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Design of a highly efficient catalyst for the oxaziridinium-mediated epoxidation of olefins by Oxone®

Luis Bohé* and Majed Kammoun

Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif sur Yvette, France

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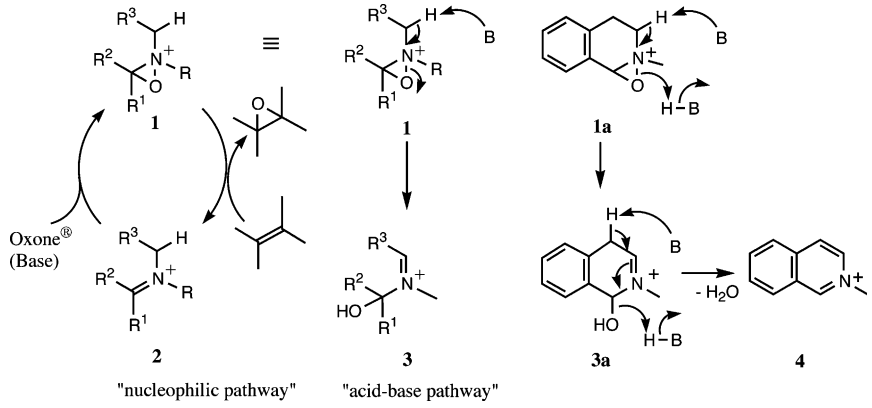
Abstract—2,3,3-Trimethyl-7-nitro-3,4-dihydroisoquinolinium tetrafluoroborate is a highly efficient catalyst for the oxaziridinium-mediated epoxidation of a variety of olefins, including monosubstituted ones.

The potential of oxaziridinium salts as electrophilic-oxygen transfer reagents has emerged clearly since the pioneering reports on oxaziridinium chemistry by X. Lusinchi and co-workers.[1] Some time later, this group described the oxidation of thioethers,[2] amines and imines[3] and established that oxaziridinium salts epoxidize the carbon–carbon double bonds of simple olefins.[4] They also showed that nonracemic oxaziridiniums are suitable reagents for the asymmetric epoxidation of prochiral olefins.[5] The catalytic versions of the epoxidation reactions were also developed by means of an oxaziridinium-mediated system (Scheme 1) in which the oxaziridinium **1** is formed in situ from a catalytic amount of the parent iminium salt **2** and Oxone® as the oxygen source.[5,6] Epoxidation is a very important reaction in organic synthesis, and the catalytic oxaziridinium-mediated epoxidation of olefins is undoubtedly a promising method in this field. For this reason, a number of research groups have subsequently made contributions[7–12] to this area and naturally, any improvement in the global efficiency of the catalytic system may contribute to the development of this new methodology as an attractive and convenient alternative to the known and widely used epoxidation methods.



Scheme 1.

Keywords: Epoxidation; Oxaziridinium; Iminium.
* Corresponding author. Tel.: +33-0169823072; fax: +33-0169077247; e-mail: bohe@icsn.cnrs-gif.fr

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Obviously any reaction of the oxaziridinium **1** not regenerating the parent iminium **2** is deleterious to the oxygen transfer onto the carbon–carbon double bond, as this breaks the catalytic turnover. The irreversible base-catalyzed isomerization of the oxaziridinium into a carbinol–iminium **3** (which reacts further) is the most common side-reaction in these catalytic epoxidation systems mediated by a cyclic oxaziridinium.[6] The in situ-generated oxaziridinium **1** may thus evolve through two main pathways: a nucleophilic (useful) path that involves oxygen transfer and regeneration of the parent iminium salt **2**, and the competing acid–base pathway involving isomerization and loss of the catalyst (Scheme 1). It has been shown that 3,4-dihydrosoiquinolinium-derived oxaziridinium salts, either isolated[4,5,13] or generated in a catalytic system[5,6,8a–c] from the parent iminium salts, are particularly useful as epoxidation reagents. As depicted in Scheme 1, the acid–base pathway leads in this family to the corresponding isoquinolinium **4** through dehydration of the carbinol–iminium **3a** arising from the isomerization of the oxaziridinium salt **1a**.[14]

