JOC*Note*

Organocatalysis of Asymmetric Epoxidation Mediated by Iminium Salts under Nonaqueous Conditions

Philip C. Bulman Page,* David Barros,
Benjamin R. Buckley, Adel Ardakani, and
Brian A. Marples

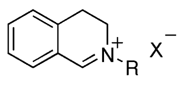
Department of Chemistry, Loughborough University,
Loughborough, Leicestershire LE11 3TU, England

p.c.b.page@lboro.ac.uk

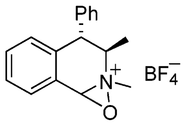
Received December 15, 2003

Abstract: The first nonaqueous conditions are described for catalytic asymmetric epoxidation mediated by iminium salt organocatalysts, providing ee values of up to 67%.

Oxaziridinium salts, first reported in 1976 by Lusinchi,[1] are extremely reactive reagents for oxygen transfer to nucleophilic substrates such as sulfides and alkenes,[2,3] and are presumed to be the active oxidants in the catalytic epoxidation of alkenes by dihydroisoquinolinium salts **1** in the presence of a stoicheiometric oxidant,[4] usually oxone.[5] Complete retention of stereochemistry is observed, suggesting a single-step oxygen transfer process. The first enantiomerically pure oxaziridinium salt **2** was reported by Lusinchi, and shown to induce asymmetric epoxidation of alkenes;[6] the corresponding iminium salt was shown to catalyze asymmetric epoxidation in the presence of oxone, and ee values of up to ca. 40% were obtained. A binaphthalene-derived iminium salt has also been reported to catalyze asymmetric epoxidation of simple alkenes,[7] and Armstrong and others have shown that even acyclic iminium salts can mediate epoxidation by oxone.[8]

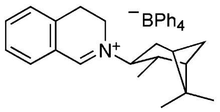


1

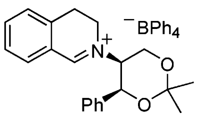


2

We have previously described chiral iminium salt epoxidation catalysts containing the asymmetric centers in an exocyclic substituent at the nitrogen atom of dihydroisoquinolinium or related salts. Three of the most effective systems are catalysts **3**, **4**, and **5**, giving ee values of up to 60% under the standard conditions in aqueous acetonitrile and using oxone as oxidant.[9] Good isolated yields of epoxides are obtained (typically around 70%). The iminium unit of **5**, with a TRISPHAT counterion, has also very recently been reported to induce up to 70% ee in the epoxidation of 1-phenylcyclohexene in the presence of 18-crown-6 in dichloromethane/water solutions, using oxone as oxidant at room temperature.[10]



3



4

The standard conditions employed in epoxidation reactions catalyzed by iminium salts involve the use of oxone as stoicheiometric oxidant, a base (2 molar equiv of Na_2CO_3 per equiv of oxone), and water/acetonitrile as solvent mixture (Scheme 1); the presence of water is essential for oxone solubility. Under the reaction conditions, there are separate aqueous and organic phases; it is possible that the catalyst acts as a phase transfer agent in these reactions.

The principal limitation to this system is the restricted range of temperatures in which the epoxidation can be performed (0 °C to room temperature). The upper limit is determined by the oxone, which decomposes relatively quickly in the basic medium at room temperature.[5] The lower limit is determined by the use of the aqueous medium; the normal ratio of the water and acetonitrile solvents used is 1:1, and this mixture freezes at around −10 °C.

One potential opportunity to enhance the enantioselectivity of the process would be provided if the reaction could be carried out at lower temperatures. This would require the development of nonaqueous reaction conditions, and because of the solubility profile of oxone, which has no significant solubility in any organic solvent, this in turn dictates a need for a new stoicheiometric oxidant, soluble in organic solvents at low temperatures. Crucially, this oxidant must not oxidize alkenes under the reaction conditions in the absence of the catalyst (background oxidation).

We tested several oxidants in an epoxidation reaction in the presence of iminium salt catalysts to determine which offers the best profile in the absence of water. These reactions were carried out at 0 °C with 1-phenylcyclohexene as substrate and **3** and/or **4** as

---

(1) Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1573. Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1577.

(2) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1987**, *28*, 6061.

(3) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 3941.

