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A Highly Enantioselective Mannich-Type Reaction of Glycine Schiff Base Catalyzed by a Cinchoninium Salt†

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A chiral phase-transfer catalyst, derived from the combination of cinchona alkaloid backbone and BINOL skeleton, enabled a Mannich reaction of glycine Schiff base with N-Boc-imines to generate *α*,*β*-diamino acid derivatives in excellent yields (up to 99%) and with high diastereo- and enantioselectivities (up to＞20∶1 *dr*, 96% *ee*).

Keywords phase-transfer catalysis, Mannich reaction, *α*,*β*-diamino acid, asymmetric catalysis, cinchoninium salt

Introduction

Phase-transfer catalysis (PTC) has been a versatile strategy in organic synthesis, featured by several advantages including simple operations and mild reaction conditions. PTC has also been exploited in industry for practical preparation of chiral molecules.[1] Recently, the use of chiral ammonium in asymmetric phase-transfer catalysis has attracted intensive attention, leading to notable accomplishments, enabling various highly enantioselective reactions to occur readily under mild conditions.[2] Among these transformations, the direct Mannich reaction[3] of a glycine Schiff bases or *α*-amino acid derivatives with imines turns out to be a straightforward protocol to stereoselectively access *α*,*β*-diamino acid derivatives[4] that have been found frequently in natural products, peptides and pharmaceutical compounds.[5]

In 2004, Maruoka and co-workers reported a Mannich-type addition of glycine Schiff base to *α*-imino esters using a chiral *N*-spiro quaternary ammonium bromide **I** as catalyst, delivering the protected 3-amino-aspartates with moderate diastereomeric ratios and enantioselectivities (Scheme 1, Eq. 1).[4a] Later, Ohshima, Shibasaki and co-workers described a tartrate-derived diammonium salt (**II**)-catalyzed asymmetric Mannich reaction of a glycine Schiff base with *N*-Boc-imines with excellent diastereoselectivity, but the enantioselectivity obtained was not satisfactory (Scheme 1, Eq. 1).[4b,4c]

More recently, Ooi and co-workers designed a chiral aminophosphonium pivalate **III**, which was able to act as an efficient phase transfer catalyst capable of rendering a Mannich-like reaction of azlactones with sulfonyl imines to give amino acid precursors with excellent enantioselectivity, but with modest diastereomeric ratios (Scheme 1, Eq. 2).[4d] A highly enantioselective Mannich reaction of azlactones with aliphatic imines was established by using a bis(betaine) catalysts (**IV**), which were derived from BINOL and quinidine, delivering *α*,*β*-diamino acid derivatives with excellent enantioselectivities but with only moderate diastereoselectivities (Scheme 1, Eq. 2).[4e] Despite of many highly stereoselective approaches available to access *α*,*β*-diamino acid derivatives,[6,7] a practical and straight-forward route still remains desirable and needs to be disclosed. Herein, we will present a highly diastereo- and enantioselective direct Mannich reaction of glycine Schiff base with *N*-Boc-imines under the phase transfer catalysis of chiral quininium salts[8-10] prepared from cinchona alkaloids and binaphthols (up to＞20/1 *dr* and 96% *ee*).

Initially, a library of chiral ammonium salts **1**—**4** were readily prepared from substitution reactions of cinchona alkaloid derivatives with structurally different aryl bromides in $CHCl_3$/EtOH at 40 ℃ by following known procedure reported previously.[11] Among them, chiral catalysts **1** and **2** were prepared from the reaction of quinine with benzyl bromide and 1-(bromomethyl)-naphthalene, respectively. On the other hand, the corresponding newly designed ammonium salts **3** featured by the installation of an additional axial chiral element were accessed by the substitution reactions of quinine with 3-(bromomethyl)-bis-O-protected (*R*)-BINOL derivatives,[4e] as described in Supporting Information.

