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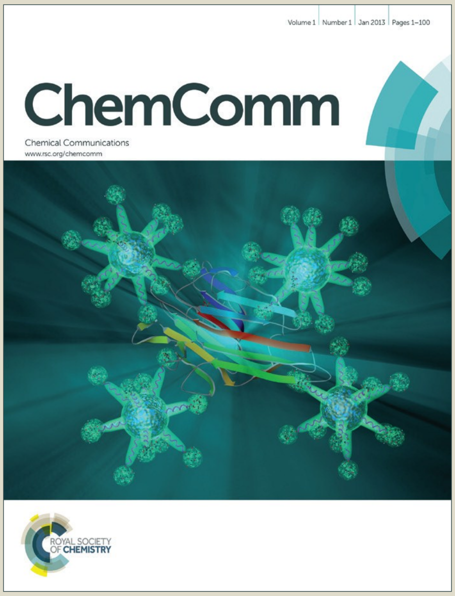

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Catalytic Enantioselective Epoxidation of Nitroalkenes

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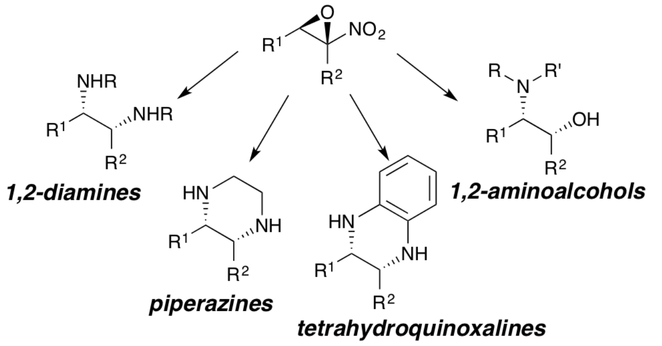
Nitroepoxides are potentially exploitable as synthons with vicinal electrophilic centers. Nevertheless, although advances have been made in the field, enantioselective epoxidation of nitroalkenes is still a challenging process. Herein we show a convenient procedure for the preparation of optically active nitroepoxides in high enantiomeric excess and high chemical yield. The kinetic data of the best catalyst have been examined by computational methods based on DFT calculations. Interestingly, the results demonstrate that the enantioselectivity of the epoxidation of nitroalkenes by this kind of catalyst is not only kinetically but thermodynamically controlled.

Nitroepoxides are an underdeveloped class of compounds with wide potential for use in chemical synthesis.[1] Nitroepoxides represent strained systems displaying two highly oxidized vicinal positions by nature of their chemical connectivity and hence are potentially exploitable as synthons with vicinal electrophilic centers. Recently we reported the transformation of nitroepoxides into 1,2-diamines[2] and saturated 1,4-diamino heterocycles such as piperazines and tetrahydroquinoxalines[3] (Scheme 1). Also the preparation of 1,2-aminoalcohols starting from nitroepoxides has been reported.[4] Hence nitroepoxides are interesting precursors for the preparation of chiral 1,2-difunctionalized compounds. Although advances have been made for preparing enantiopure nitroepoxides,[4-5] enantioselective epoxidation of nitroalkenes has remained a challenging process.[4] Herein we describe the first enantioselective epoxidation of nitroalkenes.

Chiral quaternary ammonium salts derived from cinchona alkaloids have been employed as efficient catalysts in the epoxidation of chalcones[6-10] and other asymmetric reactions such as the alkylation of ketones.[11-12]



Scheme 1. Derivatizations of nitroepoxides into chiral compounds.

We started the study of the enantioselective epoxidation of nitroalkenes by using catalyst **A**, readily prepared through benzylation of cinchonine,[6] and a-methyl nitrostyrene **1a** as a model compound. Early conditions including the use of catalyst **A** in 10 mol %, sodium hypochlorite (4.5 % active chlorine aqueous solution) and dichloromethane (0.15 M of nitroalkene) gave full conversion of α-methyl nitrostyrene **1a** into nitroepoxide **2a** (entry 1, Table 1). The best organic phase/aqueous phase ratio in terms of conversion and enantioselectivity resulted to be 2/1. All other assayed oxidants as *tert*-butyl hydroperoxide and hydrogen peroxide did not afford desired nitroepoxide. Adequate stirring of the reaction mixture to maximize the interphase reaction surface was found to be a key factor as already reported for similar reactions.[9]