(4) Hanquet, G.; Lusinchi, X.; Milliet, P. *C. R. Hebd. Seances Acad. Sci.* **1991**, *313, S11*, 625. Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727. Bohé, L.; Kammoun, M. *Tetrahedron Lett.* **2002**, *43*, 803.

(5) www.dupont.com/oxone/techinfo/.

(6) Bohé, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271. Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141.

(7) Aggarwal, V. K.; Wang, M. F. *Chem. Commun.* **1996**, 191.

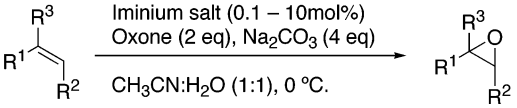
(8) Armstrong, A.; Ahmed, G.; Garnett, I.; Gioacolou, K. *Synlett* **1997**, 1075. Armstrong, A.; Draffan, A. G. *Synlett* **1998**, 646. Armstrong, A.; Ahmed, G.; Garnett, I.; Gioacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341. Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, 1810. Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587.

(9) Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3325. Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Buckley, B.; Bethell, D.; Smith, T. A. D.; Slawin, A. M. Z. *J. Org. Chem.* **2001**, *66*, 6926. Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Bethell, D.; Merifield, E. *Synlett* **2002**, 580.

(10) Lacour, J.; Monchaud, D.; Marsol, C. *Tetrahedron Lett.* **2002**, *43*, 8257.

10.1021/jo035820j CCC: $27.50

SCHEME 1



catalysts (5−20 mol %), in dichloromethane as solvent. Most of the systems examined showed either high levels of background epoxidation (alkaline hydrogen peroxide, peracids, persulfates) or very low rates of reaction even in the presence of 20 mol % of the catalytic system (perselenates, perborates, iodosobenzene diacetate). Tetra-*N*-butylammonium oxone, reported by Trost,[11] was found by DiFuria to be unsuccessful as oxidant in the epoxidation of alkenes catalyzed by metalloporphyrins;[12] DiFuria comments that Bu_4NHSO_4, which is present in the mixture, inhibits the epoxidation process. We also found tetra-*N*-butylammonium oxone to be unsuccessful as oxidant in our system.

From all of those tested, tetraphenylphosphonium monoperoxybisulfate (TPPP), reported by Di Furia for oxygen transfer to manganese porphyrins in 1994,[12] showed the best profile. A modification of oxone, TPPP is prepared by cation exchange between oxone and tetraphenylphosphonium chloride. Further crystallization of the salt from dichloromethane and hexane affords TPPP as a colorless solid in 75% yield in our hands, which iodometric titration reveals to have ca. 85% of the theoretical available oxygen. This composition was also confirmed by ^{1}H NMR spectroscopy (CD_2Cl_2), by integration of the aromatic hydrogen of the tetraphenyl moiety and the hydroperoxy proton (at ca. 9.5 ppm).

For epoxidation to proceed, the presence of base is essential under aqueous conditions when using oxone as oxidant. We were pleased to discover that, in contrast, the addition of 1 equiv of any of a range of bases (KF, TBAF, CsF, pyridine, 2,6-lutidine, DBN, DBU, DABCO, LiH, NaH) to the test reaction in dichloromethane with TPPP as oxidant did not improve the reaction; indeed, the amine bases suppressed epoxidation.

Formation of epoxide was not observed upon treatment of 1-phenylcyclohexene with TPPP in dichloromethane solution at 0 °C in the absence of catalyst. Indeed, such background epoxidation only becomes competitive with the catalyzed reaction when the temperature reaches ca. 40 °C.

TABLE 1. Asymmetric Epoxidation of 1-Phenylcyclohexene Mediated by Catalyst 4[a]

entry	solvent	temp/°C	time/min	conv/%[b]	ee/%[c]
1[d]	CH_3CN	−40	20	25	43
2	CH_3CN	−40	60	42	43
3	CH_3CN	0	50	66	34
4	CH_3CN	40	5	89	30
5[e]	CH_3CN/H_2O	0	5	100	41

[a] Epoxidation conditions: iminium salt **4** (10 mol %), TPPP (2 equiv). [b] Conversions were evaluated from the ^{1}H NMR spectra by integration of alkene and epoxide signals. [c] Enantiomeric excesses were determined by ^{1}H NMR spectroscopy in the presence of (+)-Eu(hfc)$_3$ (10 mol %). [d] 5 mol % of **4**. [e] Epoxidation conditions: iminium salt **4** (5 mol %), oxone (2 equiv), Na_2CO_3 (4 equiv), MeCN:H_2O (1:1), 0 °C.