As part of our interest in oxaziridinium chemistry and particularly in the rational design of dihydroisoquinolinium-derived catalysts able to improve the catalytic oxygen transfer process, we first examined the possibility of preventing aromatization from taking place. We thus showed that improvement in catalytic efficiency could be achieved in this way.[15] This was established by comparing the behavior of the epoxidation system catalyzed in turn by the standard iminium **2a** and the 3,3-dimethyldihydroisoquinolinium salt **2b** (Fig. 1), which generate two oxaziridiniums (**1a** and **1b**, Fig. 1) that have similar electrophilicities but different isomerizing abilities.

To achieve the same goal we also decided to test another strategy, one in which suppression of the aromatization pathway is not a prerequisite to improve the efficiency of the oxaziridinium-mediated system. This consisted of reinforcing the ratio of electrophilicity to acidity of the oxaziridinium and by so doing, favour the nucleophilic pathway over the acid–base pathway. Thus we prepared the iminium salt **2c** (Fig. 1) and evaluated its behavior in the catalytic system. Enhanced catalytic efficiency towards the unsubstituted iminium **2a** also resulted. Therefore, and given the likelihood of a synergy between both individual effects, we decided to ally the two strategies. We prepared the iminium salt **2d** (Fig. 1), which should generate an oxaziridinium (**1d,** Fig. 1) associating enhanced electrophilicity with respect to **1a** and the exclusion of the aromatization pathway.

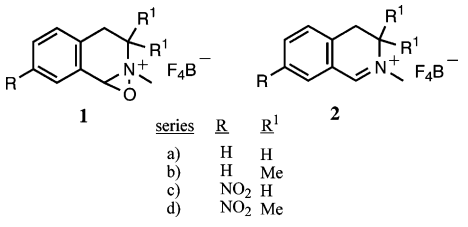


Figure 1.

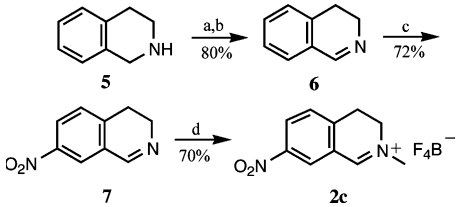
We reported earlier that the 3,3-disubstituted dihydroisoquinolinium salt **2b** is a more efficient catalyst than the unsubstituted iminium salt **2a**.[15] Here we report that the 7-substituted salt **2c** is also a more efficient catalyst than iminium salt **2a** and that these two features combined in compound **2d** produce a highly efficient catalyst for the oxaziridinium-mediated epoxidation of olefins by Oxone®.

To test the strategy which allows the aromatization pathway to remain in action we decided to prepare a dihydroisoquinolinium salt bearing on the aromatic ring an electron-withdrawing group not in conjugation with the imine bond. The helpful role that the substituent should play consists of significantly enhancing the electrophilicity, but without at the same time significantly increasing the acidity of the α-hydrogen atoms of the oxaziridinium generated in the catalytic system. If this could be achieved the nucleophilic pathway (Scheme 1) should be favored thus improving the catalytic efficiency.

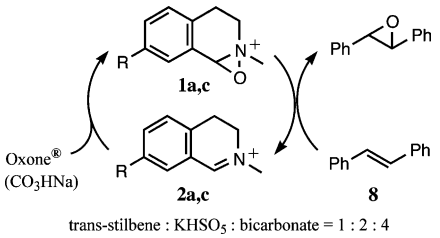
To put this strategy into practice, the introduction of a nitro group on C7 seemed a convenient option. The iminium salt **2c** was synthesized from commercially available tetrahydroisoquinoline **5**, which was oxidized to **6** in two steps through the corresponding chloramine. Then the dihydroisoquinoline **6** was nitrated following a described procedure.[16] This highly regioselective step leads to the 7-nitro-3,4-dihydroisoquinoline **7**,[16,17] which was finally alkylated with trimethyloxonium tetrafluoroborate leading to **2c** (Scheme 2).

