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Catalytic Enantioselective Oxaziridination

Lennart Lykke, Carles Rodríguez-Escrich, and Karl Anker Jørgensen*

Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Supporting Information

ABSTRACT: The first catalytic enantioselective synthesis of oxaziridines is presented. The oxidation of aryl and alkyl aldimines with *m*-CPBA under organocatalytic conditions using cinchona alkaloid-derived catalysts furnished optically active oxaziridines in good yields and high enantioselectivities (up to 94% ee). Mechanistic investigations indicate a stepwise enantioselective oxidation process.

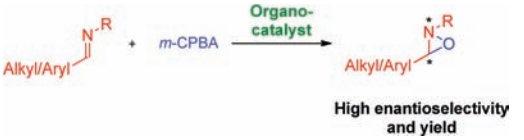
The oxidation of organic molecules is a cornerstone in chemistry, and tremendous progress has been presented in both industry and academia. However, a challenge in oxidation chemistry is the development of greener, more efficient and selective methods. In particular, metal-free oxidations constitute an interesting approach, as toxic wastes and undesired byproduct are minimized.[1] Oxaziridines play a central role in organic chemistry as purely organic oxidants that can act as aprotic, neutral species capable of transferring oxygen or nitrogen to a plethora of other functionalities.[2] Indeed, chiral nonracemic oxaziridines are versatile reagents in asymmetric organic synthesis. Nevertheless, to the best of our knowledge, no catalytic enantioselective protocol leading to optically active oxaziridines has been reported.

The synthesis of oxaziridines[3] was first reported in the mid-1950s,[4] and because of the strained nature of these compounds and the weak N−O bond, they show unusual reactivity,[5] including hydroxylation of unactivated C−H bonds.[6] A remarkable property of oxaziridines is that they possess a configurationally stable nitrogen atom,[7] and optically active oxaziridines with nitrogen as the only stereocenter have been reported.[8]

Electron-deficient oxaziridines such as *N*-sulfonyl oxaziridines, oxaziridinium salts, and perfluorinated oxaziridines have found extensive use as electrophilic oxygen donors.[9] The application of optically active oxaziridines as oxidizing agents has proven to be a reliable strategy in asymmetric syntheses such as enantioselective hydroxylation of enolates;[9a] asymmetric epoxidation of olefins;[9b,c] and enantioselective oxidation of sulfides,[9d] disulfides,[9e] selenides,[9f] and sulfenimines.[9g]

N-Sulfonyl imines can be oxidized by *m*-chloroperoxybenzoic acid (*m*-CPBA) or Oxone under biphasic conditions using phase-transfer catalysis, affording racemic *trans*-oxaziridines in excellent yields.[10] Several protocols for the oxidation of chiral imines leading to optically active oxaziridines have been developed. In 1986, Davis et al.[11] demonstrated the diastereoselective oxaziridination of camphorsulfonyl imine to give enantiopure (camphorylsulfonyl)oxaziridine. The use of chiral-auxiliary-based imines,[12] chiral peracids,[13] or cyclization of nitrones in an inclusion complex with chiral diols[14] for the enantioselective synthesis of oxaziridines has also been investigated. More recently, a catalytic enantioselective peroxidation of acyl imines to give the open *N*, *O*-acetals was reported by Antilla et al.[15] We now report the first catalytic asymmetric synthesis of oxaziridines using a chiral Brønsted base catalyst (Scheme 1).

Scheme 1. Organocatalytic Enantioselective Oxidation of Imines to Oxaziridines



The studies were initiated by examining the oxaziridination of *N*-tosyl benzaldimine (**1a**)[16] with *m*-CPBA, hydrogen peroxide, sodium hypochlorite, Oxone, TEMPO, or a hypervalent iodine compound as the oxidant. A series of different organocatalysts was screened for the oxidation reaction of **1a**, and the cinchona alkaloid-based catalysts showed the most promising results with *m*-CPBA as the oxidant[17] (Table 1). On the basis of previous works wherein racemic oxidation was carried out using phase-transfer catalysis,[10a] the initial screenings were performed with the quaternary ammonium salt **3a**. Thus, under biphasic conditions consisting of toluene and saturated aqueous $NaHCO_3$ (10:1), oxaziridine **2a** was obtained in full conversion but with low enantioselectivity (6% ee) (entry 1). To our delight, applying the bifunctional hydroquinine-derived thiourea catalyst **3b** in the absence of an aqueous base also furnished **2a** in full conversion with an improved enantioselectivity of 40% ee, although significant imine hydrolysis was observed (entry 2). Interestingly, it was discovered that chiral bases such as cinchona alkaloids[18] **3c**−**f** in nondried toluene[19] catalyzed the reaction in full conversion with up to 59% ee (entries 3−6). It was observed that a catalyst bearing a free hydroxyl group at the 9- or 6′-position (**3f** or **3h**, respectively) gave better results in terms of enantioselectivity; however, the dihydroxylated catalyst **3g** was found to be less stereoselective (entry 7), which is not surprising because **3f** and **3h** exhibited opposite stereoinduction. These results indicate Brønsted base/hydrogen-bonding bifunctional activation. Furthermore, catalysts derived from the hydroquinidine scaffold (**3g**−**i**)[18a] were found to induce the highest enantioselectivity. It should be mentioned that only oxaziridines having the trans configuration were observed throughout the present work.