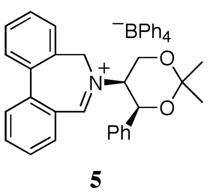
TABLE 2. Asymmetric Epoxidation of 1-Phenylcyclohexene Mediated by Catalyst 5

entry	solvent	temp/°C	time/min	conv/%[b]	ee/%[c]
1	CH_3CN	−40	3	100	67
2	CH_3CN	0	3	100	58
3	CH_3CN	40	1	100	50
4	CH_3CN	80	3	100	47
5[d]	CH_3CN/H_2O	0	5	100	59

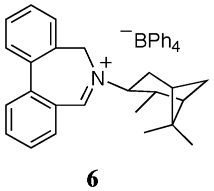
[a] Epoxidation conditions: iminium salt **5** (10 mol %), TPPP (2 equiv). [b] Conversions were evaluated from the ^{1}H NMR spectra by integration of alkene and epoxide signals. [c] Enantiomeric excesses were determined by ^{1}H NMR spectroscopy in the presence of (+)-Eu(hfc)$_3$ (10 mol %). [d] Epoxidation conditions: iminium salt **5** (5 mol %), oxone (2 equiv), Na_2CO_3 (4 equiv), MeCN:H_2O (1:1), 0 °C.

Because iminium salt **4** had proved to be our most effective catalyst under the aqueous conditions, it was selected for a temperature study of the epoxidation reaction. We had found acetonitrile to provide somewhat better enantioselectivities than dichloromethane when used as solvent, and a series of reactions was carried out with 1-phenylcyclohexene as substrate, acetonitrile as the solvent, and 2 equiv of TPPP as the stoicheiometric oxidant. The results are shown in Table 1; entry 5 shows the result obtained under aqueous conditions with the same catalyst and oxone as oxidant. As the temperature of the reaction decreases, the enantioselectivity increases (entries 1 to 4), and the rate of conversion to epoxide is reduced. The highest ee (43%) was observed when the reaction was carried out at −40 °C (entry 2). Under these conditions, the conversion to epoxide was 42% after 1 h.

We have recently reported a new family of catalysts, including **5** and **6**, in which the dihydroisoquinolinium moiety has been replaced by a biphenyl structure fused to a seven-membered cyclic azepinium salt. A binaphthalene-derived seven-membered-ring system achiral at the nitrogen substituent has previously been reported.[7]



5



6

Catalyst **5** was tested under the new nonaqueous conditions with 1-phenylcyclohexene as the substrate. The highest ee (67%) was again obtained at the lowest temperature, and the ee values are substantially higher than those obtained with catalyst **4**. Table 2 shows iminium salt **5** to be the catalyst of choice, not only in terms of enantioselectivity, but also in terms of the reaction rate: the catalyst appears to be very reactive in acetonitrile, complete conversion being observed after only 3 min at −40 °C. Entry 5 shows the result obtained under aqueous conditions with the same catalyst and oxone as oxidant.

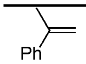
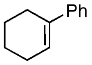
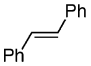
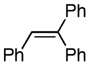
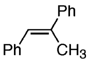
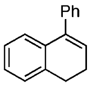
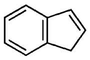
These ee values are among the best ever obtained in any epoxidation mediated by iminium salts described by our group or others. The ee obtained when the reaction is performed at 80 °C (entry 4) is surprisingly high at 47% considering the high degree of background epoxi-

---

[11] Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532.

[12] Campestrini, S.; Di Furia, F.; Labat, G.; Novello, F. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2175.

