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Quaternary ammoniums and a cationic sodium complex as supramolecular catalysts in ring-opening of epoxides by amines

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ABSTRACT

Supramolecular ionic organocatalysts and a metal-based catalyst were investigated in the ring-opening of epoxides by amines, without any artifice to enhance conversion (i.e., solvophobic effect, extended reaction time, heating, excess of amine, high catalyst loading). Different β-amino-alcohols were obtained in satisfying conversion (50–80%) in 24 h, under mild conditions.

1. Introduction

The ring-opening reaction of epoxides by amines is a common route to β-amino-alcohols, which are well-known chiral auxiliaries as well as structural components of natural and synthetic bioactive compounds.[1] Moreover, the aminolysis of epoxides still remained a model reaction to evaluate new catalysts as C–O bond activators. The outcome of ring-openings strongly depended on classical electronic and steric effects on reactants. Concerning regioselectivity, the favoured product resulted from the nucleophilic attack on the less hindered epoxide carbon (β-attack), except in the case of styrene oxides where α-attack was the major one. Concerning stereochemistry, under neutral or basic conditions, an SN_2 mechanism was admitted and *trans* β-amino-alcohols were obtained. To better control the formation of products, the enantioselective ring-opening of epoxides was extensively catalyzed by metal-based complexes and enzymes.[2] Additionally, experimental conditions (microwave irradiation,[3] solvent-free[4]) and solvent effects (ionic liquid,[5] hexafluoro-2-propanol,[6] water[7–9]) were also evaluated to improve yields. Current limitations originated from poorly nucleophilic amines (low yields), and other ones were due to protocols that required high temperatures, extensive reaction times, high catalyst loadings or an excess of amine to avoid side-products (mainly bis-adducts).

Over the last decade, research efforts also concentrated on organocatalyzed ring-opening of epoxides, in organic solvents and water.[10] In particular, Hydrogen-bonding catalysis was the most popular strategy. So, Schreiner and Kleiner reported that a thiourea provided with electron-withdrawing groups (TUS, 10 mol %, Scheme 1), catalyzed the aminolysis of epoxides by aliphatic amines in dichloromethane (27–85%) and in water (60–97%), due to hydrophobic effects.[11] Solvent-free conditions at 60 °C were reported for the aminolysis of several epoxides catalyzed by different thioureas (80–100%, 0.2–45 h).[12] A *N*-tosyl urea (10 mol %) catalyzed the addition of anilines to styrene and (*E*)-stilbene oxides in high yields in dichloromethane (75–92%, 3–6 days, one regioisomer).[13] Besides, *N*-formyl-L-proline (10 mol %) was investigated as a catalyst in dichloromethane, towards the ring-opening of styrene oxide by aniline (99% yield, 48 h, 20 °C).[14] In water, the scope of this acid was broader, allowing reactions of anilines in 48 h with several epoxides (44–99%) and their ring-openings by aliphatic amines in 24 h (71–80%). A polystyrene supported poly(amido-amine) dendrimer was also reported to promote the ring-opening of cyclohexene, styrene and 2-butene oxides by anilines in 1,4-dioxane (G3 at 2 mol %, 50 °C, 12–36 h, yield: 85–98%).[15] The catalyst was recycled six times with a limited loss of activity (yield: 98–90%). Finally, chiral amidinium salts (10 mol %) were shown to catalyze the ring-opening of cyclohexene oxide by aniline (2 equiv) in dichloromethane (20 °C, 6 h, yield: 99%).[16] No asymmetric induction was observed on the product. Thus, despite its efficiency in the activation of C=O, $-NO_2$ and C=N bonds, H-bonding

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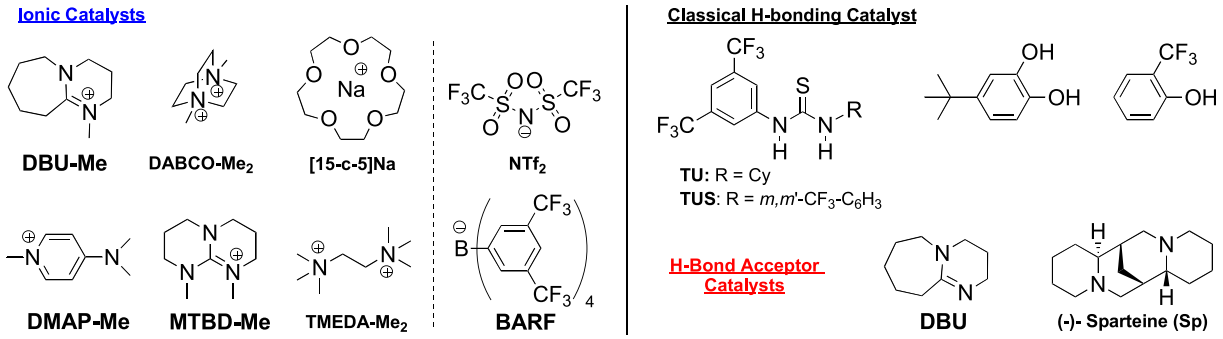

Scheme 1. Structures of supramolecular organocatalysts and a sodium(I)-based catalyst.

catalysis appeared to moderately activate single C–O bonds of epoxides, due to the lower binding abilities of this functional group. Currently, H-bonding catalysts involved in ring-openings by amines could be efficient using protocols that favoured extensive reaction time (>24 h), heating (50–60 °C), high catalyst loading (≥10 mol %) or reactant excess. Moreover the role of water as a solvent was still unclear (i.e., in water or on water).[17]