Then initial reaction conditions were changed in order to increase enantioselectivity. By increasing the concentration of nitroalkene in dichloromethane to 0.3 M, enantioselectivity improved slightly (entry 2, table 1). The effect of catalyst load was also tested with no significative increase of enantioselectivity for 20 mol % and a reduction of enantioselectivity when 5 mol % of catalyst **A** was used (entry 3). Solvent screening revealed chloroform as a better solvent than dichloromethane by increasing enantiomeric ratio up to 74/26 (entry 4, table 1). Water miscible solvents such as methanol and tetrahydrofuran did not afford reaction product and toluene was not a good solvent for catalyst **A**, probably due to low solubility (entry 5).

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Then catalyst screening was carried out. Among all prepared quaternary ammonium salts derived from cinchonine, catalyst **B** having an ortho-susbstituent at the benzyl group did not improve the reaction, and catalysts **C** and **D** (entries 7-8) displaying para-substituents improved the enantioselectivity respect to catalyst **A**. We were pleased to find that catalyst $\mathbf{E_1}$[7] having a 9-anthracenylmethyl substituent gave even higher enantioselectivity (entry 9).

Optimization of the reaction conditions with catalyst $\mathbf{E_1}$ were next assayed. The concentration of the reaction was confirmed to be 0.3 molar as the best option (entry 9 vs. entry 10). When carbon tetrachloride was used as a solvent instead of chloroform, enantiomeric excess increased (entry 11). To avoid the use of carbon tetrachloride as non-environmentally friendly solvent, toluene was also assayed giving a similar result to carbon tetrachloride (entry 12), although the reaction resulted to be slower.

Curiously, catalyst $\mathbf{F_1}$ having non-planar and bulky substituent 2,5-diphenyl benzyl[13] (entry 13) gave opposite enantiomer compared to catalyst $\mathbf{E_1}$ in low enantioselectivity. O-Allyl derivative catalysts $\mathbf{E_2}$ and $\mathbf{F_2}$ gave opposite enantiomer compared to catalyst $\mathbf{E_1}$ (entries 14-15), denoting the importance of free hydroxyl group for controlling enantioselectivity.

Finally, a range of temperatures between 0 ^oC and -40 ^oC were next assayed in order to increase enantioselectivity. A temperature of -20 ^oC (entry 17) was found to be the best situation committed for the highest enantiomeric ratio (97/3) and high chemical yield (92 % isolated yield) and prevent freezing the aqueous phase of the reaction mixture. 8 % was established as the minimum catalyst load (entry 19). This reaction has been scaled up to 200 mg of nitroalkene **1a**. Pseudoenantiomer catalyst **G** gave reverse enantioselectivity (entry 18) compared to cinchonine-derived counterpart E_1, and enantioselectivity was lower. Determination of the absolute configuration of compound **2a** was carried out by X-ray analysis, which proved to be the (2*S*, 3*R*) enantiomer (Scheme 2).[13]

The tolerance of this catalytic enantioselective epoxidation to the presence of different substituents in alpha and beta positions of the nitroalkene was then evaluated (Scheme 2).

Nitroalkenes having an aryl group at the beta position and an alkyl group at the alpha position (**1a-1f** and **1j-1m**, Scheme 2) afforded the corresponding nitroepoxide in high stereoselection and high chemical yield. If both substituents are aryl groups (**1g**), then corresponding nitroepoxide is also obtained with high enantioselectivity and high chemical yield. Finally epoxidation reaction was assayed over a nitroalkene having alkyl groups at both positions (compound **1h** and **1i**), in this case the reaction was not enantioselective and afforded nitroepoxide in low chemical yield (Scheme 2). This result denotes that the group in beta position needs to be an aryl group for reaction to be efficient. Beta-disubstituted nitroalkenes could not be assayed due to the limitations associated with their preparation.

