

Chiral Ammonium Betaines: A Bifunctional Organic Base Catalyst for Asymmetric Mannich-Type Reaction of α -Nitrocarboxylates

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A betaine, historically regarded as *N,N,N*-trimethylglycine, can be chemically defined as a neutral compound with an onium ion center bearing no hydrogen atom and an anionic moiety that is not adjacent to the cationic site. If the onium center consists of a nitrogen atom, it is classified as a quaternary ammonium salt.¹ In contrast to intermolecular ion-pairing ammonium salts, a quaternary ammonium betaine possessing an anion as its embedded functionality is inherently amenable to modification of the entire structure of the organic ion pair. Additionally, an ammonium betaine containing a basic anion could be capable of deprotonating a pronucleophile (Nu-H) to furnish an onium ion as its conjugate acid form (Figure 1). The acidic proton thus generated could direct the counterionic nucleophile at a defined position through the hydrogen-bonding interaction, thereby rendering a structured intermolecular ion pair. Although these properties of an ammonium betaine, in combination with an appropriate chiral scaffold, would offer a new approach to homogeneous catalysis of bifunctional² chiral onium salts, research in this direction has remained elusive. Herein, we report the design of chiral quaternary ammonium betaines of type **3** (Scheme 1) and demonstrate its potential as an enantioselective organic base catalyst³ in a direct Mannich-type reaction.⁴

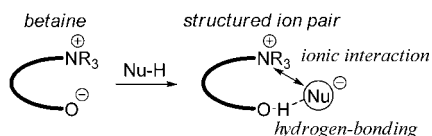


Figure 1. Ammonium betaine as a structural platform to induce bifunctional catalysis.

First, we synthesized quaternary ammonium chloride **1** as a precursor and sought an appropriate condition for the preparation of chiral ammonium betaine **2** possessing an aryloxy moiety as a basic functionality. Treatment of **1** with anhydrous tripotassium phosphate in acetone afforded **2** as a bench stable, yellowish solid as shown in Scheme 1.⁵ To evaluate the performance of **2** as an organic base catalyst, we selected α -substituted α -nitrocarboxylate **6** as a suitable pronucleophile and examined its Mannich-type reaction with *N*-Boc aldimines on the basis of a recent efficient protocol for the asymmetric synthesis of α -substituted α,β -diamino acids.⁶ Thus, an initial attempt was made by treating *tert*-butyl 2-nitropropionate (**6a**) with benzaldehyde-derived *N*-Boc imine **5a** in the presence of **2** (5 mol %) in toluene at 0 °C for 20 h. This revealed that **2** was indeed able to act as a catalyst, though its activity and stereoselectivity were insufficient (entry 1 in Table 1). Encouraged by this observation, we next assembled the betaines of type **3** with the expectation that the C_2 -symmetric conjugate acid would induce a high level of stereocontrol.⁷ Interestingly, while **3a** did not improve enantioselectivity despite the increase in catalytic activity (93% yield in 10 h) (entry 2), incorporation of phenyl substituents at the *ortho* position of the aryloxy moiety (**3b**) resulted

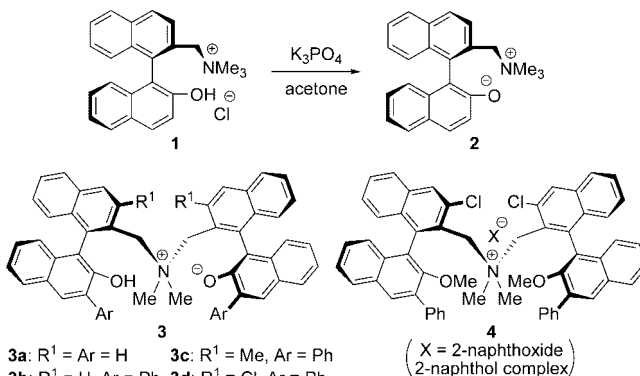
Scheme 1. Chiral Ammonium Betaines **2** and **3**

Table 1. Effect of the Catalyst Structure on the Reactivity and Stereoselectivity of the Direct Mannich-Type Reaction of *tert*-Butyl 2-Nitropropionate (**6a**)^a

Reaction scheme showing the asymmetric addition of an imine (**5a**) and an α -nitro ester (**6a**) catalyzed by **2**, **3**, or **4** (5 mol%) in toluene at 0 °C to form the chiral amide product (**7a**).

entry	catalyst	time (h)	yield ^b (%)	dr ^c (syn:anti)	ee ^d (%)
1	2	20	40	1:1.2	12/18
2	3a	10	93	1:1	−24/16
3	3b	8.5	93	1:1	98/95
4	3c	2	91	2.0:1	99/90
5	3d	5	95	4.1:1	99/91
6 ^e	3d	8	97	3.9:1	99/93
7	4	5	97	1.3:1	−5/5

^a Unless otherwise noted, the reaction of **5a** (1.1 equiv) and **6a** (0.1 mmol) in toluene (0.2 mL) was conducted in the presence of catalyst (5 mol %) at 0 °C for the given reaction time. ^b Isolated yield. ^c Determined by ¹H NMR analysis of the crude reaction mixtures. ^d Determined by chiral HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane–isopropyl alcohol (10/1) as solvent. Absolute and relative configurations were determined by comparison with literature data after derivatization.^{6b} ^e Reaction run using 1 mol % of the catalyst.

