

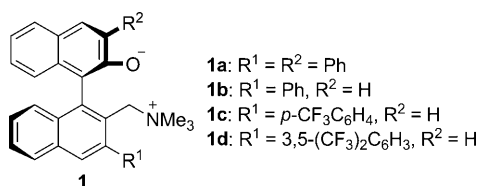
# Nucleophilic Catalysis

## Chiral Ammonium Betaines as Ionic Nucleophilic Catalysts\*\*

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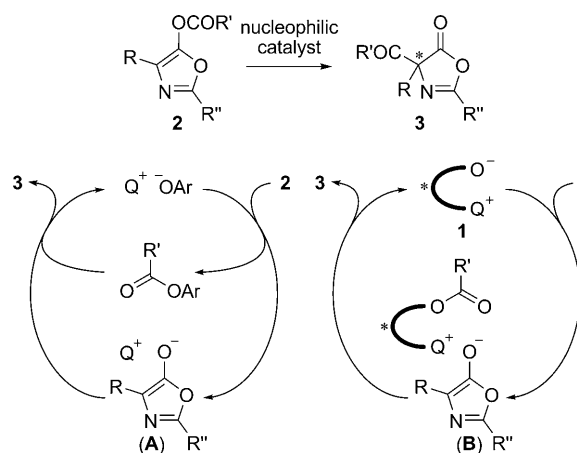
Asymmetric nucleophilic catalysis has been extensively studied over the last several decades and plays an increasingly important role in modern asymmetric synthesis.<sup>[1]</sup> The general definitive feature of this catalysis is that a Lewis basic catalyst reacts with a substrate to give a reactive ionic intermediate through the formation of a new covalent bond, which will be eventually cleaved by the elimination of the catalyst. In this respect, an anionic molecule could function as a potentially more nucleophilic catalyst for initiating the reaction, compared to the commonly utilized electronically neutral molecules, but it generates a rather stable intermediate bearing no charge (see below). Hence, research toward exploiting the reactivity of anionic molecules for the development of a new type of nucleophilic catalysis, that is, enantioselective ionic nucleophilic catalysis, has met with limited success.<sup>[2,3]</sup>

We recently introduced the chiral ammonium betaine **1** as a new, yet intriguing structural motif as an organic molecular catalyst.<sup>[4,5]</sup> The basic character of its anionic site (aryloxylate)



and the hydrogen-bonding capability of its conjugate acid (arylhydroxide) appeared to be the key features for realizing highly enantioselective Mannich-type reactions. Given that the aryloxylate functionality has a nucleophilic character, we envisioned that **1** could be evolved into a chiral nucleophile after appropriate structural manipulations.<sup>[6]</sup>

Acyl transfer reactions by means of nucleophilic catalysts are the fundamental molecular transformation in synthetic organic chemistry. Among these reactions, the Steglich rearrangement,<sup>[7]</sup> which is the rearrangement of 5-oxazolyl carbonate into 4-carboxylactones, offers an attractive process for establishing a tetrasubstituted stereogenic center, and also serves as a model system for evaluating the efficiency of chiral nucleophilic catalysts (Scheme 1);<sup>[8,9]</sup> the



**Scheme 1.** Working hypothesis for the Steglich rearrangement with an onium aryloxide (Q<sup>+</sup>OAr<sup>−</sup>) as an ionic nucleophilic catalyst. Left cycle: a conventional intermolecular onium salt. Right cycle: an intramolecular onium salt such as chiral ammonium betaine of type **1**.

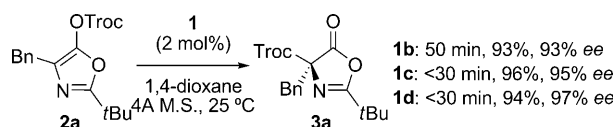
pioneering work in this field was reported by Ruble and Fu for a synthetic analogue of DMAP.<sup>[9a]</sup> However, the use of an ionic nucleophile, such as onium aryloxylate (Q<sup>+</sup>OAr<sup>−</sup>), in this reaction has been difficult, probably because of the presumed low reactivity of the in situ generated, electronically neutral aryl ester (R'COOAr) toward the onium enolate **A** (left cycle). In contrast, in the betaine catalysis, the rate-limiting carbon–carbon bond formation would proceed in a pseudo-intramolecular manner, and the unique ion-pair intermediate **B** could have the potential to not only circumvent the reactivity problem but also induce an unprecedented level of stereocontrol (right cycle). Herein, we present the highly enantioselective Steglich rearrangement using chiral ammonium betaines as nucleophilic ionic catalysts.

