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Novel *N*-Phosphonio Imine-Catalyzed Epoxidation Reactions

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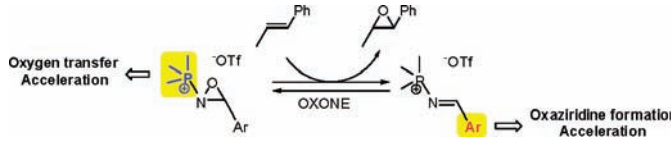
ABSTRACT



A new type of acyclic *N*-phosphonio imine catalyst for selective epoxidations has been synthesized. The activity of these imine catalysts can easily be modulated by varying its substituents. The substituent attached to the imine nitrogen atom is particularly important for an efficient oxygen transfer.

Organocatalysis has become a field of central importance in organic synthesis as an alternative to the well-established transition-metal-catalyzed transformations.[1] The organocatalytic oxidation of functionalized and unfunctionalized olefins has emerged as a very versatile and important synthetic tool since the resulting epoxides are highly useful building blocks for the synthesis of complex molecules.[2] The most productive organocatalytic processes so far have involved ketones (**I**) and iminium salts (**II**) as catalysts which can be converted using oxone, into, respectively, highly reactive dioxiranes (**I-O**) and oxaziridinium (**II-O**) species.[3] In contrast, oxaziridines (**III-O**) constitute a class of strained heterocycles exhibiting a remarkable stability. Therefore, they are much less reactive in oxidation reactions compared to dioxiranes (**I-O**) and oxaziridinium salts (**II-O**)[2−5] and, depending on the substituents, show a different reactivity such as electrophilic amination.[6] However, the relatively inert oxaziridines **III-O** have been activated by Lewis acids to achieve the selective oxidation of sulfides.[4i] In fact, the oxidizing power[7] and reactivity of oxaziridines[8] is strongly related to steric

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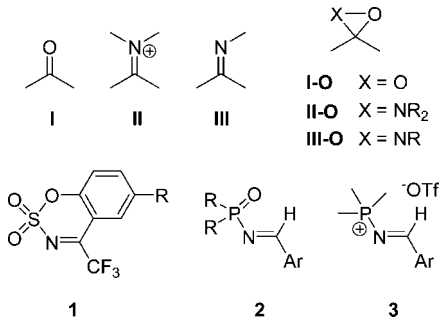
and electronic factors. Indeed, it has been recently reported that the benzoxathiazine **1** (cyclic imine **III**) shows an extraordinary catalytic activity in epoxidation reactions and in the hydroxylation of aliphatic C−H bonds.[9] This suggests that the reactivity of imines **III** should be more easily tuned compared to that of ketones **I** and iminium salts **II**, which are only strong oxidizing catalysts.



In order to develop a new family of electron-deficient imine catalysts, we present here the synthesis of *N*-phosphonio imines, which are remarkably stable in aqueous media, and the preliminary results obtained in selective catalytic epoxidation of olefins.

The previously reported *N*-phosphinoyl oxaziridines prepared from the corresponding imines **2** show a poor reactivity in oxidation reactions.[10] Therefore, the epoxidation proceeds very slowly and sometimes requires thermal activation. In fact, we have confirmed that **2** does not show any catalytic activity for the epoxidation of olefins in the presence of a stoichiometric amount of oxidant (buffered oxone solution with K_2CO_3 in CH_3CN/H_2O). Taking into account that reactivity of oxaziridines **III-O** is strongly related to the electron-withdrawing character of the substituents,[8] *N*-phosphonio imines **3**, instead of *N*-phosphinoyl imines, were considered.

