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Effect of the medium on the oxaziridinium-catalyzed enantioselective epoxidation

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Abstract—TRISPHAT salts of chiral iminium cations allow, in combination with 18-C-6, the use of biphasic CH_2Cl_2/water conditions, which can improve the enantioselectivity of the oxone-mediated epoxidation. © 2002 Published by Elsevier Science Ltd.

Stereoselective oxidative functionalization of unactivated C–C double bonds is a topic of great interest in today's chemistry and much activity has been devoted to the asymmetric transfer of oxygen atoms.[1] Recently, the epoxidation of olefins by oxaziridinium cations has been studied because of the faculty of iminium ions—formed along with the desired epoxides—to react with Oxone® (potassium peroxymonosulfate) and regenerate the reactive oxaziridinium species.[2] Successful enantioselective variants of this catalytic reaction have been developed using as precatalysts non-racemic cyclic and acyclic iminium salts (Fig. 1).[3]

Generally, the chemical yields are good but the enantioselectivities only moderate. Combinations of CH_3CN and water have been used as solvent mixtures, as the reagents usually dissolve in these homogenous (monophasic) conditions.[4] Herein, we report that the combined use of TRISPHAT counterions (**1**, Fig. 2) and of catalytic amounts of 18-C-6 allows the use of biphasic CH_2Cl_2/water conditions which can improve—in the case of iminium precatalyst **2a**—the enantioselectivity of the epoxidation (enantiomeric ratio, e.r. from 2.4:1 to 7.2:1 for the epoxidation of 1-phenyl-dihydronaphthalene **6**). The recent report by Page et al. on the synthesis and the use of iminium cation **2a** for the enantioselective epoxidation prompted us to disclose our own results.[5]

Mechanistic and computational studies have revealed that the oxygen transfer reaction from oxaziridium cations to olefins happens in one step via charged *spiro* transition states.[6] We thus wondered whether the stereoselectivity of the asymmetric reaction could benefit from less polar solvent conditions as a 'destabilization' of the diastereomeric transition states might result in more discriminating stereoselective interactions. Previously, the synthesis and resolution of

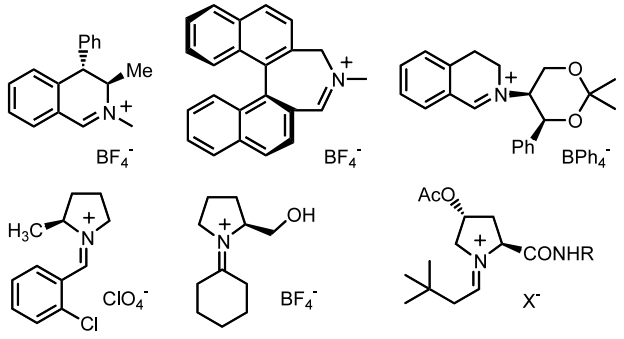

Figure 1. Known chiral iminium precatalysts.

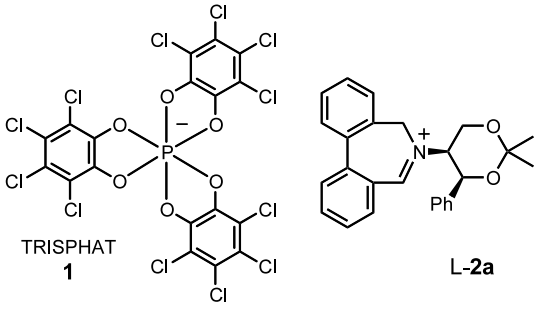

Figure 2. TRISPHAT anion **1** and iminium precatalyst (4*S*,5*S*)-**2a** derived from L-(+)-acetonamine.