The reaction was generally conducted by the addition of a 1,4-dioxane solution of 2-*tert*-butyl-4-benzyl-5-oxazolyl 2,2,2-trichloroethyl carbonate (**2a**) to a stirred mixture of **1** (2 mol %) and powdered 4 Å molecular sieves<sup>[10]</sup> in 1,4-dioxane at 25 °C.<sup>[11]</sup> Since an initial attempt with **1a**<sup>[4]</sup> as a catalyst showed its ineffectiveness in terms of both reactivity and stereoselectivity, we prepared **1b**, which lacks a substituent at the 3 position of the aryloxylate moiety (R<sup>2</sup>) to bring out the inherent nucleophilicity of the aryloxy anion. As expected, the rearrangement in the presence of **1b** proceeded cleanly to give the desired product **3a** in 93 % yield, and with an enantiomeric excess of 93 % (Scheme 2).<sup>[12]</sup> Notably, the characteristic yellow color of betaine **1b** instantaneously lightened with the addition of one drop of a solution of **2a**, which implies the formation of the intermediate **B**. Indeed, the analysis of this mixture by ESI/MS methods showed a peak corresponding to acylated **1b** (*m/z* 592), thus corroborating

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**Scheme 2.** Steglich rearrangement catalyzed by **1**. Bn = benzyl, Troc = 2,2,2-trichloroethoxycarbonyl.

rating our conjecture. After a while, without the addition of more **2a**, the original yellow color gradually returned, indicating the regeneration of the betaine **1b**, which was also verified by the detection of protonated **1b** ( $m/z$  418) in the ESI/MS measurements. This unique phenomenon would support the validity of the proposed reaction mechanism and confirm that the carbon–carbon bond formation is the rate-limiting step in this catalysis.<sup>[9a]</sup> Interestingly, the installation of an electron-withdrawing aromatic unit, such as the *para*-trifluoromethylphenyl (**1c**) or 3,5-bis(trifluoromethyl)phenyl (**1d**) group, on the naphthyl unit that possesses a pendent ammonium cation ( $R^1$ ) led to an enhancement of the catalytic efficiency; this enhancement was visually observed as the reaction mixture retained its yellow color throughout the reaction. The enantioselectivity was synchronously improved to 95% *ee* and 97% *ee* when using **1c** and **1d**, respectively.

With the optimized catalyst structure in hand, the general applicability of the asymmetric catalysis of the Steglich rearrangement by **1d** was investigated using a series of amino acid derived enol carbonates **2**; the representative examples are listed in Table 1. Substrates with simple alkyl (entries 1–5), substituted benzylic (entries 6–8), or functionalized alkyl side chains (entries 9 and 10) were efficiently transformed into the corresponding 4-(2,2,2-trichloroethoxy-

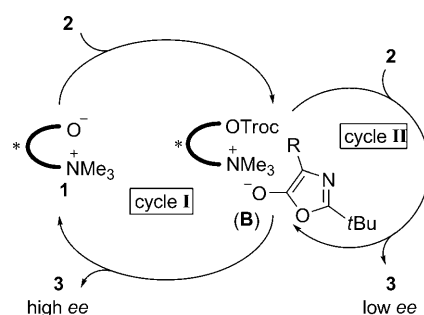
**Table 1:** Substrate scope.<sup>[a]</sup>

Entry	R	<b>3</b>	Yield [%] <sup>[b]</sup>	<i>ee</i> <sup>[c]</sup> [%]
1	CH <sub>3</sub>	<b>3b</b>	99	96
2	CH <sub>2</sub> CH <sub>3</sub>	<b>3c</b>	99	96
3	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub>	<b>3d</b>	96	96
4	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	<b>3e</b>	97	97
5 <sup>[d]</sup>	(CH <sub>3</sub> ) <sub>2</sub> CH	<b>3f</b>	94	95
6	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>3g</b>	98	97
7	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>3h</b>	97	96
8	<i>o</i> -FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>3i</b>	96	95
9	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub>	<b>3j</b>	91	94
10	CH <sub>3</sub> S(CH <sub>2</sub> ) <sub>2</sub>	<b>3k</b>	95	96

[a] Unless otherwise noted, the reactions were performed on 0.25 mmol scale in 2.5 mL of 1,4-dioxane with 4 Å M.S. at 25 °C. See the Supporting Information for more details. [b] Yields of isolated products are reported. [c] Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase. Absolute configurations of **3b–k** were assigned by analogy to **3a**. [d] The reaction was carried out at 40 °C.

