

# Organocatalysis of asymmetric epoxidation mediated by iminium salts: comments on the mechanism

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**Abstract**—Non-aqueous conditions developed for catalytic asymmetric epoxidation mediated by iminium salt organocatalysts have allowed NMR spectroscopy to be carried out on the reaction mixtures for the first time.

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## 1. Introduction

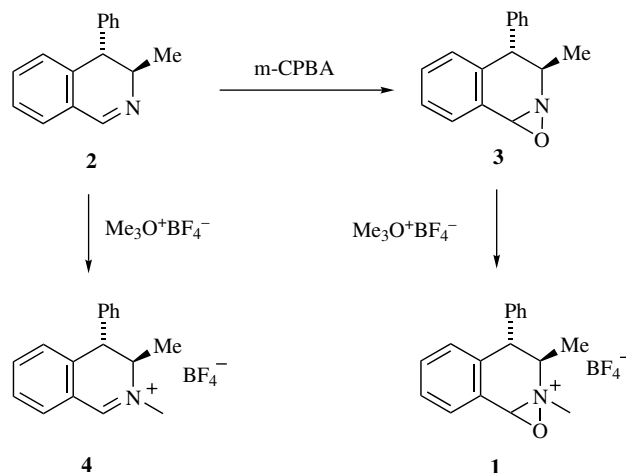
Oxaziridinium salts, generated by oxidation of iminium salts, are useful electrophilic oxidants for olefin epoxidation.<sup>1</sup> A number of asymmetric systems and other modifications have been devised.<sup>2–4</sup> The stoichiometric oxidant used by other research groups in these reactions is invariably oxone and water must be present in the reaction mixture in order to provide oxone solubility. As a result, the reactions cannot be carried out at low temperature. A base, typically sodium carbonate, must also be added. The organic co-solvent used is usually acetonitrile, although Lacour has shown that dichloromethane may be used in the presence of a crown ether.<sup>5</sup>

We have recently reported modified reaction conditions that enable iminium salt-catalysed epoxidation reactions to be carried out in organic solvents, including dichloromethane and acetonitrile, in the absence of water.<sup>6</sup> This was accomplished by using tetraphenylphosphonium monoperoxybisulfate (TPPP) as the stoichiometric oxidant.<sup>7</sup>

## 2. Results and discussion

Lusinchi has described the treatment of imine **2** with *m*-CPBA to generate the corresponding oxaziridine **3**, and subsequent quaternization with Meerwein's salt to form the first enantiomerically pure oxaziridinium salt **1**, which was used as a stoichiometric oxidant,

generating epoxides with levels of enantioselectivity similar to those observed in reactions catalysed by the corresponding iminium salt **4** (10 mol %), in the presence of oxone, under the usual aqueous acetonitrile conditions (Scheme 1). However, none of the intermediates generated from any iminium salt under these catalytic reaction conditions has been isolated.



Scheme 1.

The ability to carry out epoxidation reactions in the absence of water and base has enabled us to investigate the intermediates present during reactions through the medium of NMR spectroscopy. These studies were carried out at various temperatures, employing iminium tetraphenylborate salt **5** as catalyst, 1-phenylcyclohexene as

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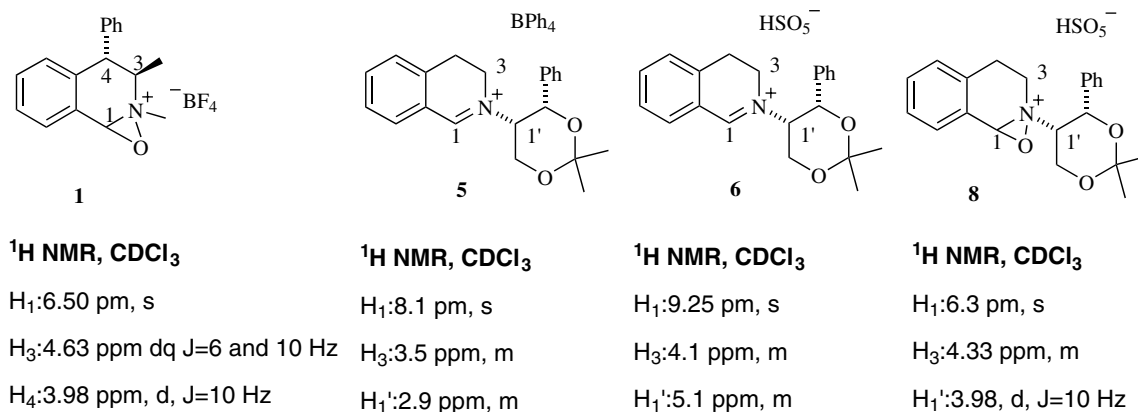


Figure 1.

substrate and TPPP as the stoichiometric oxidant, in deuteriated dichloromethane or chloroform.