in remarkable enantioselectivity (entry 3). Further, the introduction of substituents to the other *ortho* position of the binaphthyl component (*R*¹) was found to be associated with improvement of diastereoselectivity, and the use of chloro-substituted **3d** led to the preferential formation of a syn isomer with almost complete enantiocontrol (entries 4 and 5). It should be noted that the catalyst loading can be reduced to 1 mol % without any detrimental effect on the stereoselectivity (entry 6). Meanwhile, the importance of the zwitterionic nature of **3d** for stereocontrol was clearly demonstrated by comparing it with intermolecular ion-pairing chiral quaternary ammonium 2-naphthoxide **4**.⁸ Although a similar reaction rate was induced by **4**, the loss of stereoselectivity implies

Table 2. Substrate Scope of Chiral Ammonium Betaine **3d**-Catalyzed Direct Mannich-Type Reaction^a

entry	R ²	R ³	time (h)	yield ^b (%)	dr ^c (syn:anti)	ee ^d (%)
1	<i>p</i> -Cl-C ₆ H ₄	Me	8	>99	3.6:1	99/91
2	<i>p</i> -Br-C ₆ H ₄		6	96	3.8:1	99/92
3	<i>p</i> -MeO-C ₆ H ₄		9	96	5.0:1	99/72
4	<i>p</i> -MeOCO-C ₆ H ₄		3	95	4.4:1	99/92
5	<i>o</i> -Me-C ₆ H ₄		10	91	5.2:1	98/93
6	2-furyl		6	>99	4.4:1	99/96
7 ^e	1-naphthyl		15	96	3.8:1	98/91
8 ^e	PhCH ₂ CH ₂		10	91	2.0:1	97/92
9 ^e	CH ₃ (CH ₂) ₇		11	97	2.2:1	99/91
10 ^e	Ph	Et	24	93	3.2:1	99/87

^a Unless otherwise specified, the reaction of **5** (1.1 equiv) with **6** (0.2 mmol) was carried out in toluene (0.4 mL) under the influence of **3d** (1 mol %) at 0 °C for the given reaction time. ^b Isolated yield. ^c Determined by ¹H NMR analysis of the crude reaction mixtures. ^d Determined by chiral HPLC analysis using a chiral column, see the Supporting Information for details. ^e Reaction run using 1.5 equiv of **5**.

the crucial role of the proximal phenolic proton as a hydrogen-bonding donor in forming the expected structured ion pair (entry 7).⁹

With the information on the catalytic and chiral efficiencies of **3d** at hand, the scope of this direct Mannich-type reaction was explored. The representative results are summarized in Table 2. Generally, 1 mol % of **3d** was sufficient for a smooth reaction in toluene at 0 °C, giving **7** in excellent chemical yield. The trend of the stereochemical outcome was the syn selectivity and the rigorous enantiocontrol observed for both diastereomers. With aromatic *N*-Boc imines, the present system tolerated the incorporation of both electron-withdrawing and electron-donating substituents including the methoxycarbonyl group (entries 1–5). A near-identical level of reactivity and selectivity was attained in the reactions with imines derived from furfural and 1-naphthaldehyde (entries 6 and 7). Moreover, aliphatic aldehyde-derived imines appeared to be good Mannich acceptors albeit certain decrease in the diastereoselectivity was detected (entries 8 and 9). As evident from the result of the reaction with α -nitrobutanoate, other α -nitrocarboxylates

bearing different α -substituents could also be employable as pronucleophiles (entry 10).

In summary, we have devised a chiral ammonium betaine as a highly enantioselective organic base catalyst in the direct Mannich-type reaction of α -substituted α -nitrocarboxylates with various *N*-Boc imines. We believe the chemistry described here represents a new direction for the design of bifunctional, chiral quaternary ammonium salts and their utilization as homogeneous organic molecular catalysts. Intensive research in this direction is underway in our laboratory.

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Supporting Information Available: Representative experimental procedures and spectral data of **1**–**4** and **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (5) Chiral ammonium betaine **2** can also be prepared by passing a solution of **1** in methanol through the ion-exchange resin [Amberlyst A-26 (OH)] followed by evaporation. Thus, once **1** is converted to the corresponding ammonium hydroxide, it would immediately undergo neutralization to liberate H₂O, forming intramolecular ion-pairing **2**. We also confirmed that **1** itself could not catalyze the present Mannich-type reaction at all.
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- (7) Chiral ammonium betaines **3b–d** can also be readily prepared by treatment of their precursors with 0.1 M aqueous solution of NaHCO₃ (see the Supporting Information).
- (8) **4** was prepared from the corresponding ammonium hydroxide according to the literature procedure: Tozawa, T.; Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Asian J.* **2007**, 2, 123.
- (9) For the catalysis of intermolecular ion-pairing, chiral quaternary ammonium phenoxide, see ref 8 and references therein.

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