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Performance of C_1-symmetric chiral ammonium betaines as catalysts for the enantioselective Mannich-type reaction of α-nitrocarboxylates

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Dedicated to Professor Henri Kagan on the occassion of his 80th birthday

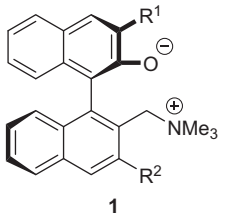
ABSTRACT

The catalytic performance of C_1-symmetric chiral ammonium betaines in the enantioselective direct Mannich-type reaction of α-nitrocarboxylates with *N*-Boc imines has been investigated. The most effective catalyst structure has been identified; this provides a reliable synthetic route to a variety of enantiomerically enriched α-tetrasubstituted α,β-diamino acid derivatives.

1. Introduction

Over the last two decades, chiral quaternary ammonium salts have been emerging as a useful and reliable organic molecular catalyst for effecting various stereoselective transformations under mild conditions.[1] Previously elaborated chiral quaternary ammonium salts can be classified as intermolecular ion-pairing ammonium salts, and they exhibit catalytic activity in either heterogeneous (biphasic) or homogeneous systems. In both cases, the reactivity and selectivity strongly depend on the three-dimensional structure of the chiral ammonium cations as well as the properties of the counter anions. In 2008, we developed a chiral ammonium betaine, an intramolecular ion-pairing quaternary ammonium aryloxide, as a new class of ammonium salts, and successfully demonstrated its ability to function as a bifunctional organic base catalyst in a homogeneous system by achieving the highly enantioselective direct Mannich-type reaction of α-nitrocarboxylates with *N*-Boc imines.[2,3] In the case of ammonium betaine, the entire structure of the organic ion pair can be fine-tuned by the structural modification of the backbone. Moreover, because the conjugate acid of the betaine is a quaternary ammonium cation possessing a phenolic proton, it could form a structured ion pair with a nucleophilic anion through electrostatic and hydrogen-bonding interactions, which constitutes a key element for inducing rigorous enantiocontrol. Quite recently, we introduced the second generation of this class of ammonium salts, C_1-symmetric chiral ammonium betaine of type **1** (Fig. 1), and succeeded in determining its discrete intramolecular ion-pairing structure by single-crystal X-ray diffraction analysis. This new, structurally simple ammonium betaine exhibited high catalytic and stereocontrolling abilities, enabling the highly stereoselective Mannich-type reaction of 2-alkoxythiazol-5(4*H*)-ones, a unique α-amino acid-derived nucleophile that affords certain synthetic advantage.[4]

During our continuing efforts to explore the scope and limitations of **1** as an organic base catalyst, we were interested in its performance in the direct Mannich-type reaction of α-nitrocarboxylates **3** with *N*-Boc imines **2** (see Table 2), mainly for the following two reasons: (1) this catalytic asymmetric protocol represents one of the simplest strategies to access variable precursors of α-tetrasubstituted α,β-diamino acids that are potentially valuable intermediates of biologically active, functionalized molecules; however, only a handful of effective catalyst systems have been reported in the literatures;[5,6] (2) such an investigation offers an appropriate opportunity for evaluating the validity of having consolidated the structural features of our initially devised, pseudo C_2-symmetric chiral ammonium betaine into **1**; this would strengthen the basis for pursuing further molecular design of this type of ammonium betaines. Herein, we report a set of results of this study.



1

1a: $R^1 = R^2 = Ph$
1b: $R^1 = Ph$, $R^2 = Cl$
1c: $R^1 = p$-^{t}Bu-C_6H_4, $R^2 = Cl$
1d: $R^1 = 3,5$-(^{t}Bu)$_2$-C_6H_3, $R^2 = Cl$

Figure 1. Structure of C_1-symmetric chiral ammonium betaine **1**.

2. Results and discussion

Initially, the reaction of *tert*-butyl 2-nitropropionate **3a** with benzaldehyde-derived *N*-Boc imine **2a** was conducted in the presence of a catalytic amount of **1a** (1 mol %) in toluene at 0 °C. Smooth bond formation occurred, and after 10 h of stirring the de-

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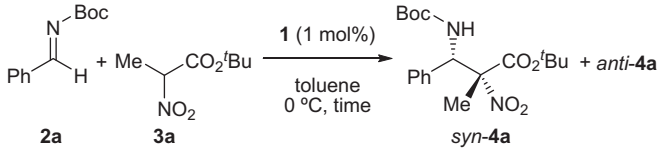
Table 1
Effect of substituent on each naphthyl group of chiral ammonium betaine **1**[a]