The screening indicated that catalyst **3h** was promising (entry 8), so attempts to improve the reaction parameters were performed.

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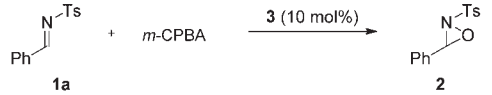
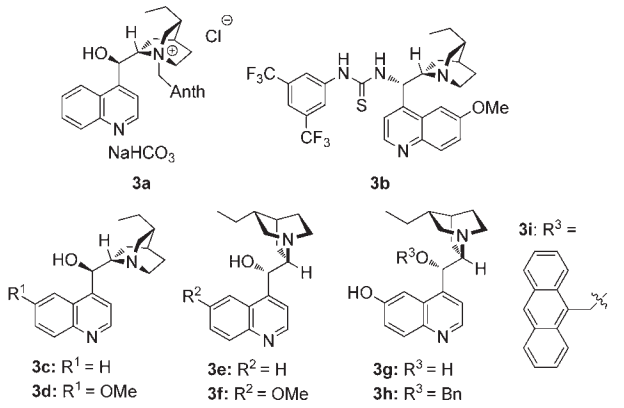
Table 1. Screening of Reaction Conditions for the Enantioselective Oxaziridination of *N*-Tosyl Benzaldimine (1a)[a]





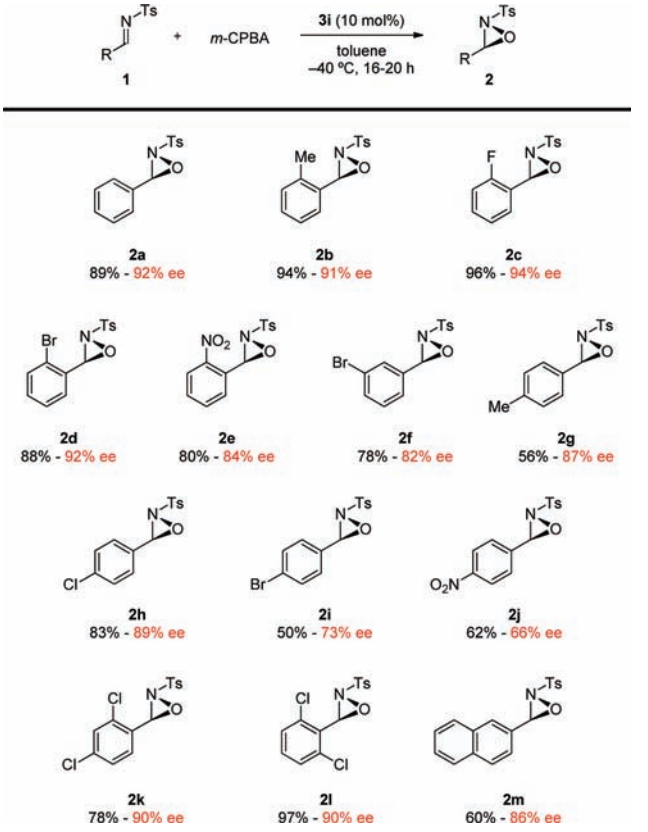
entry	cat	solvent	temp (°C)	conc (M)	% conv (% yield)[b]	% ee[c]
1[d]	**3a**	toluene	−24	0.2	>95	6
2	**3b**	toluene	−24	0.2	>95	−40
3	**3c**	toluene	−24	0.2	>95	21
4	**3d**	toluene	−24	0.2	>95	46
5	**3e**	toluene	−24	0.2	>95	−35
6	**3f**	toluene	−24	0.2	>95	−59
7	**3g**	toluene	−24	0.2	>95	27
8	**3h**	toluene	−24	0.2	>95	70
9	**3h**	toluene	−24	0.1	>95 (74)	76
10	**3h**	CH_2Cl_2	−24	0.1	>95 (30)	54
11	**3h**	$CHCl_3$	−24	0.1	>95 (39)	54
12	**3h**	pentane	−24	0.1	>95 (44)	30
13	**3h**	heptanes	−24	0.1	>95 (51)	18
14	**3h**	*o*-xylene	−24	0.1	>95 (27)	68
15	**3h**	*m*-xylene	−24	0.1	>95 (56)	76
16	**3h**	toluene	−40	0.1	>95 (84)	82
17	**3i**	toluene	−40	0.1	>95 (89)	92