The catalyst candidates (**3a**−**d**) were synthesized as shown in Figure 1: (i) in the first step, the *N*-phosphino imines (**4a**−**d**) were obtained from the corresponding *N*-trimethylsilyl imines[11] which readily react with the bis(diisopropylamino)chlorophosphine;[12,13] (ii) in the second step, the phosphine center was alkylated using 1 equiv of methyl triflate, affording *N*-phosphonio imines (**3a**−**c**) in good yields

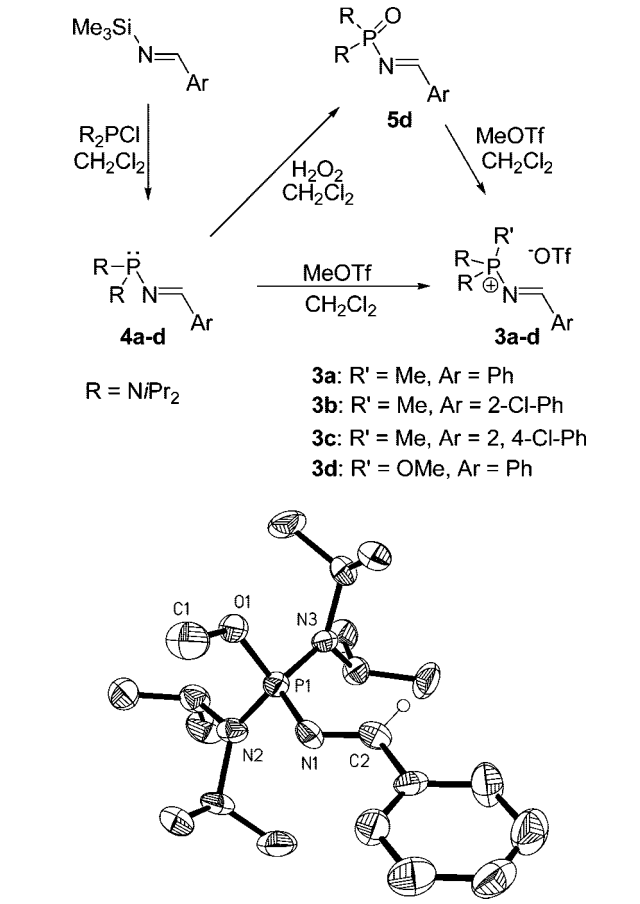


Figure 1. Synthesis of *N*-phosphonio imines (**3a**−**d**) and X-ray diffraction structure of **3d**. The counteranion (trifluoromethanesulfonate) was omitted for clarity.

(67−74%).[14] In the case of **3d**, bearing an electronegative alkoxy substituent, the *N*-phosphinoyl imine **5d** was first prepared by oxidation of **4d** with hydrogen peroxide. The structure of **3d** was unambiguously established by an X-ray diffraction analysis (Figure 1).

The corresponding *N*-phosphonio oxaziridines (**6a**−**d**) were obtained by oxidation in CH_2Cl_2 at 0 °C with *meta*-chloroperbenzoic acid (*m*-CPBA, 1 equiv) in the presence of sodium hydrogen carbonate (1 equiv) (Figure 2).[15] Oxaziridines (**6a**−**c**) are perfectly stable in organic solvents (CH_2Cl_2, THF) under air and moisture conditions, whereas the higly reactive **6d** slowly gives back imine **3d**.

The reactivity of the oxaziridines **6a**−**d** with *trans*-β-methylstyrene was found to be strongly dependent on the nature of the P and Ar substituents. Particularly, the presence

(7) Although the highly electrophilic perfluorooxaziridines show the exceptionally strong oxidizing power, any catalytic oxidation reaction using corresponding imines have been reported: Petrov, V. A.; Resnati, G. *Chem. Rev.* **1996**, *96*, 1.

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(11) Hart, D. J.; Kanai, K.; Thomas, D. G.; Kuei. Yang, T. *J. Org. Chem.* **1983**, *48*, 289.

(12) A similar reactivity of *N*-trimethylsilylimine with sulfonylchlorides is already known: Georg, G. I.; Harriman, G. C. B.; Peterson, S. A. *J. Org. Chem.* **1992**, *57*, 1224.