We proposed to evaluate ionic catalysts towards the C–O bond activation, in dichloromethane to avoid a major solvent effect. Besides, catalyst loadings and reaction times were restricted (5 mol %, 24 h, respectively), temperature was maintained at 20 °C, and reactants were introduced in equimolar quantities. So, a series of new supramolecular catalysts were chosen (Scheme 1): quaternary ammoniums organocatalysts capable of $N^+–CH_3^{\delta+}\cdots O–C$ interactions and a sodium(I) encapsulated in 15-crown-5 ether ([15-c-5]Na) to favour a $Na^+\cdots O–C$ interaction, i.e., a weak coordination bond also called ion–dipole interaction. The discrete cationic sodium complex is solely presented in this study, as the same crown-ether complexes of Li^+ and K^+ are not available. Indeed, the lithium(I) complex is not a well-defined compound as a mixture of (1:1) and (2:1) (15-c-5:Li^+) complexes is obtained. As a consequence, its catalytic activity could not be rationalized. In addition, the discrete potassium(I) complex was prepared with the [18-c-6] macrocycle using NTf_2 and BARF as counterions. The ring-opening of 1,2-epoxyhexane and cyclohexene-oxide by pyrrolidine in presence of this catalyst induced slightly lower conversions (±5%) than in presence of [15-c-5]Na. A detailed investigation of alkali- and alkali-earth crown-ether complexes could shed light on this phenomenon and will be reported in due course.

For a comparison sake, some classical H-bond donors, such as thioureas (TU and Schreiner's Thiourea TUS) and phenol derivatives were also reported. We recently described these ionic and neutral catalysts in the ring-opening polymerization of cyclic esters, based on an efficient activation of C=O bonds.[18] Additionally, the impact of a catalytic system, composed of a donor+an acceptor, using well-known H-bond acceptor catalysts (DBU and (−)-sparteine) were evaluated under the same conditions, as potential activators of nucleophile through H-bonding (N···H-Nu).

Herein, the ring-opening of four representative epoxides provided with aromatic and aliphatic substituents, were achieved with different nucleophilic amines. So, disubstituted (*E*)-stilbene and cyclohexene oxides, as well as monosubstituted styrene oxide and 1,2-epoxyhexane were chosen to compare reactivity and to evaluate regioselectivity in the latter two cases. Four aliphatic amines were selected according to their nucleophilic parameter in acetonitrile (N):[19] di-isobutylamine (hindered amine), *n*-butylamine (N=15.27) as well as cyclic amines, such as piperidine (N=17.35) and pyrrolidine (N=18.64).[20]

2. Results and discussion

The proposed mechanism is relying on a classical activation between catalysts and reactants through H-bonds (Fig. 1):[11,18] (i) the C–O bond of epoxide can be H-bonded to quaternary ammoniums, phenols or thioureas meanwhile forming a cation–dipole interaction with sodium(I) in [15-c-5]Na, (ii) tertiary amines (DBU or sparteine) can be H-bonded to the nucleophile, then activating its nucleophilicity, (iii) in principle, both catalysts could simultaneously activate the reactants, provided no competitive H-bonds existed in the medium. Indeed, we previously demonstrated that some H-bond donor and acceptor catalysts could preferentially be H-bonded together, and then low conversions were observed.[21] In addition, the products of ring-opening, β-amino-alcohols might also interfere in the mechanism through their alcohol and amine groups as H-bond donors and acceptors.

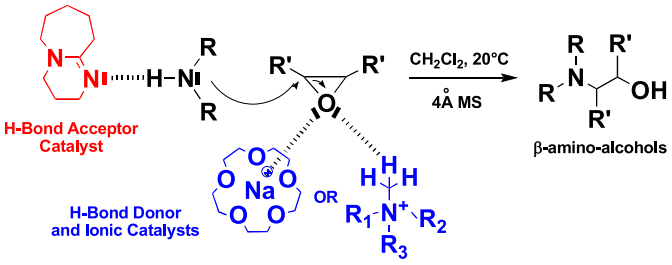

Fig. 1. Non-covalent activation of substrates (epoxide or/and amine) in the aminolysis of epoxides.

To better assess the plausible interactions present in the reaction medium, geometry optimizations at the B3LYP/6-31G* level were achieved on different (1:1) mixtures of H-bonding compounds, in vacuum (Fig. 2). As a model reaction, the ring-opening of 1,2-epoxybutane by piperidine was examined in the presence of two representative H-bonding catalysts (donor and acceptor), i.e., 4-^{t}Bu-catechol and DBU.[22] Even if these simulations were not fully representative of the experimental conditions of ring-opening, they showed the possible supramolecular interactions between the species present in the medium, and their relative strength (see Table S1, Supplementary data).

As proposed in the mechanism, 1,2-epoxybutane is H-bonded to 4-^{t}Bu-catechol ($d_{O1\cdots H1}$=1.99 Å, Fig. 2a) meanwhile DBU is weakly interacting with piperidine ($d_{N1\cdots H1}$=2.54 Å, Fig. 2b). This result suggests that DBU should poorly activate the nucleophile. A possible interaction between two catalysts is highlighted by the formation of an H-bonded complex between 4-^{t}Bu-catechol and DBU ($d_{N1\cdots H1}$=2.07 Å, Fig. 2c). The H-bond donor catalyst 4-^{t}Bu-catechol could also interact with piperidine ($d_{N1\cdots H1}$=2.00 Å, Fig. 2d), with