Addition of TPPP (1.0 mol equiv) to a solution of iminium salt **5** in CD<sub>2</sub>Cl<sub>2</sub> resulted in an immediate change in <sup>1</sup>H NMR spectrum: In the new species, all signals are still present, but are shifted by 0.6–1.2 ppm downfield (Fig. 1). The proton at the iminium carbon atom is still present, at 9.25 ppm in <sup>1</sup>H NMR spectrum and at 168.48 ppm in <sup>13</sup>C spectrum. The signal at 1641 cm<sup>-1</sup>, which we believe corresponds to the iminium double bond, is still visible in the infrared spectrum.

At the same time, a colourless material was precipitated from the solution. We have characterized this material as tetraphenylphosphonium tetraphenylborate by <sup>1</sup>H NMR spectroscopy and mass spectrometry. The new species formed in solution under these conditions does not induce epoxidation of 1-phenylcyclohexene over 3 h at room temperature. Accordingly, we believe this first intermediate to be iminium salt **6**, the product of ion exchange between the two salts (Scheme 2).

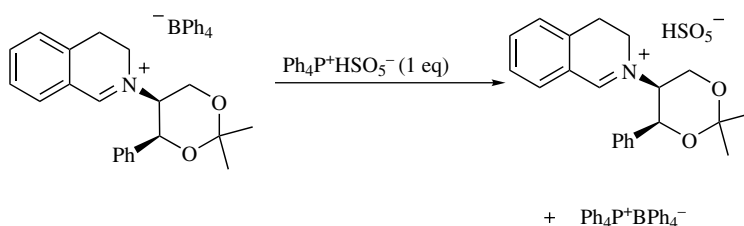
Treatment of a solution of salt **6** with additional TPPP, however, generates a new species in addition to **6**. The new species lacks the iminium proton signal at 9.25 ppm in <sup>1</sup>H NMR spectrum; instead, a new signal at 6.35 ppm is visible. This new species is rather unstable and decomposes relatively quickly (ca. 30 min at -30 °C), but as soon as it is detectable, the addition of the alkene leads to an immediate and very rapid epoxide formation. We have shown that TPPP does not itself promote epoxidation. Two possible structures for this intermediate can immediately be postulated, both arising

from nucleophilic attack of peroxybisulfate at the iminium carbon atom: a neutral intermediate **7**, the product of simple addition; and the corresponding oxaziridinium salt **8**, produced by the addition and cyclization with expulsion of bisulfate ion (Scheme 3).

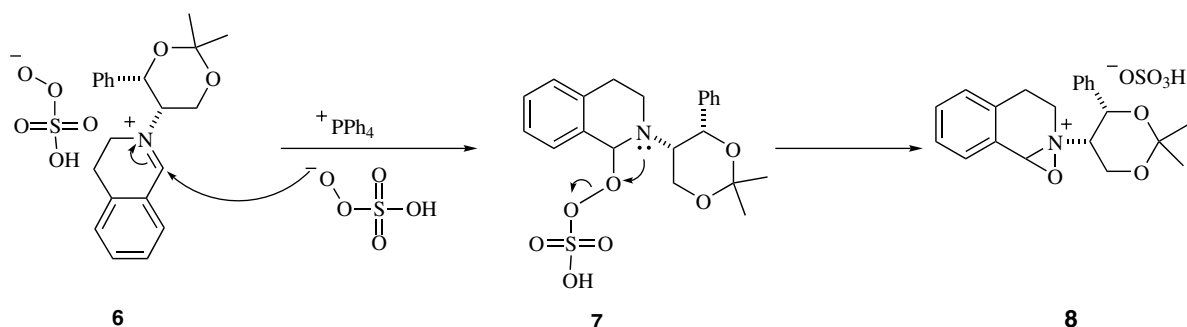
Comparisons of the <sup>1</sup>H chemical shifts of this new intermediate with those of the only oxaziridinium salt so far described **1** (Fig. 1), coupled with the fact that the addition of *m*-CPBA to intermediate **6** results in the formation of an intermediate with an identical <sup>1</sup>H NMR spectrum to that produced by addition of TPPP, suggests that the new species is oxaziridinium salt **8**.

As the relative quantity of TPPP added is increased, so the proportion of **8** present in the mixture immediately after addition increases (Table 1).

When carrying out asymmetric epoxidation reactions mediated by TPPP in organic solvents, we found that the amount of TPPP added had no effect upon enantioselectivity. However, the temperature of the reaction has a profound effect upon the enantioselectivity of the reaction (Scheme 4); for example, 1-phenylcyclohexene oxide was formed with 50% ee when iminium salt **9** was employed as catalyst at -78 °C, but when the reaction was repeated at 0 °C, only 26% ee was observed. We found the mixing of the iminium salt and TPPP in the absence of alkene to be extremely exothermic; for example, if the iminium salt (10 mol %) was added in one portion to a solution of TPPP and alkene in acetonitrile, internal temperatures can rise from -40 to 0 °C, and enantioselectivity can fall from 43% to 34% ee, when employing catalyst **5**.



Scheme 2.



Scheme 3.