Table 1. Optimization of epoxidation reaction[a]

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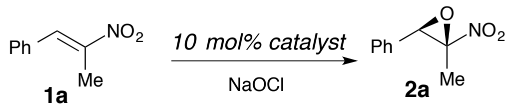
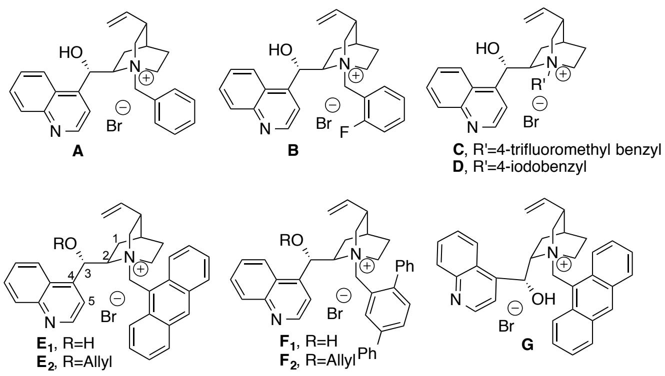


Entry	catalyst	solvent	Conc. (M)	T (ºC)	t (h)	e.r. (%)[b]	Conv. (%)[c]
1	**A**	DCM	0.15	23	2	58/42	100
2	**A**	DCM	0.3	23	2	59/41	94
3[d]	**A**	DCM	0.3	23	2	54/46	70
4	**A**	$CHCl_3$	0.3	23	2	74/26	70
5	**A**	Tol.	0.3	23	24	ND[e]	20
6	**B**	$CHCl_3$	0.3	23	2	53/47	65
7	**C**	$CHCl_3$	0.3	23	2	81/19	94
8	**D**	$CHCl_3$	0.3	23	3.5	81/19	100
9	$\mathbf{E_1}$	$CHCl_3$	0.3	23	2	83/17	100
10	$\mathbf{E_1}$	$CHCl_3$	0.6	23	2.5	78/22	100
11	$\mathbf{E_1}$	CCl_4	0.3	23	2	89/11	100
12	$\mathbf{E_1}$	Tol.	0.3	23	6	87/13	100
13	$\mathbf{F_1}$	Tol.	0.3	23	4	41/59	80
14	$\mathbf{F_2}$	Tol.	0.3	23	5	25/75	96
15	$\mathbf{E_2}$	Tol.	0.3	23	4.5	33/67	90
16	$\mathbf{E_1}$	Tol.	0.3	0	16	90/10	100
17	$\mathbf{E_1}$	Tol.	0.3	-20	16	97/3	92[f]
18	**G**	Tol.	0.3	-20	24	18/82	100
19[d]	$\mathbf{E_1}$	Tol.	0.3	-20	16	97/3	92[f]



[a] NaOCl as 4.5 % active chlorine aqueous solution. Organic phase/aqueous phase 2/1. [b] Determined by HPLC ChiralPak IA. [c] Conversion measured by ^1H NMR of the crude reaction mixtures. [d] 5 mol % of catalyst for entry 3; 8 mol % of catalyst for entry 19. [e] Not determined. [f] Isolated chemical yield.

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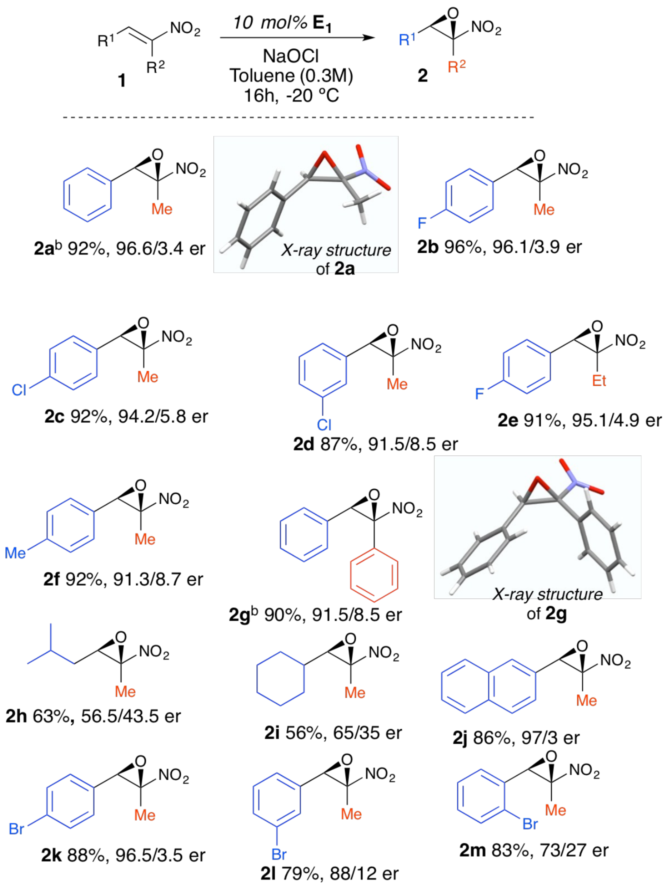

[a] e.r. was determined by HPLC ChiralPak IA. Isolated chemical yield is shown.
[b] Absolute configuration was determined by x-ray crystallography.