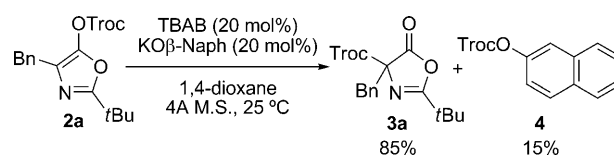
carbonyl)oxazolones **3** in high chemical yields with uniformly excellent and record levels of enantioselectivity. It should be emphasized that enol carbonates bearing a sterically demanding  $\alpha$  substituent such as the valine-derived substrate, a challenging substrate so far, can be accommodated by simply increasing the reaction temperature to 40 °C (entry 5).

In the present system, the stereoselectivity was strongly dependent upon substrate concentration, and it was of critical importance to maintain a low concentration of **2** to achieve an excellent enantiomeric excess. In fact, enantioselectivity was decreased to 87% *ee* when the reaction was performed by adding **1d** to a solution of **2a** under otherwise identical reaction conditions. This observation could provide an additional mechanistic clue to the **1d**-catalyzed Steglich rearrangement, that is, the existence of two reaction pathways. One is a highly stereoselective, pseudo-intramolecular bond-formation reaction (Scheme 3, cycle I), and the other is a less



**Scheme 3.** Possible reaction pathways for the Steglich rearrangement catalyzed by **1**.

stereoselective intermolecular reaction of the chiral ammonium enolate **B** with **2** (cycle II). To assess the involvement of cycle II, the reactivity of **2** as an acyl transfer reagent toward ammonium enolates was evaluated by the experiment shown in Scheme 4. The rearrangement of **2a** was carried out in a similar manner in the presence of the in situ generated ion-pair, tetrabutylammonium  $\beta$ -naphthoxide (20 mol %),<sup>[13]</sup> which afforded **3a** in 85% yield together with the 2,2,2-trichloroethyl  $\beta$ -naphthyl carbonate **4** (15% yield). The concomitant isolation of **4** in amounts comparable to that of the catalyst used, clearly indicates that **3a** was mainly produced through the reaction of **2a**-derived tetrabutylammonium enolate with **2a** itself. Therefore, chiral ammonium enolate **B** could also react with **2**, and this intermolecular bond-forming process would compete with the pseudo-intramolecular reaction of **B**. This is probably the origin of the concentration dependence of the stereoselectivity, and the



**Scheme 4.** In situ generated TBAO- $\beta$ -Naph as the catalyst for the reaction of **2a**.

addition of the substrate to the catalyst solution is crucial for allowing the pseudo-intramolecular process to predominate as it essentially relies on the ion-pair nature of **1**.

In conclusion, the nucleophilic nature of chiral ammonium betaines has been revealed and successfully applied to the an enantioselective Steglich rearrangement. This new, yet attractive function of ammonium betaines as ionic nucleophilic catalysts opens new opportunities for the development of asymmetric nucleophilic catalysis.

## Experimental Section

A magnetic stirrer bar and 4 Å molecular sieves (100 mg) were placed in a test tube under argon atmosphere. The 4 Å M.S. were then dried with a heat gun under reduced pressure for 5 min and the test tube was refilled with argon. Ammonium betaine **1d** (2.77 mg, 0.005 mmol) and 1,4-dioxane (1.0 mL) were added to the test tube successively under argon atmosphere at 25 °C. A solution of **2a** (101.7 mg, 0.25 mmol) in 1,4-dioxane (1.5 mL) was then added to the yellow mixture dropwise over 15 min. Upon completion of the addition, the reaction mixture was additionally stirred for 10 min, after which a 0.5 M solution of trifluoroacetic acid in toluene (20.0 µL) was introduced. The reaction mixture was filtered with CHCl<sub>3</sub> to remove the 4 Å M.S. and the filtrate was concentrated. The crude residue was purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (50:1→5:1) to afford **3a** (95.6 mg) in 94 % yield and the enantiomeric excess of **3a** was measured by HPLC analysis (DAICEL CHIRALPAK AS-H) (97 % *ee*).

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- [10] The addition of 4 Å molecular sieves was crucial for avoiding protonation of reactive ammonium enolate by a small amount (<5 %) of water which was contaminated from slightly hygroscopic onium salt **1**.
- [11] Under the representative conditions, we also attempted the reactions of benzyl and phenyl carbonate derivatives with **1d** as a catalyst, which gave unsatisfactory results: benzyl carbonate analogue of **2a**; [a low conversion (40 °C for 30 min)]; phenyl carbonate analogue of **2a** [76 % yield with 83 % *ee* (25 °C for 30 min)].
- [12] The absolute configuration of **3a** was determined by X-ray diffraction analysis after derivatization (CCDC 772979 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)). See the Supporting Information for details.
- [13] The generation of tetrabutylammonium β-naphthoxide in solution was confirmed by <sup>1</sup>H NMR analysis.