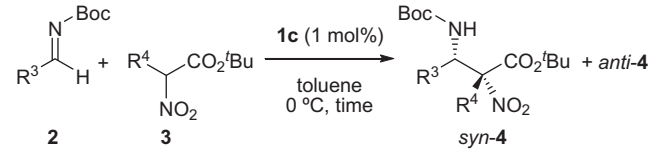


2a **3a** *syn*-**4a**

Entry	**1**	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	**1a**	10	92	2.1:1	90
2	**1b**	8	89	2.6:1	93
3	**1c**	8	98	3.2:1	95
4	**1d**	36	91	1.6:1	47

[a] Reactions were carried out with 0.22 mmol of **2a**, 0.2 mmol of **3a**, and 0.002 mmol of **1** in 0.4 mL of toluene at 0 °C under argon atmosphere.
[b] Isolated yields were reported.
[c] Diastereomeric ratio was determined by ^{1}H NMR analysis of crude mixture.
[d] Enantiomeric excess was analyzed by chiral HPLC. Absolute configuration was assigned based on the previous report.[2]

Table 2
Scope of substrate for **1c**-catalyzed Mannich-type reaction of α-nitrocarboxylates with *N*-Boc imines[a]



2 **3** *syn*-**4**

Entry	**2**(R^3)	**3**(R^4)	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	*p*-Br−C_6H_4	Me	6	95	3.1:1	93
2	*p*-Cl−C_6H_4	Me	6	99	2.8:1	95
3	*p*-CO_2Me−C_6H_4	Me	3	97	2.8:1	94
4	*p*-MeO−C_6H_4	Me	9	99	3.8:1	95
5	*o*-Me−C_6H_4	Me	12	90	5.9:1	90
6[e]	1-Naph	Me	15	99	4.4:1	92
7	2-Furyl	Me	6	99	2.3:1	96
8[e]	Ph	Et	24	99	2.1:1	94

[a] Reactions were carried out with 0.22 mmol of **2**, 0.2 mmol of **3**, and 0.002 mmol of **1c** in 0.4 mL of toluene at 0 °C under argon atmosphere.
[b] Isolated yields were reported.
[c] Diastereomeric ratio was determined by ^{1}H NMR analysis of crude mixture.
[d] Enantiomeric excess was analyzed by chiral HPLC.
[e] 1.5 equiv of **2** was used.

sired Mannich adduct **4a** was obtained in 92% yield. Although its diastereomeric ratio was relatively low (*syn*/*anti* = 2.1:1), the enantiomeric excess of the major *syn* isomer was determined to be 90% ee (Table 1, entry 1). It was of interest that the replacement of the phenyl substituent of the naphthyl unit bearing a pendent ammonium cation moiety (R^2) by the sterically less demanding chlorine atom slightly improved the stereoselectivities (entry 2). Notably, the steric bulkiness of the aromatic nuclei at the 3 position of the aryloxylate unit (R^1) was revealed to have significant influence on the catalytic performance of **1**. For instance, the use of **1c** possessing a 4-*tert*-butylphenyl group as R^1 led to an improvement in both the diastereo- and enantioselectivities (entry 3), whereas a substantial decrease in catalytic efficiency and stereoselectivities was observed when 3,5-di-*tert*-butylphenyl-substituted **1d** was tested (entry 4). Consequently, the most stereoselective catalyst **1c** was selected for further investigations.

Since the optimal structure of **1** as a catalyst was thus identified, we next examined the applicability of the present method. As shown in Table 2, a series of aromatic *N*-Boc imines with substituents having different electronic properties could be employed, and the general trend of selectivity was the moderate diastereocontrol and the rigorous enantiofacial discrimination for the major *syn* isomer (entries 1–5). It should be added that the incorporation of the *ortho* substituent seemed to be associated with a higher diastereoselectivity (entry 5). This system also tolerated heteroaromatic imines such as 2-furylaldehyde-derived one, in which the highest level of enantioselectivity was attained (entry 7). Moreover, *tert*-butyl 2-nitrobutanoate **3b** appeared to be a suitable pro-nucleophile for the **1c**-catalyzed direct Mannich-type protocol (entry 8).

3. Conclusion

We have demonstrated that structurally simplified, C_1-symmetric chiral ammonium betaines of type **1** can function as effective catalysts for the enantioselective direct Mannich-type reaction of α-nitrocarboxylates through appropriate tuning of the backbone structure. We believe that the present study not only enhances the synthetic value of this particular transformation as a reliable tool for the catalytic asymmetric synthesis of α-tetrasubstituted α,β-diamino acid derivatives but also underscores the potential of the intramolecular ion-pairing, chiral quaternary ammonium salts as an organic molecular catalyst.

Acknowledgments

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