Scheme 2. Epoxidation of nitroalkenes.[a]

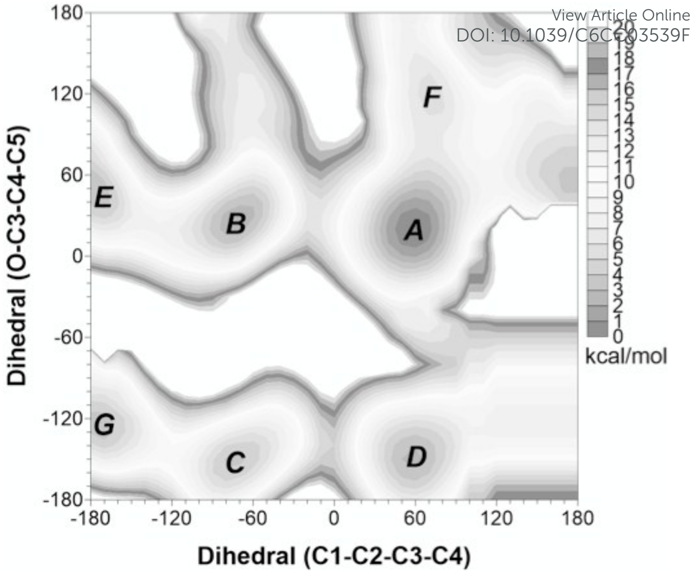

Fig.1 Gas phase PES computed at B97d/6-31+G(d,p) level as a function of the dihedral angles describing the relative orientation of the quinolone moiety and -OH group of E1 catalyst. See 2D figure of **E$_1$** in Table 1 for numbering of the atoms.

In order to explain the experimental data, quantum molecular simulations have been employed to study the observed catalytic enantioselective epoxidation of nitroalkene **1a** by catalyst **E$_1$**. All calculations have been carried out in toluene solution with the conductor-like polarizable continuum model (CPCM),[14] as implemented in Gaussian 09 package.[15] The calculations have been performed at density functional theory (DFT) level with the B97d hybrid functional,[16] which has been proved to provide exceptionally good performance for non-covalently bound systems[16] involving large polynuclear aromatic molecules.[17] (see Supporting Information for details of the computational methods). The selected reaction was the one corresponding to the entry 17 in Table 1. The first step of the study was exploring the possible conformers adopted by the catalyst **E$_1$** in toluene. In this regard, a Potential Energy Surface (PES) has been generated as a function of the dihedral angles describing the relative orientation of the quinoline moiety (Figure 1), similarly to previous conformational analysis of different cinchona alkaloid scaffolds.[18]

All possible conformations of **E$_1$** catalyst were explored (Supporting Information). From the two lowest energy **E$_1$** conformers, A and B in Figure 1, the study of the binding of the ClO$^-$ and the nitroalkene **1a** substrate provides different reactant complex, RC, conformations (see Supporting Information). Interestingly, while the conformation of just the **E$_1$** catalyst is comparable to the one observed for other cinchona-based catalysts,[19] this is not the case when comparing the RCs. Indeed our most stable RCs for the epoxidation, that come from the A conformation of **E$_1$** catalyst in Fig 1, show π-π stacking interactions between the catalyst and the substrate (Figure 2), which was not detected in the indanone-catalyst complexes previously reported for the cinchoninium ion asymmetric phase transfer catalysed alkylation reaction.[18] Moreover, the ClO$^-$ moiety interacts by a hydrogen bond with the hydroxyl group of the catalyst in both RCs dictating the orientation and interaction between the nitroalkene and the catalyst. The difference between both RCs structures depends on the π-π stacking interaction that is established between the nitroalkene and the aryl substituent of the catalyst; while RC in A.II.1 interacts through the anthracenyl moiety of the catalyst, RC in A.II.2 interacts through the quinoline moiety. Interestingly, there is no significant difference in energy between both conformations. Nevertheless, this is not the case when comparing the transition states, TSs, and product complexes, PCs, that connect with the RCs. Thus, the reaction from RC A.II.1 shows lower energy barrier than the reaction from RC A.II.2 (8.4 vs. 12.5 kcal·mol^{-1}), and more stable PCs (-44.2 and -41.4 kcal·mol^{-1}, respectively). Importantly, the nitroepoxides that are obtained in both reactions are different enantiomers: (2*S*,3*R*)-nitroepoxide in reaction from A.II.1 and (2*R*,3*S*)-nitroepoxide in reaction from A.II.2. According to the relative energies of their corresponding TSs and PCs, (2*S*,3*R*)-nitroepoxide would be the most favorable enantiomer when employing catalysts **E$_1$** from the thermodynamic and kinetic point of view. This computational result is in very good agreement with the experimental data reported in Table 1 entry 17, where 2*S*,3*R* enantiomer is obtained in a 97/3 ratio.

