	(**4**) $CF_3COC_8F_{17}$	30% H_2O_2	HFIP	5	25
7	(**4**) $CF_3COC_8F_{17}$	UHP	TFE	2	15
8	(**4**) $CF_3COC_8F_{17}$	UHP	CH_2Cl_2	0	0

[a]Reaction conditions: ethyl 10-undecenoate (1 mmol), catalyst (0.1 mmol), UHP or 30% aq. H_2O_2 (3 mmol), HFIP (3 mL), 25 °C. [b] All catalysts were used as their hydrate forms. [c] The epoxide was the only product. Measured by GC.

With the exception of trifluoroacetaldehyde (**1**), a significant enhancement of reactivity was observed in the presence of a catalyst. Conversion rates measured after 4 h and 24 h of reaction clearly show that ketone **4** (R = C_8F_{17}) is the most efficient catalyst, even more so than hexafluoroacetone. Similarly, the effect of the length of fluorinated chain on the H_2O_2/fluoroketone catalysis was recently reported.[18] In this catalysed reaction, HFIP is still required for the efficient release of H_2O_2 from UHP (entries 5, 7 and 8). It must be noted that ketone **4** has already been used successfully in the epoxidation of dodec-1-ene in HFIP, with Oxone® as primary oxidant.[21]

The optimised reaction conditions, now requiring only 3−5 mol % of ketone **4**, and 1.2 equiv. of UHP, have been applied to the epoxidation of various olefins (Table 4).

Table 4. Catalysed epoxidation reaction with ketone **4** and UHP in HFIP [a]

Entry	Olefin	Ketone **4** [mol%]	Temp. [°C]	Time [h]	Yield [%][b]
1		3	25	0.75	79[c]
2		3	25	1	85
3		3	25	5	93
4		5	25	48	89
5		5	40	24	91
6		5	40	24	94
7		5	40	48	92

[a] Reaction conditions: olefin (1 mmol), catalyst (0.03−0.05 mmol), UHP (1.2 mmol), HFIP (1 mL), 25−40 °C. [b] Yield of isolated product. [c] Yield of monoepoxide (oxidation of trisubstituted double bond), 1:1 mixture of diastereoisomers.

Under these conditions, reactions proceeded faster than in the absence of catalyst, and complete conversion of all olefins, including the less reactive ones, was observed.

Conclusion

This study demonstrates that the ability of HFIP to activate H_2O_2, combined with its ability to release H_2O_2 from its urea adduct, makes the UHP/HFIP system efficient and safe for epoxidation under mild conditions. Epoxidation of reactive olefins can be performed without any catalyst. It is also possible to recover urea, unchanged UHP and HFIP. For unreactive double bonds, catalysis is required and we have shown that perfluorodecan-2-one **4**, used in 3−5 mol % with 1.2 equiv. of UHP in HFIP, is an excellent catalyst for complete conversion into oxiranes.

Experimental Section

General: UHP (Aldrich), olefins (Aldrich or Fluka), catalysts **1** and **2** (Central Glass), catalyst **3** (Acros) and HFIP (Central Glass) were used as received. Catalyst **4** was prepared according to the literature.[20] Gas chromatography was conducted with Hewlett Packard 4890.

Uncatalysed Epoxidation of Cycloctene with UHP. Typical Procedure: UHP (282 mg, 3 mmol) was added to a well-stirred mixture of cyclooctene (110 mg, 1 mmol) in HFIP (3 mL), at 25 °C. After 10 h (reaction was monitored by GC), the homogeneous mixture was cooled to 0 °C, and *tert*-butyl methyl ether (3 mL) was added to precipitate urea and unchanged UHP. The mixture was then filtered through silica gel. Evaporation of the solvents afforded the pure cyclooctene oxide (115 mg, 91%).

Epoxidation of Ethyl 10-Undecenoate with UHP Catalysed by Ketone 4. Typical Procedure: UHP (113 mg, 1.2 mmol) was added to a well-stirred mixture of ethyl 10-undecenoate (212 mg, 1 mmol) and fluoroketone **4** hydrate (27 mg, 0.05 mmol) in HFIP (3 mL), at 25 °C. After 48 h (reaction was monitored by GC), the homogeneous mixture was cooled to 0 °C, and *tert*-butyl methyl ether (1 mL) was added to precipitate urea and unchanged UHP. The mixture was then filtered through silica gel. Evaporation of the solvents afforded the pure ethyl 10-undecenoate oxide (203 mg, 89%).

Acknowledgments

We thank Central Glass Co., Ltd for kindly providing dichlororotrifluoroacetone (**2**) and HFIP. We also thank the European Contract of Research Training Network ("Fluorous phase" HPRN CT 2000-00002) and the European Union (COST-Action "Fluorous medium" D12/98/0012) for support.

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Received March 27, 2002
[O02176]