With iminiun salt **2c**[18] in hand we were able to compare its catalytic activity in the epoxidation of *trans*-stilbene to that of the standard iminium **2a**.[6] In the catalytic system involving the oxaziridinium **1c** the epoxidation of *trans*-stilbene **8** is notably faster than in the reference system involving the oxaziridinium **1a**. Even with half the loading of catalyst **2c** with respect to catalyst **2a** (5 mol% of **2c** vs 10 mol% of **2a**), the system mediated by the oxaziridinium **1c** epoxidized *trans*-stilbene **8** about two times faster than the standard system mediated by oxaziridinium **1a** (Scheme 3 and Table 1, entry 3 vs entry 1).

We now had in hand two simple and at least complementary ways to improve the catalytic efficiency of the standard iminium salt **2a**. Thus it seemed clear that the individual features of **2b** and **2c** associated in a new compound should potentiate its catalytic activity with



Scheme 2. (a) $NaOCl_{(aq)}$, Cl_2CH_2; (b) NaOH, MeOH–Cl_2CH_2; (c) KNO_3–H_2SO_4, rt 2 h, 60 °C 4 h; (d) $MeO^+F_4B^-$, Cl_2CH_2, rt.



Scheme 3. Epoxidation of *trans*-stilbene with iminium salts **2a**,**c** as catalysts.

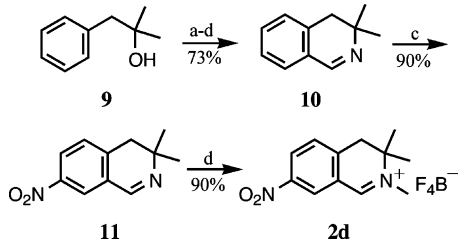
Table 1. Epoxidation of *trans*-stilbene with iminium salts **2a**–**d** as catalysts[a]

Entry	Catalyst	R	R^1	Loading (mol%)	Time (h)[b,c]
1[6]	**2a**	H	H	10	16
2[15]	**2b**	H	Me	10	7
3	**2c**	NO_2	H	5	6
4	**2d**	NO_2	Me	5	1.5

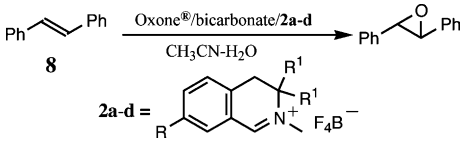
[a] Reaction conditions: molar ratio olefin/$KHSO_5$/$NaCO_3H$ = 1:2:4, CH_3CN–H_2O (3%), rt.
[b] Time at which 100% conversion is attained.
[c] Reactions monitored by TLC and/or ^1H NMR spectroscopy.

respect to its precursors **2b** and **2c**. To test this hypothesis we synthesized the dihydroisoquinolinium salt **2d** from the commercially available tertiary alcohol **9** (Scheme 4). The formamide from step (a)[19] was cyclized following a three-step sequence[20] into the dihydroisoquinoline **10**.[21] This imine was nitrated regioselectively, following the same procedure as for (**7**→**2c**),[16] and the resulting nitro derivative **11**[22] was methylated with the Meerwein salt, trimethyloxonium tetrafluoroborate, leading to **2d**.[23]

The catalytic activity of the iminium salt **2d** was then compared to those of its precursors **2a**–**c** in the same test reaction used before (Scheme 5). We were pleased to find



Scheme 4. (a) KCN, AcOH–H_2SO_4, rt; (b) oxalyl chloride; Cl_2CH_2; (c) $FeCl_3$; (d) MeOH, H_2SO_4; (e) KNO_3–H_2SO_4, rt 2 h, 60 °C 4 h; (f) $MeO^+F_4B^-$, Cl_2CH_2, rt.



Scheme 5.