A deep analysis of the RCs, TSs and PCs structures reveals that the π-π stacking interaction between the aromatic rings of the catalysts and the substrate are important to stabilize and to orient the two moieties in RCs. This explains that the epoxidation of nitroalkenes **2h** and **2i**, having no aromatic substituent, were not enantioselective. Nevertheless, the presence of hydrogen bond interactions and the most favourable conformation of the catalyst appear to be the factor determining the relative energies of TSs and PCs that, in turn, determines the ratio of obtained enantiomers.

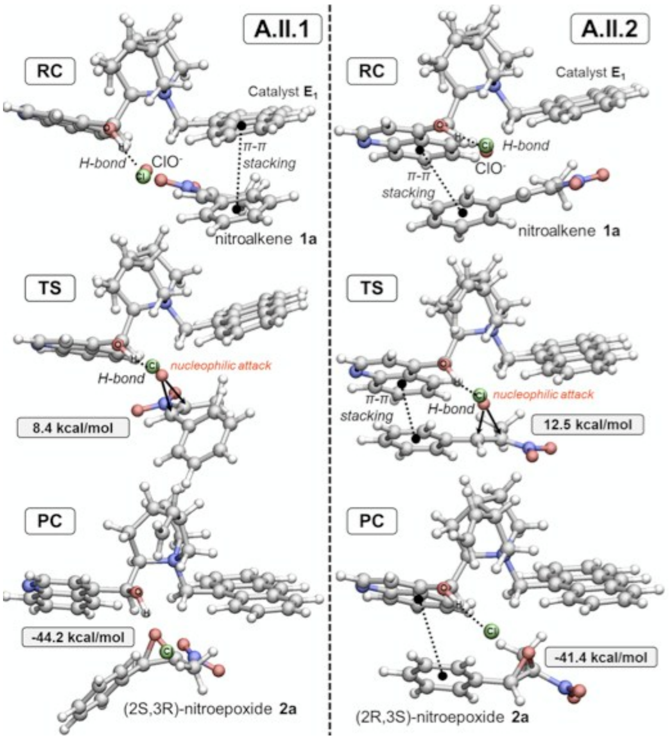

Fig.2 Optimized structures and relative energies of RC, TS and PC of the epoxidation of nitroalkene **1a** catalyzed by $\mathbf{E_1}$ starting from the most stable conformations of the 1a–ClO-–E_1 reactant complexes.

It is important to point out that the epoxidation of nitroalkene **1a** catalyzed with $\mathbf{E_1}$ has been also studied from different conformers (see Supporting Information). Any alternative reaction path has been revealed as not only thermodynamically but kinetically less favourable than the reaction from A.II.1 displayed in Figure 2.

In summary, we report herein an enantioselective epoxidation of nitroalkenes using cinchonine-derived $\mathbf{E_1}$ as a catalyst and sodium hypochlorite as an oxidant. The process represents an efficient preparation of enantiopure nitroepoxides with wide potential for use in chemical synthesis. Our theoretical analysis, based on DFT calculations, shows that the enantioselectivity of the catalyst is dictated not so much by the π-π stacking interaction established between the aromatic rings of the catalyst and the substrate but by the relative orientations of the three reactive species that are in fact unfavorably constrained if a π-π stacking interaction appears with the quinoline moiety of the catalyst.

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