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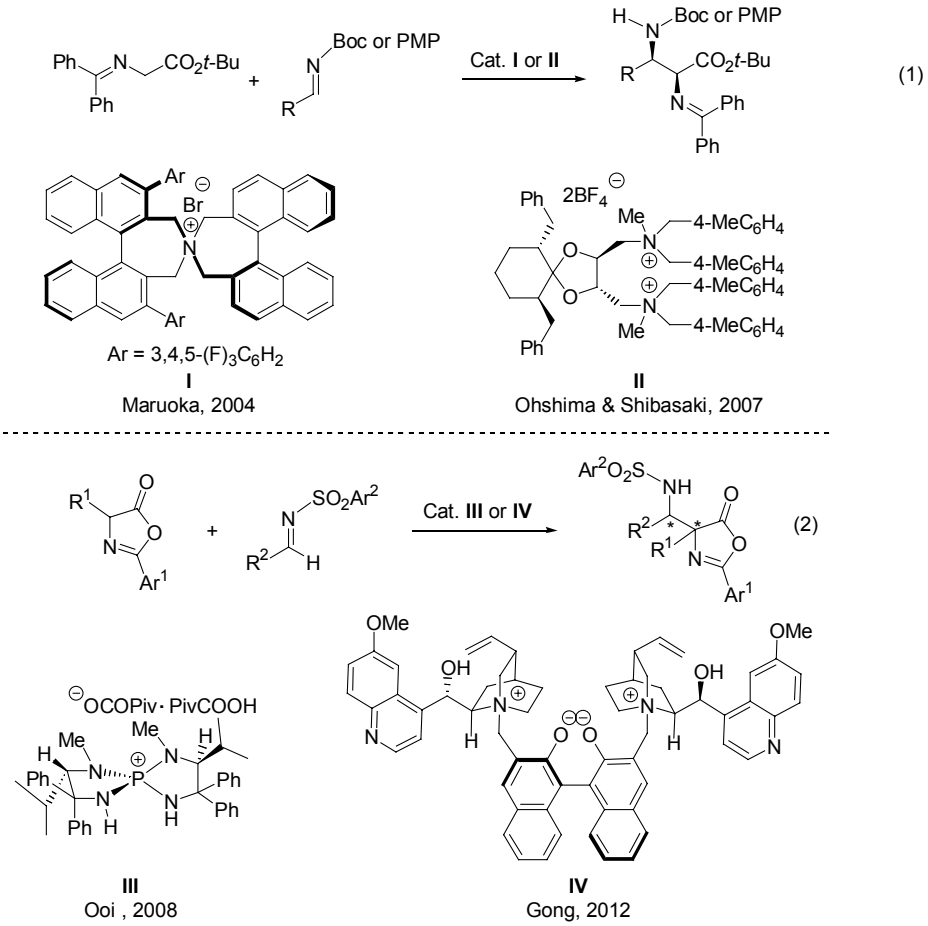
† Dedicated to Professor Chengye Yuan and Professor Li-Xin Dai on the occasion of their 90th birthdays.

Scheme 1 Chiral organocatalysts in Mannich-type reaction of a glycine Schiff base derivatives with imines



The ammonium salts **4** represent the derivatives of **3** by alkylation of the OH at C-9 of the quinine moiety and have been prepared by following procedures similar to those for the preparation of **3** (See Supporting Information).

Experimental

Representative procedure for asymmetric Mannich reaction

To a mixture of *N*-(diphenylmethylene) glycine *tert*-butyl ester (**5**) (29.5 mg, 0.10 mmol), (2*R*,4*R*,8*S*)-1-(((*R*)-2,2'-bis(anthracen-9-ylmethoxy)-1,1'-binaphthyl-3-yl)methyl)-2-((*S*)-hydroxy(6-methoxyquinolin-4-yl)-methyl)-8-vinyl-1-azoniabicyclo[2.2.2]octane bromide (**3c**) (10.8 mg, 0.01 mmol), Cs_2CO_3 (65.2 mg, 0.20 mmol) and Na_2SO_4 (100 mg, 0.70 mmol) in toluene (0.7 mL) was added a solution of (*E*)-*tert*-butyl 4-methoxybenzylidenecarbamate (**6a**) (28.2 mg, 0.12 mmol) in toluene (0.3 mL) at −20 ℃. After 48 h, the reaction was quenched with water. The aqueous layer was extracted with EtOAc (10 mL×3). The combined organic layers were dried over anhydrous magnesium sulfate and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel [*V*(hexane)/*V*(ether)＝10/1] to give *tert*-butyl 3-(*tert*-butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-(4-methoxyphenyl) propaonate (**7a**).