**Table 1.** Comparison of the ratio of intermediates **6** and **8** with increasing equivalents of TPPP

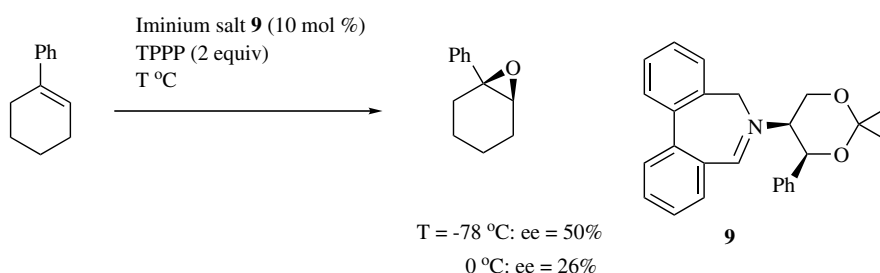
Entry	Equivalents of TPPP	Ratio <b>6</b> : <b>8</b>
1	1.0	33.3:1
2	1.5	5.6:1
3	2.0	5.6:1
4	2.5	3.2:1
5	10.0	2.4:1
6	20.0	1.5:1

The optimum conditions involved the cooling of a solution of TPPP in the reaction medium to the desired temperature; the catalyst and substrate are also separately dissolved in the reaction solvent and cooled to the desired temperature. A solution of catalyst was added dropwise to a solution of oxidant, in order to minimize the increase in reaction temperature, which is allowed to stabilize before dropwise addition of the substrate; the alkene was added last to help maintain the epoxidation process at a constant temperature. Addition of TPPP to

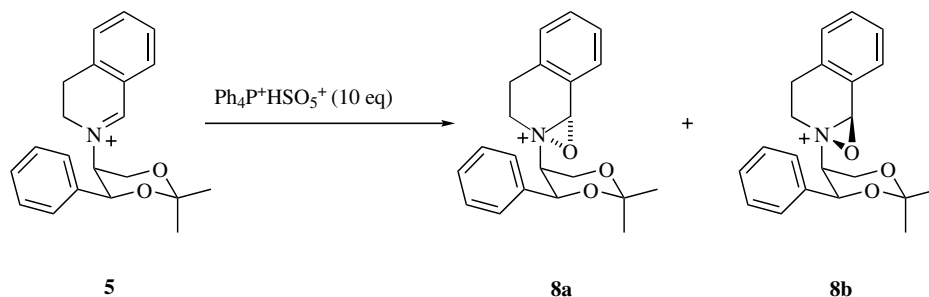
a solution of the catalyst and alkene gives poorer epoxide ees.

In principle, nucleophilic attack by the peroxybisulfate ion could occur at either diastereotopic face of the iminium unit, giving rise to two diastereoisomeric oxaziridinium species. In the case of catalyst **5**, upon addition of TPPP (10 mol equiv) in acetonitrile at  $-40\text{ }^{\circ}\text{C}$ , only one set of signals is evident in the  $^1\text{H}$  NMR spectrum for oxaziridinium ion **8**, suggesting that only one diastereoisomer is present, to which we tentatively assigned structure **8a** on the basis of the known structure of **5** in the crystal (Scheme 5).

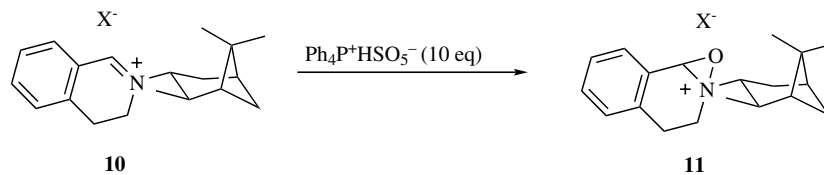
In the case of catalyst **10** (where  $\text{X} = \text{BPh}_4$ ), however, a diastereoisomeric ratio of 73:27 was observed for the oxaziridinium species **11**. It is intriguing that changing the counter-ion present affected the ratio of diastereoisomers formed (Table 2). Epoxidation of 1-phenylcyclohexene with these four catalysts suggests that there may be a relationship between the ratio of the two dia-



Scheme 4.



Scheme 5.

**Table 2.** Counter-ion effects on the ratio of diastereoisomers of **11** formed on addition of TPPP

Entry	Counter-ion	ee <sup>a</sup>	Ratio of diastereoisomers <sup>b</sup>
1	BPh <sub>4</sub>	33	73:27
2	BF <sub>4</sub>	32	66:33
3	PF <sub>6</sub>	31	69:31
4	ClO <sub>4</sub>	22	58:42

<sup>a</sup> Ee of 1-phenylcyclohexene oxide, epoxidation conditions: iminium salt (10 mol %), TPPP (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, –30 °C, 24 h.

<sup>b</sup> Conditions: TPPP (10 equiv), CD<sub>2</sub>Cl<sub>2</sub>, 0 °C.

stereoisomeric oxaziridinium salts formed and the enantiomeric excess of the epoxide generated therefrom.

### Acknowledgements

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