TABLE 3. Asymmetric Epoxidation of Unfunctionalized Alkenes Mediated by Iminium Salt 5

	Aqueous Conditions[a]		Anhydrous Conditions[b]			
Alkene	conv[c] /%	ee[d] /%	time /h	conv[c] /%	ee[d] /%	config[e]
	100	24	2.0	100	3	(+)-(R)
	100	60	0.05	100	67	(–)-(1S,2S)
	90	15	0.2	100	14	(–)-(1S,2S)
	90	59	1.0	78	60	(+)-(S)
			1.0	50	40	(–)-(1S,2S)
	95	37	0.05	100	24	(–)-(1S,2S)[f]
	90	41	1.0	100	22	(–)-(1S,2R)
	100	10	2.0	83	26	(–)-(1S,2R)

[a] Epoxidation conditions: iminium salt **5** (5 mol %), oxone (2 equiv), Na_2CO_3 (4 equiv), MeCN:H_2O (1:1), 0 °C, 2 h. [b] Epoxidation conditions: iminium salt **5** (10 mol %), TPPP (2 equiv), −40 °C, CH_3CN. [c] Conversions were evaluated from the ^1H NMR spectra by integration of alkene and epoxide signals. [d] Enantiomeric excesses were determined by ^1H NMR spectroscopy in the presence of (+)-Eu(hfc)$_3$ (10 mol %) or by chiral HPLC on a Chiracel OD column. [e] Absolute configurations of the major enantiomers were determined by comparison of optical rotations with values reported in the literature. [f] Reaction carried out at 80 °C.

dation under these conditions (shown to be 20% in a separate experiment) coupled with the instability of the parent oxone at this temperature.[5] It should be noted that epoxidations carried out with catalysts **3** and **6** under the new anhydrous conditions gave only poor conversions to epoxide.

Use of iminium salt catalyst **5** in acetonitrile at −40 °C is thus the reaction system that gave the highest enantioselectivity in the epoxidation of 1-phenylcyclohexene employing TPPP as oxidant under nonaqueous conditions. Table 3 shows the results of the application of this system to the epoxidation of several other alkenes. The results obtained under aqueous conditions with the same catalyst and oxone as oxidant are also shown.

In most cases, the ee values observed from reactions conducted under the new nonaqueous conditions with TPPP as oxidant are similar to or greater than those obtained when using the aqueous conditions and oxone as oxidant. The reaction is simple to carry out, and the workup involves merely addition of diethyl ether, filtration through $MgSO_4$, and evaporation of the solvent.

Experimental Procedures

Preparation of Tetraphenylphosphonium Monoperoxysulfate. Oxone triple salt ($2KHSO_5$:$KHSO_4$:K_2SO_4) (15.0 g, 48.8 mmol with respect to $KHSO_5$) was dissolved in deionized water (300 mL) with magnetic stirring at 10−15 °C (water bath). Tetraphenylphosphonium chloride (15.0 g, 40.0 mmol) in distilled dichloromethane (300 mL) was gradually added over 5 min. After an additional 30 min, the organic layer was separated, and solvent was removed under reduced pressure to afford a colorless solid. The crude salt was transferred to a fritted glass funnel and washed with distilled water (2 × 75 mL). The solid that remained was recrystallized from dichloromethane/hexane to afford colorless crystals, containing about 85% available oxygen (15.4 g, 70%). δ_H (250 MHz; $CDCl_3$) 7.64 (8 H, m), 7.78 (8 H, m), 7.89 (4 H, m), 8.92 (1 H, s).

General Procedure for Catalytic Asymmetric Epoxidation of Simple Alkenes Mediated by Iminium Salts with Tetraphenylphosphonium Monoperoxysulfate. Tetraphenylphosphonium monoperoxysulfate (2 equiv with respect to the substrate) was dissolved in the desired solvent (2 mL per 0.1 g of oxidant) and cooled to the required temperature. To this was added the iminium salt as a solution in the solvent (0.5 mL per 0.1 g of oxidant). This iminium salt solution was cooled to the same temperature as the solution containing the oxidant and added dropwise to it over 15−20 min; the temperature of the reaction vessel was monitored to minimize the increase in temperature during the addition. The substrate (100 mol %) was added as a solution in the reaction solvent (0.5 mL per 0.1 g of oxidant) in the same manner as the catalyst. The reaction was stirred at the same temperature until the substrate was completely consumed by TLC. Diethyl ether (precooled to the reaction temperature) (20 mL per 0.1 g of oxidant) was added to precipitate the remaining oxidant. The solution was filtered through Celite, and the solvents were removed under reduced pressure to give the epoxide product. Pure samples were obtained by column chromatography, eluting with ethyl acetate/light petroleum (1:99).

Acknowledgment. This investigation has enjoyed the support of the EPSRC. We are indebted to Prof. Ruggero Curci for useful discussions.

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035820J