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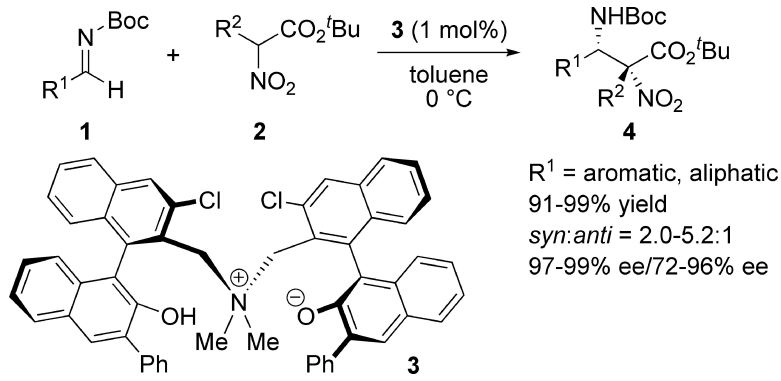

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Chiral Ammonium Betaines: A Bifunctional Organic Base Catalyst for Asymmetric Mannich-Type Reaction of α-Nitrocarboxylates

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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 bifunctional[2] 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 catalyst[3] in a direct Mannich-type reaction.[4]

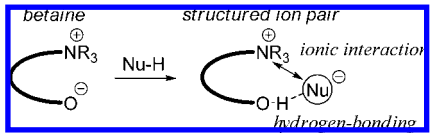


Figure 1. Ammonium betaine as a structural platform to induce bifunctional catalysis.

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**

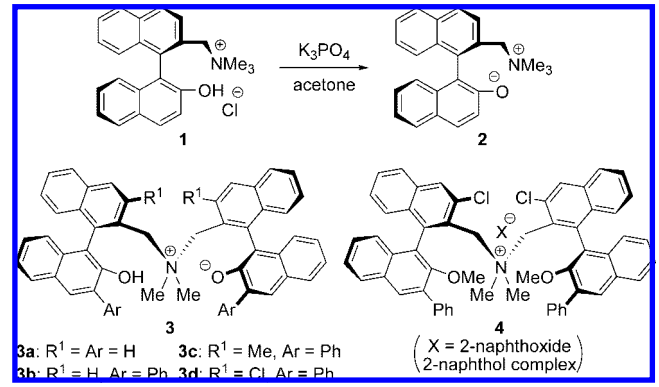
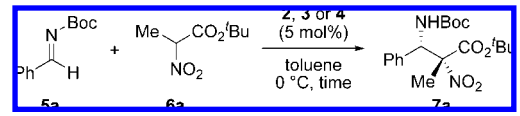


Table 1. Effect of the Catalyst Structure on the Reactivity and Stereoselectivity of the Direct Mannich-Type Reaction of *tert*-Butyl 2-Nitropropionate (**6a**)[a]



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 ^{1}H 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

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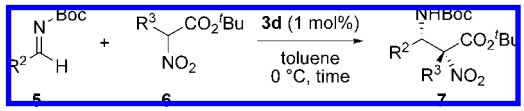
Table 2. Substrate Scope of Chiral Ammonium Betaine **3d**-Catalyzed Direct Mannich-Type Reaction[a]



entry	R^2	R^3	time (h)	yield[b] (%)	dr[c] (syn:anti)	ee[d] (%)
1	*p*-Cl-C_6H_4	Me	8	>99	3.6:1	99/91
2	*p*-Br-C_6H_4		6	96	3.8:1	99/92
3	*p*-MeO-C_6H_4		9	96	5.0:1	99/72
4	*p*-MeOCO-C_6H_4		3	95	4.4:1	99/92
5	*o*-Me-C_6H_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]	$PhCH_2CH_2$		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 ^{1}H 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 H_2O, forming intramolecular ion-pairing **2**. We also confirmed that **1** itself could not catalyze the present Mannich-type reaction at all.
(6) (a) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362. (b) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (c) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866.
(7) Chiral ammonium betaines **3b**−**d** can also be readily prepared by treatment of their precursors with 0.1 M aqueous solution of $NaHCO_3$ (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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