(13) Typical procedure for the synthesis of **4**: To a CH_2Cl_2 solution of bis(diisopropylamino)chlorophosphine (1.0 g, 3.75 mmol) was slowly added, at 0 °C, the *N*-trimethylsilyl benzaldimine (0.66 g, 3.75 mmol). After 2 h at rt, all volatiles were removed under vacuum. After precipitation by adding CH_3CN, compound **4a** was obtained as a yellow powder (50%).

(14) Typical procedure for the synthesis of **3**: To a CH_2Cl_2 solution of **4a** (840 mg, 2.5 mmol) was slowly added, at 0 °C, methyl trifluoromethanesulfonate (310 μl, 2.5 mmol). After 30 min at rt, all volatiles were removed under vacuum. Compound **3a** was obtained by crystallization in CH_2Cl_2/Et_2O at −30 °C (74%).

(15) Typical procedure for the synthesis of **6**: To a mixture of **3a** (150 mg, 0.3 mmol) and sodium hydrogen carbonate (79.5 mg, 0.75 mmol) in CH_2Cl_2 (1 mL) was added, at rt, a solution of *m*-chloroperbenzoic acid (129.5 mg, 0.75 mmol). After 3 h, the solution was filtrated, and the evaporation of the solvent gave the corresponding oxaziridine **6a** (41%).

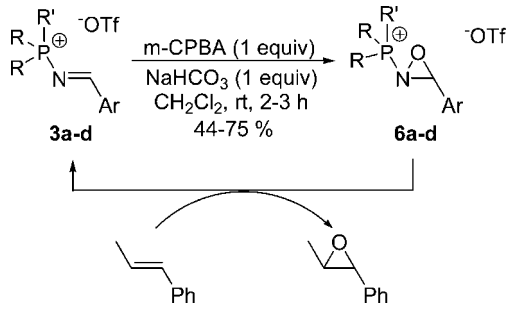


Figure 2. Synthesis of *N*-phosphonio oxaziridines (**6a**−**d**) and their reaction with *trans*-*β*-methylstyrene.

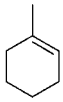
of the alkoxy substituent at the phosphorus center has the most pronounced influence on reactivity. Indeed, the oxaziridine **6d** oxidizes the alkene much faster (76% of conversion in 5 min) than **6a** (26% in 1 h) or **6c** (56% in 30 min).[16]

In contrast to the previously reported air-sensitive *N*-phosphinoyl imines **2**,[11] the *N*-phosphonio imines **3a**−**d** are stable in aqueous media, allowing the development of a catalytic process. Therefore, we tested, at 0 °C,[17] the epoxidation reaction of 1-phenylcyclohexene in the presence of **3d** as catalyst (10 mol %) and oxone (200 mol %) as oxidant, in CH_3CN/H_2O (1/1) solution. The reaction gave quantitatively the corresponding epoxide in 3 h, whereas any trace of epoxide was observed without catalyst **3d**, clearly indicating the catalytic activity of **3d**.

To evaluate the substituent effect on the catalytic activity of *N*-phosphonio imines (**3a**−**d**), the epoxidation reactions of two different olefins, 1-methylcyclohexene and the less reactive *trans*-*β*-methylstyrene, were considered.

As shown in Table 1, good to high catalytic activities of **3a**−**d** were observed with the reactive 1-methylcyclohexene. As expected, the catalyst bearing the electron-donating methyl group on the phosphorus atom and an unactivated phenyl substituent (**3a**) is the less active. The highest catalytic activity was observed with imine **3c**, which presents the 2,4-dichloroaryl substituent. However, with the less reactive methylstyrene, the reaction catalyzed by **3c** proceeded slower (79%, 16 h) compared to the reaction with **3d** (75%, 5 h).