[a] All reactions were performed using **1** (0.10 mmol), **3** (0.01 mmol), and *m*-CPBA (0.14 mmol) until full conversion was observed by TLC. [b] Isolated by flash chromatography (FC). [c] Determined by chiral-stationary-phase HPLC. [d] 10% sat. $NaHCO_3$(aq) was used as a cosolvent.

Diluting the reaction had a positive effect on the enantioselectivity (entry 8 vs 9); furthermore, solvent screening revealed toluene to be optimal with respect to both yield and enantioselectivity (entries 9−15). Lowering the temperature to −40 °C enhanced the enantioselectivity (entry 16); however, further cooling prolonged the reaction time significantly but gave no additional improvement in enantioselectivity. Applying the anthracenyl-modified catalyst **3i**[18a] under the optimized conditions furnished the oxaziridine product **2a** in very high yield and excellent enantioselectivity (entry 17).

Encouraged by this result, a representative selection of aromatic *N*-tosyl aldimines was prepared in order to investigate the generality of the enantioselective oxaziridination reaction (Scheme 2). We were pleased to find that the high efficiency demonstrated by catalyst **3i** for the model reaction could be expanded to the oxaziridination of a broad range of imines. In particular, those

Scheme 2. Scope of the Enantioselective Oxaziridination of Aromatic Aldimines[a]



[a] All reactions were performed using **1** (0.20 mmol), **3i** (0.02 mmol), and *m*-CPBA (0.28 mmol) in 2 mL of toluene. Isolated yields were determined by FC and ee's by chiral-stationary-phase HPLC.

having ortho-substituted aromatic groups furnished the optically active oxaziridine products in good to excellent yields and enantioselectivities (products **2b**−**e**,**k**,**l**). Imines with aromatic substituents having an electronic nature ranging from slightly electron-donating to electron-withdrawing also participated successfully in the enantioselective oxaziridination. It should be mentioned that two electron-rich imines (*p*-$MeOC_6H_4$ and 2-furanyl) were also tested; however, no product formation was observed, in accordance with earlier attempts to synthesize these compounds.[20] Interestingly, two disubstituted imines were employed in the reaction and gave high to excellent yields with high enantioselectivity (**2k** and **2l**). Additionally, a 2-naphthyl-based imine also gave rise to the corresponding oxaziridine **2m** in good yield with high enantioselectivity.

Having investigated the oxaziridination of aromatic aldimines, we considered the possibility of expanding the developed methodology to aliphatic *N*-tosyl aldimines. A representative selection of imines was prepared to demonstrate the generality of the reaction, and we were pleased to find that catalyst **3i** promoted the enantioselective formation of optically active aliphatic oxaziridines (Scheme 3). Employing linear imines afforded the product oxaziridines in moderate yields with high enantioselectivities (**2n** and **2o**). Interestingly, α-branched imines also participated smoothly in the reaction, affording products **2p**−**r** in good to excellent yields with high to excellent enantioselectivities. Finally, we investigated the possibility of employing a substrate

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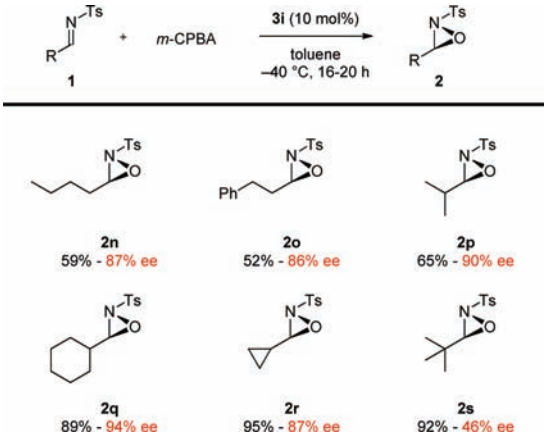
Scheme 3. Scope of the Enantioselective Oxaziridination of Aliphatic Aldimines[a]