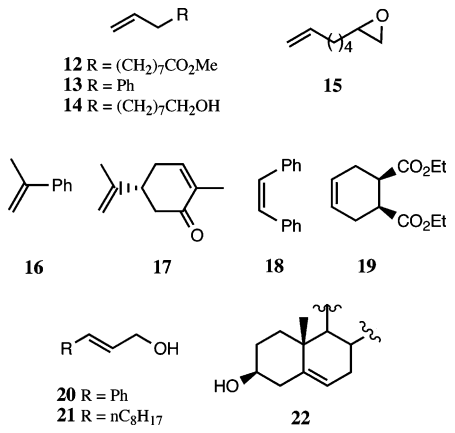


Figure 2.

that the iminium salt **2d** was by far the best catalyst in this series (Table 1). Even with half the loading of catalyst, the system mediated by the oxaziridinium **1d** achieved the epoxidation of *trans*-stilbene in about one-tenth of the time required by the standard system mediated by oxaziridinium **1a** (Table 1, entry 4 vs entry 1).

The superior catalytic efficiency of the dihydroisoquinolinium salt **2d** was also evident in the epoxidation of the less reactive terminal double bond of olefin **12** (Fig. 2). The catalytic epoxidation of this undecylenic ester was sluggish with 10 mol% of the iminium salt **2b** as catalyst, reaching a maximum conversion of 40%.[15] With the same loading (10 mol%) of the new catalysts **2c** and **2d**, the catalytic system involving iminium **2c** was somewhat more efficient leading to a moderate increase in the conversion, which reached 50%, but the catalytic system involving the iminium **2d**, proved to be highly efficient making the conversion to rise to ca. 90% (Table 2, entry 1). Moreover, essentially equal conversions, which confirmed the high catalytic efficiency of iminium **2d**, were attained in the catalytic epoxidations of the monosubstituted olefins **13**–**15** (entries 2–4).

The results of the oxaziridinium **1d**-mediated oxidation of a variety of di- and trisubstituted olefins are also given in Table 2. These substrates (**16**–**22**) were conveniently epoxidized using 5 mol% of the iminium salt **2d** as catalyst (entries 5–11). The epoxidation of L-(−)-carvone **17** occurred selectively on the exocyclic double bond leading to a 1:1 mixture of diastereoisomers[24] (entry 6).

The epoxidation of the cyclic olefin **19** (entry 8) showed a stereoselection most likely resulting from a favored approach of the oxaziridinium **1d** from the less hindered face of **19**, thus leading to a mixture of the *anti*- and *syn*-epoxides in the molar ratio 3.8:1.[25] Similar selectivity (*anti*) has been reported in the peracid epoxidation[26] of the homologous methyl ester. In contrast, the epoxidation of cholesterol **22** produced a mixture of the β- and α-epoxides in the molar ratio 3.3:1[27] (entry 11). This time the β-selectivity observed in the catalytic oxaziridinium-mediated system differed from the known

Table 2. Epoxidation of olefins using iminium salt **2d** as catalyst[a]

Entry	Olefin	Catalyst loading (mol%)	Time (h)[b]	Conversion (%)[c]
1	**12**	10	6	92
2	**13**	10	6	85
3	**14**	10	6	89
4	**15**	10	6	85
5	**16**	5	2	100
6	**17**	5	4	100[d]
7	**18**	5	4	100
8	**19**	5	4	100[e]
9	**20**	5	2	100
10	**21**	5	6	100
11	**22**	5	2	100[f]

[a] Reaction conditions: molar ratio olefin/$KHSO_5$/$NaCO_3H$ = 1:2:4, CH_3CN–H_2O (3%), rt.
[b] Reactions monitored by TLC and/or ^1H NMR spectroscopy.
[c] Conversion to the epoxide determined by ^1H NMR analysis of the crude product integrating the epoxide versus unchanged olefin.
[d] Exclusively exocyclic epoxide, 1:1 mixture of diastereoisomers (ratio determined by ^1H NMR spectroscopy).
[e] Molar ratio *syn*:*anti* = 1:3.8 determined by ^1H NMR spectroscopy.
[f] Using CH_3CN/dioxane (1:1)-H_2O (3%) as solvent, molar ratio α/β = 1:3.3 determined by ^1H NMR spectroscopy.

α-preference in the peracid epoxidation of this substrate,[28] thus suggesting that factors stronger than the steric interactions during the reagent's approach govern the stereochemistry of the oxaziridinium **1d**-mediated epoxidation of this more substituted double bond.