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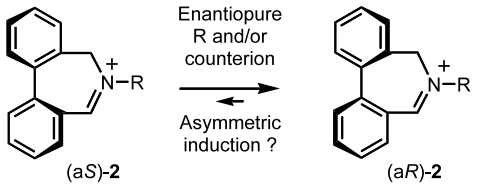
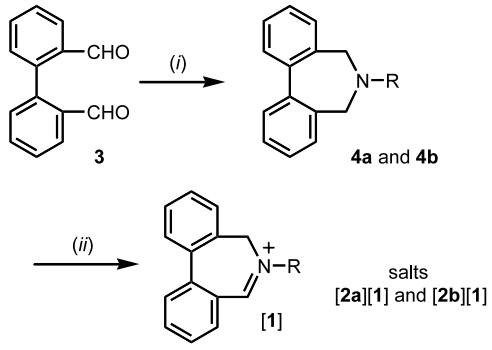


Figure 3. Possible asymmetric induction from chiral substituents and counterions.



Scheme 1. Synthesis of iminium precatalysts **2a** (R = D-(−) or L-(+)-acetonamine) and **2b** (R = *n*-Pr): (i) $NaBH_3CN$, RNH_2, AcOH, CH_3CN, **4a** (77%) and **4b** (94%); (ii) a. I_2, AcOK, EtOH, reflux, b. [R_3NH][**1**], chromatography over SiO_2: [**2a**][**1**] (60–68%) and [**2b**][**1**] (62%).

tris(tetrachlorobenzenediolato)phosphate(v) **1**, known as TRISPHAT, was reported.[7] This chiral anion (Δ and Λ enantiomers) is an efficient NMR chiral shift and resolving agent for cationic organic and organometallic derivatives.[8] More importantly for this study, its lipophilicity confers to its salts an affinity for organic solvents and, once dissolved, the ion pairs do not partition in aqueous layers (AL).[9] It was thus expected, in biphasic solvent conditions, that the TRISPHAT salts of iminium and oxaziridinium cations would react in the less polar organic layer (OL, CH_2Cl_2) rather than in the polar aqueous one.

We decided to develop the chemistry of diphenylazepinium cations of type **2**, not yet reported at the start of this study, as literature precedents indicated that such derivatives would exhibit atropisomeric (a*R*) and (a*S*) conformations, which would interconvert freely in solution by rotation around the biphenyl axis.[10] Introduction of chiral substituents on the backbone and/or ion pairing with enantiopure anions would lead to the formation of diastereomeric intramolecular and/or intermolecular interactions, which could shift the conformational equilibrium towards one preferred (a*R*) or (a*S*) diastereomer (Fig. 3).[10,11] If so, good asymmetric efficiency was envisioned as the structure of the precatalysts would resemble Aggarwal's conformationally rigid dinaphthazepinium derivative, which is one of the most efficient precatalyst.[3b]

Previous results by Page et al. on the use of (4*S*,5*S*)-5-amino-2,2-dimethyl-6-phenyl-1,3-dioxane (or L-(+)-acetonamine) as a source of asymmetric induction in oxaziridinium-catalyzed epoxidations, convinced us to use this primary amine in conjunction with the diphenylazepinium skeleton.[3c] Synthesis of derived iminium cation **2a** was realized in two steps (Scheme 1). Reductive amination of biphenyl-2,2′-dicarbaldehyde **3**[12] in the presence of D-(−) or L-(+)-acetonamine, $NaBH_3CN$ and AcOH afforded desired D-(−)- and L-(+)-**4a** in 77% yield.[13] Finally, treatment of compounds **4a** with I_2/AcOK in boiling EtOH afforded the desired iminium species as their iodide salts.[14]

In situ association with TRISPHAT anions was realized by chromatography under previously reported conditions. To take into account a possible influence of the chirality of the anion, all four diastereomeric ion pairs [L-**2a**][Δ-**1**], [L-**2a**][Λ-**1**], [D-**2a**][Δ-**1**] and [D-**2a**][Λ-**1**] were prepared and afforded in moderate overall yields (60–68%).[15] Cation **2b** made from achiral 1-propyl-amine was also synthesized following the same conditions and salt [**2b**][Δ-**1**] was afforded in decent yield (62% from **3**).