Table 1. Epoxidation of Olefins (1-Methylcyclohexene, *trans*-*β*-Methylstyrene) Using Different Imine Catalysts (**3a**−**d**)[a]

substrate	catalyst	t (h)	convn (%)[b]
	**3a**	2.5	75
	3b	3	96
	3c	1.5	98
	3d	3	99
	**3a**	20	45
	3b	10	74
	3c	16	79
	3d	5	75

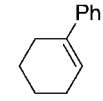
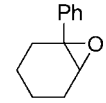
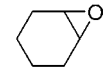
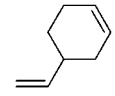
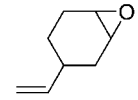
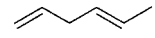
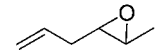
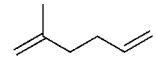
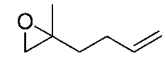
[a] Olefin (0.39 mmol, 1.0 equiv), Oxone (0.79 mmol, 2.0 equiv), catalyst (0.039 mmol, 0.1 equiv), and Na_2CO_3 (1.5 mmol, 4.0 equiv) in CH_3CN/H_2O (2 mL, 1:1) at 0 °C. [b] Determined by GC.

These results clearly show that the rates of the two steps of the catalytic cycle (oxaziridine formation/oxygen atom transfer) are strongly dependent on the imine substituents. With the less reactive *trans*-*β*-methylstyrene as substrate, the rate of the reaction is limited by the kinetic of the second step (oxygen atom transfer) which depends of the reactivity of the oxaziridine. Therefore, the high catalytic activity of imine **3d** for this substrate suggests that the oxygen atom transfer step is strongly affected by the nature of the phosphonio fragment, which is in agreement with the reactivity of the corresponding oxaziridine (**6d**).

On the other hand, with a more reactive substrate (1-methylcyclohexene) the rate-determining step is the oxaziridine formation which goes faster with **3c** than with **3d**. Indeed, electron-withdrawing groups at the imine carbon mainly accelerate the formation of the active oxaziridine species, which starts with the nucleophilic attack of peroxide salt. In fact, after the reaction, partial decompositions of catalysts **3b** and **3c** were observed (hydrolysis of the imine fragment), while **3a** and **3d** remained intact in the same conditions. This result is in agreement with a stronger electrophilic character of the imine function in **3b** and **3c**.

The scope of the epoxidation reaction catalyzed by **3d** was then evaluated using various olefins (Table 2). The results show that catalyst **3d** is particularly efficient for di- or trisubstituted alkenes. Moreover, this system is highly selective for internal olefins. Indeed, in the case of dienes presenting both internal and terminal double bonds, only the latter one was oxidized (entries 3−5).

Table 2. Catalytic Epoxidation Reactions of Various Alkenes Using **3d**[a]

entry	substrate	product	t (h)	convn (%)[b]
1			3	99
2			7	95
3			6	57
4			45	84
5			24	60

[a] Olefin (0.39 mmol, 1.0 equiv), Oxone (0.79 mmol, 2.0 equiv), **3d** (0.039 mmol, 0.1 equiv), and Na_2CO_3 (1.5 mmol, 4.0 equiv) in CH_3CN/H_2O (2 mL, 1:1) at 0 °C. [b] Determined by GC.

In conclusion, we successfully synthesized a new type of imine catalyst for epoxidation reactions: the *N*-phosphonio imines. Of particular interest, the rates of the two catalytic steps (oxaziridine formation and oxygen atom transfer) are strongly related to the nature of the imine substituents. Electron-withdrawing substituents on the imine carbon mainly increase the electrophilic character and therefore accelerate the oxaziridine formation. Whereas, the oxygen transfer step from the active oxaziridine species is dramatically affected by the electron-withdrawing character of the phosphonio fragment. The development of a chiral version of *N*-phosphonio imine catalysts is under active research.

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

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(16) To a $CDCl_3$ solution of oxaziridine **6** (0.036 mmol) was added, at rt, *trans*-β-methylstyrene (0.036 mmol). The reaction was monitored by ^1H NMR to determine the conversion of the olefin into the corresponding epoxide.

(17) Probably due to the slow decompositon of oxone at rt, the epoxidation reaction is more efficient at 0 °C.