In conclusion, we have developed a highly efficient dihydroisoquinolinium-derived catalyst for the oxaziridinium-mediated epoxidation of olefins by Oxone®. This iminium salt **2d**, an easily prepared and handled crystalline solid, not only improves the epoxidation of di- and more substituted olefins but also seems well suited for the efficient catalytic epoxidation of monosubstituted olefins thus enlarging, from a practical standpoint, the scope of this methodology. Experimental work to confirm this point is underway.

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18. 2-Methyl-7-nitro-3,4-dihydroisoquinolinium tetrafluoroborate **2c**. mp: 191–192 °C (CH_3COCH_3–Et_2O). ^1H NMR (CD_3CN, 200 MHz): 3.41 (t, 2H); 3.82 (s, 3H); 4.1 (t, 2H); 7.74 (d, 1H, J = 8.3 Hz); 8.58 (dd, 1H, J = 8.3 Hz, J = 2.2 Hz); 8.63 (d, 1H, J = 2.2 Hz); 8.96 (s, 1H). ^{13}C NMR (CD_3CN, 50 MHz): 25.24; 48.66; 50.49; 125.79; 127.91; 130.57; 132.04; 143.68; 148.13; 166.35. MS (FAB): 191 ($M^{+\cdot}$−tetrafluoroborate), 59%; 299 (M^++thioglycerol), 100%. Anal. Calcd for $C_{10}H_{11}N_2O_2BF_4$: C, 43.20; H, 3.99; N, 10.08. Found: C, 43.09; H, 3.72; N, 9.92.
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22. 3,3-Dimethyl-7-nitro-3,4-dihydroisoquinoline **11**. mp: 105–106 °C (hexane). ^{1}H NMR ($CDCl_3$, 250 MHz): 1.27 (s, 6H); 2.84 (s, 2H); 7.33 (d, 1H, $J = 8.2$ Hz); 8.16 (d, 1H, $J = 2.3$ Hz); 8.21 (dd, 1H, $J = 2.3$ Hz, $J = 8.2$ Hz); 8.32 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 28.1 (2 C); 38.08; 55.24; 121.83; 125.84; 128.05 (2 C); 129.24; 143.12; 155.31. MS (EI): 204 (M^+, base peak). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.73; H, 6.05; N, 13.51.
23. Data for 2,3,3-trimethyl-7-nitro-3,4-dihydroisoquinolinium tetrafluoroborate **2d**. mp: 162 °C (CH_3COCH_3–Et_2O). ^{1}H NMR (CD_3 $COCD_3$, 250 MHz): 1.66 (s, 6H); 3.61 (s, 2H); 3.99 (s, 3H); 7.87 (d, 1H, $J = 8.4$ Hz); 8.65 (dd, 1H, $J = 2.3$ Hz, $J = 8.4$ Hz); 8.8 (d, 1H, $J = 2.3$ Hz); 9.38 (s, 1H). ^{13}C NMR (CD_3COCD_3, 62.5 MHz): 25.76 (2 C); 41.55; 45.74; 65.93; 128.13; 130.47; 133.04; 134.04; 146.48; 150.3; 169.71. MS (FAB): 219 [($M^{+\cdot}$−tetrafluoroborate), base peak]; 327 [(219+thioglycerol), 18%]. Anal. Calcd for $C_{12}H_{15}N_2O_2BF_4$: C, 47.09; H, 4.94; N, 9.15. Found: C, 46.84; H, 4.64; N, 9.11.
24. The diastereoisomer ratio was determined by ^{1}H NMR (Cl_3CD) analysis of the crude product, integrating the C9 methyls at δ 1.31 ppm (s, 3H) and δ 1.33 ppm (m, 3H).
25. Molar ratio *syn*:*anti* determined by ^{1}H NMR (Cl_3CD) analysis of the crude product, integrating the oxiranic protons at δ 3.18 ppm (m, 2H, *anti*-epoxide) and δ 3.23 ppm (m, 2H, *syn*-epoxide).
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