Initial experiments were performed with 1-phenyl-cyclohexene **5** as substrate (Table 1). Under classical acetoni-

Table 1. Asymmetric epoxidation of 1-phenyl-cyclohexene **5** by diphenylazepinium precatalysts

Entry[a]	Iminium	Anion	Solvent medium	Additive	Conversion (%)[b]	Yield (%)[c]	E.e. (%)[d]	E.r.[d]	Conf.[e]
1[f]	L-**2a**	BPh_4	CH_3CN:H_2O 1:1	–	100	–	60	4:1	(*S*,*S*)
2	L-**2a**	Λ-**1**	CH_3CN:H_2O 1:1	–	100	–	61	4.1:1	(*S*,*S*)
3	**2b**	Δ-**1**	CH_3CN:H_2O 1:1	–	100	69	0	–	–
4	L-**2a**	Λ-**1**	CH_2Cl_2:H_2O 3:2	–	0	0	–	–	–
5	**2b**	Δ-**1**	CH_2Cl_2:H_2O 3:2	–	0	0	–	–	–
6	L-**2a**	Δ-**1**	CH_2Cl_2:H_2O 3:2	18-C-6 (2.5 mol%)	90	78	69	5.4:1	(*S*,*S*)
7	L-**2a**	Λ-**1**	CH_2Cl_2:H_2O 3:2	18-C-6 (2.5 mol%)	100	77	69	5.4:1	(*S*,*S*)
8	D-**2a**	Δ-**1**	CH_2Cl_2:H_2O 3:2	18-C-6 (2.5 mol%)	100	88	70	5.7:1	(*R*,*R*)
9	D-**2a**	Λ-**1**	CH_2Cl_2:H_2O 3:2	18-C-6 (2.5 mol%)	100	82	69	5.4:1	(*R*,*R*)
10	**2b**	Δ-**1**	CH_2Cl_2:H_2O 3:2	18-C-6 (2.5 mol%)	97	89	0	–	–

[a] Unless otherwise indicated, all epoxidations were carried out at rt for 3 h with 0.2 mmol of 1-phenyl-cyclohexene, 0.2 mmol of Oxone®, 0.8 mmol of $NaHCO_3$ and 5 mol% of precatalyst.

[b] Conversion was calculated from the ratio of 1-phenyl-cyclohexene and 1-phenyl-cyclohexene-oxide in GC and/or by ^1H NMR.

[c] Yield based on conversion after flash column chromatography.

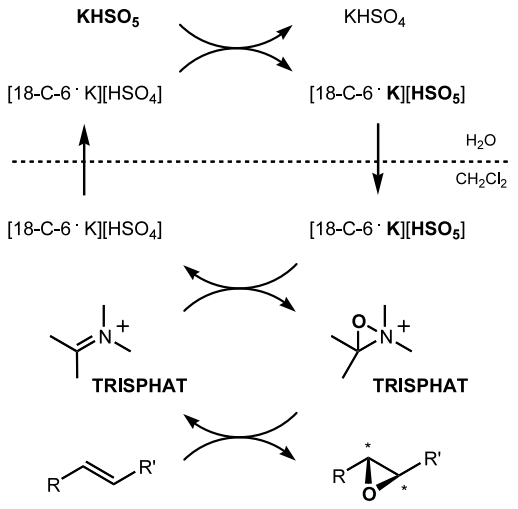
[d] Determined by chiral HPLC (Chiracel OD-H).

[e] The configuration of the major enantiomer of the epoxide is indicated as (*S*,*S*) or (*R*,*R*).

[f] See Ref. 5.

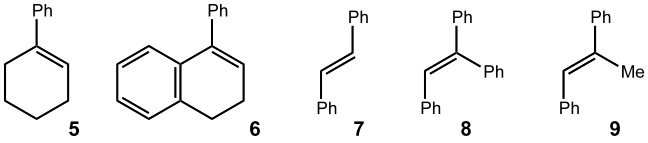
trile/water conditions, compound **5** reacted with Oxone®, $NaHCO_3$ and salt [L-**2a**][Λ-**1**] (5 mol%) to give (1*S*,2*S*)-1-phenylcyclohex-1-ene oxide in high yield (entry 2). The enantiomeric excess of the epoxide (e.e. 61%) was virtually identical to the one observed by Page et al. (e.e. 60%) with salt [L-**2a**][BPh_4] as precatalyst (Table 1, entry 1). This result seemed logical as ion pairs are separated by the solvent in polar media:[16] iminium ion L-**2a** reacts on its own with little influence from the chemical or chiral nature of the counterion.[17]