[a] All reactions were performed using **1** (0.20 mmol), **3i** (0.02 mmol), and *m*-CPBA (0.28 mmol) in 2 mL of toluene. Isolated yields were determined by FC and ee's by chiral-stationary-phase HPLC.

having a tertiary substituent; the imine derived from pivalaldehyde underwent oxaziridination to give **2s** in excellent yield, although the enantioselectivity dropped significantly to 46% ee. This indicates that even though the catalyst has high substrate tolerance, substrates with too much steric bulk do not fit in the catalyst "pocket".

To obtain mechanistic information about the enantioselective oxidation of the imines to oxaziridines, a series of experiments was performed (see the Supporting Information). The oxaziridination of imine **1c** was investigated using different concentrations of catalyst **3i**. Reducing the catalyst concentration from 0.10 to 0.025 M caused only a minor decrease in the enantioselectivity of oxaziridine **2c**, as the enantiomeric ratio changed from 97:3 to 93:7. These results support a monomeric catalyst as the active species. This is further supported by the results of low-temperature ^{1}H NMR spectroscopic studies of **3i**, wherein no signals that could be attributed to a dimeric catalyst were observed.[21] The kinetics of the oxaziridination was also investigated, and a pseudo-first-order relationship was found for both the imine (**1a**) and *m*-CPBA. Furthermore, a Hammett study applied to the *para*-substituted aromatic imines **1a**,**g**−**j** showed no correlation between the induced enantioselectivity and the σ value, in contrast to what has been observed for metal-catalyzed asymmetric epoxidation.[22] Finally, a competition experiment between *N*-tosyl benzaldimine **1a** and the corresponding *o*-nitrophenyl-substituted imine **1e** showed that the **2a**/**2e** product ratio was 1:15. In a similar competition study, oxaziridine **2c** was obtained in a 3.3:1 ratio relative to **2b**. These kinetic experiments indicate nucleophilic attack of the oxygen atom of the peracid to the carbon atom of the imine. On the basis of the results obtained, we propose a stepwise mechanism[23] in which the rate-determining step consists of a dual Brønsted base/hydrogen-bonding activation step involving both the imine and *m*-CPBA (Figure 1). We propose that the quinuclidine nitrogen atom is protonated by the peracid to generate a tight ion pair, while the hydroxy group coordinates to the oxygen atom of the sulfonyl group, bringing the two reactants into close proximity (**A**). Next, attack of the oxidant on the imine generates a transient α-aminoperoxy structure (**B**) that

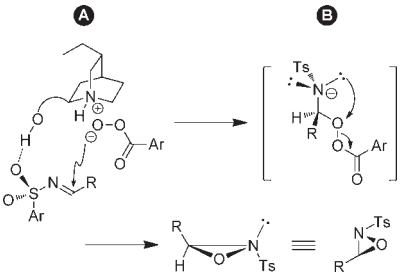


Figure 1. Schematic model of the stepwise oxaziridination mechanism.

quickly collapses to the oxaziridine, giving rise to the thermodynamically favored *trans*-oxaziridine.

Determination of the absolute configuration of the optically active oxaziridines was carried out by X-ray analysis of **2k**, which proved to be the *S*,*S* enantiomer (Figure 2).[24] Hence, the remaining oxaziridines **2** were assigned by analogy assuming a common reaction pathway.

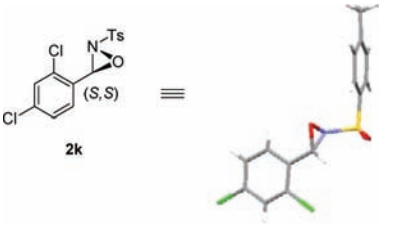


Figure 2. Single-crystal X-ray structure of **2k**.

In conclusion, this work constitutes the first example of catalytic enantioselective oxaziridination. The developed methodology takes advantage of a Brønsted base-catalyzed oxidation of aromatic and aliphatic *N*-tosyl aldimines with *m*-CPBA and affords *N*-tosyl oxaziridines in high to excellent yields (up to 97%) with high to excellent stereocontrol (up to 94% ee) in an easy and completely metal-free protocol. Mechanistic investigations based on kinetic studies and competition experiments indicate a stepwise mechanism. Further investigations concerning the synthetic utility of this stereoselective protocol are being studied.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data, chromatograms, NMR spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
kaj@chem.au.dk

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