Biphasic CH_2Cl_2/water conditions were then tried and initial attempts were disappointing as no epoxide could be found in the crude mixtures from reactions performed with precatalysts [L-**2a**][Λ-**1**] and [**2b**][Δ-**1**] (entries 4 and 5). We reasoned that this lack of reactivity was not the result of the biphasic conditions per se but rather the consequence of the tight containment of the reagents in two separate liquid phases: the organic TRISPHAT salts in the OL and Oxone® in the AL. If so, addition of 18-C-6 to the mixture would be sufficient to establish a transport mechanism of $KHSO_5$ between the AL and OL, and permit the oxidation in the OL of the iminium cation into its reactive oxaziridinium derivative (Scheme 2). Reactions were thus performed again with a catalytic amount of 18-C-6 (2.5 mol%) and yielded the desired epoxide in decent isolated yields (77–89%) and higher enantiomeric purity (e.e. 69–70%). The influence of the chiral nature of TRISPHAT was tested and little or no effect was monitored as reactions with diastereomeric salts [L-**2a**][Δ-**1**], [L-**2a**][Λ-**1**], [D-**2a**][Δ-**1**] and [D-**2a**][Λ-**1**] led essentially to the same enantiomeric excesses (Table 1, entries 6–9). With [**2b**][Δ-**1**], no selectivity was observed (Table 1, entry 10). One possibility to explain this lack of influence displayed by the chiral anion is to consider the poor asymmetric induction of anion **1** onto the (a*S*) and (a*R*) conformational equilibrium.[18,11]



Scheme 2. Plausible mechanism for the biphasic oxaziridinium-catalyzed epoxidation.

Other prostereogenic di- and trisubstituted olefins (**6**–**9**) were tested with this novel biphasic protocol and the results are summarized in Table 2. Epoxide formation was observed with usually quantitative conversion (^{1}H NMR, GC) and good overall isolated yields (64–85%).



Generally, enantioselectivities for the reactions performed under biphasic conditions were higher than those reported by Page et al. for the homogenous conditions.[5] In the case of **6**, 1-phenyl-3,4-dihydronaphthalene oxide was obtained in much higher enantiomeric excess (76% versus 41%). Interestingly, a reversal of the absolute configuration—(+)-(1*R*,2*S*) instead of (−)-(1*S*,2*R*) in homogenous conditions—was observed for product 1-phenyl-3,4-dihydronaphthalene oxide.[19]

In conclusion, we have shown that the ion pairing of an iminium cation with TRISPHAT anions allows the use of strict biphasic conditions, which can lead to higher enantioselectivities. Although most results have remained modest in the case of precatalyst **2a**, we

Table 2. Asymmetric epoxidation of olefins using salt [L-**2a**][Λ-**1**] as precatalyst

Entry[a]	Alkene	Precatalyst	Yield (%)[b]	E.e.[c] (%)	E.r.	Conf.	MonoΦe.e.[d]
1	**5**	[L-**2a**][Λ-**1**]	67	69	5.4:1	(*S*,*S*)	60
2	**6**	[L-**2a**][Λ-**1**]	85	76	7.2:1	(1*R*,2*S*)	41[e]
3	**7**	[L-**2a**][Λ-**1**]	85	17	1.4:1	(*S*,*S*)	15
4	**8**	[L-**2a**][Λ-**1**]	82	23	1.6:1	(*S*)	59
5	**9**	[L-**2a**][Λ-**1**]	64	42	2.4:1	(1*S*,2*S*)	37

[a] Unless otherwise indicated, all epoxidations were carried out at rt for 3 h with 0.2 mmol of alkene, 0.2 mmol of Oxone®, 0.8 mmol of $NaHCO_3$, 2.5 mol% of 18-C-6, 5 mol% of [L-**2a**][Λ-**1**] and a 3:2 mixture of CH_2Cl_2:H_2O as solvent.

[b] Yield based on conversion after flash column chromatography.

[c] Determined by chiral HPLC (Chiracel OD-H) and GC (Lipodex-E).

[d] Established by Page et al. in homogenous solvent conditions (CH_3CN:H_2O 1:1) using [L-**2a**][BPh_4] as precatalyst; see Ref. 5.

[e] Major enantiomer: (−)-(1*S*,2*R*)-1-phenyl-3,4-dihydronaphthalene oxide.

believe that these new conditions can be applied to already reported iminium salts and might lead to better results. Further studies are performed to match anion and cation structures to benefit from the asymmetric ion pairing.

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References

1. (a) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p. 649; (b) Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981–5021; (c) Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215–1225; (d) Denmark, S. E.; Wu, Z. C. *Synlett* **1999**, 847–859.
2. (a) Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727–13738; (b) Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499–3548.
3. (a) Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141–154; (b) Aggarwal, V. K.; Wang, M. F. *Chem. Commun.* **1996**, 191–192; (c) 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*, 6926–6931; (d) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341–2352; (e) Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, 1810–1812; (f) Wong, M. K.; Ho, L. M.; Zheng, Y. S.; Ho, C. Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587–2590.
4. To the noticeable exception of some olefins, see: Aggarwal, V. K. WO. 9 706 147, 1997.
5. Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Bethell, D.; Merifield, E. *Synlett* **2002**, 580–582.
6. (a) Armstrong, A.; Draffan, A. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2861–2873; (b) Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 2948–2949.
7. (a) Lacour, J.; Ginglinger, C.; Favarger, F. *Tetrahedron Lett.* **1998**, 4825–4828; (b) Lacour, J.; Ginglinger, C.; Grivet, C.; Bernardinelli, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 608–609.
8. Lacour, J.; Jodry, J. J.; Monchaud, D. *Chem. Commun.* **2001**, 2302–2303 and references cited therein.
9. This property has led to successful applications of **1** as a chiral selector in asymmetric extraction processes: Lacour, J.; Goujon-Ginglinger, C.; Torche-Haldimann, S.; Jodry, J. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3695–3697; Jodry, J. J.; Lacour, J. *Chem. Eur. J.* **2000**, *6*, 4297–4304.
10. Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551–1554 and references cited therein.
11. In principle, D_3-symmetric **1** is suitable for the chiral recognition of C_2-symmetric organic cations, although in practice, low induction is usually observed: Lacour, J.; Londez, A.; Goujon-Ginglinger, C.; Buß, V.; Bernardinelli, G. *Org. Lett.* **2000**, *2*, 4185–4188; Pasquini, C.; Desvergnes-Breuil, V.; Jodry, J. J.; Dalla Cort, A.; Lacour, J. *Tetrahedron Lett.* **2002**, *43*, 423–426 and this paper.
12. Large scale preparation of **3** was realized by ozonolysis of phenanthrene: Agranat, I.; Rabinovitz, M.; Shaw, W.-C. *J. Org. Chem.* **1979**, *44*, 1936–1941.
13. To simplify the denomination of the chiral entities, symbols L and D were maintained for **2a** and **4a**; L and D meaning configurations (4*S*,5*S*) and (4*R*,5*R*) for the acetonamine moiety, respectively.
14. Leonard, N. J.; Leubner, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 3408–3411.
15. Salts [Bu_3NH][Λ-**1**] (e.r. >39:1) and [cinchonidinium][Δ?**1**] (d.r. >39:1) were used for the anion-exchange reactions.
16. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; 2nd ed.; VCH: Weinheim, 1988.
17. This result is confirmed by the lack of asymmetric induction in the reaction of **5** with precatalyst [**2b**][Δ-**1**] under homogenous polar conditions (Table 1, entry 3).
18. VT-NMR experiments (^{1}H NMR, 400 MHz, $CDCl_3$) were performed and showed at 253 K, a 1.8:1 ratio of signals for diastereomeric (a*S*) and (a*R*) conformations, and this for both [L-**2a**][Λ-**1**] and [L-**2a**][Δ-**1**] salts. For compound [**2b**][Δ-**1**], no induction was observed.
19. This inversion in the sense of configuration might be the explanation for the decrease in selectivity in the enantioselective epoxidation of acyclic **8**, compound **8** being structurally related to **6**.