Results and Discussion

The chiral ammonium salts **1**—**4** were evaluated for the Mannich reaction of *tert*-butyl glycinate **5** and *N*-Boc imine **6a**. The reaction was conducted in toluene at 0 ℃ and in the presence of Cs_2CO_3 (2 equiv.), wherein anhydrous Na_2SO_4 was added to remove residual water and thereby to avoid the hydrolysis of imines. As shown in Table 1, although all the catalysts were able to accelerate the reaction, basically favouring the generation of *syn*-diamine adduct **7a**, the stereoselectivity was greatly dependent on the structure of ammonium salts. Either **1** or **2** enabled the reaction to give **7a** in a high yield and with high diastereomeric ratio, but a very low enantioselectivity was obtained (entries 1 and 2). Interestingly, much higher enantioselectivities were observed upon using the ammonium salts **3** incorporated with an additional axial chirality as the catalysts, suggesting that the additional chirality really exerted great impact on the stereochemical control (entries 3—5). In particular, promising stereochemical outcomes of 67% *ee* and 8/1 *dr* were obtained in the presence of **3c** (entry 5). In sharp contrast, the catalysts **4a**—**4c** with the

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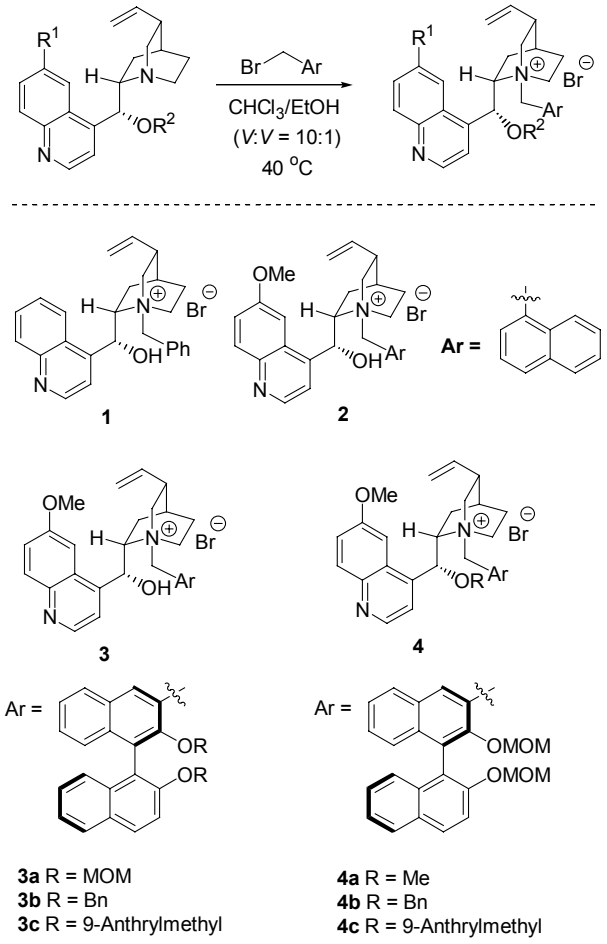
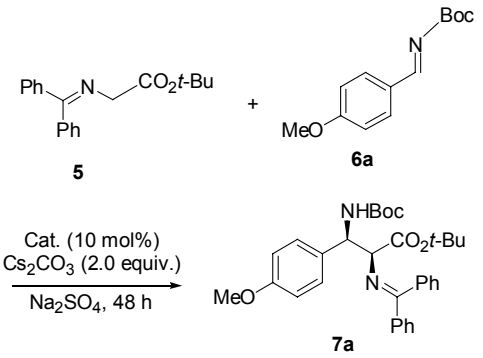
Scheme 2 Synthesis of catalyst library



hydroxyl of the quinine moiety being protected by alkyl groups offered much diminished enantioselectivities, but gave slightly improved diastereoselectivity (entries 6—8). These results clearly indicated that the hydroxyl group in ammonium salts may coordinate with the enolate generated from the protonation of substrate **5** with base, by the hydrogen-bonding interaction, to improve the enantioselectivity.[10e,12] In the presence of the optimal catalyst **3c**, a variety of solvents were examined and found that toluene appeared to be the most suitable media (entries 5, 9—13). Significantly, conducting the reaction at –20 ℃ led to a considerable improvement in the diastereomeric ratio (13/1) and enantioselectivity (86% *ee*) (entry 5 vs. 14). To clarify the role played by the axial chirality in the catalysis, the (*S*)-binaphthyl skeleton was adopted in the synthesis of **3c'**, an epimer of catalyst **3c**. Under the otherwise identical conditions, similar yield and diastereoslectivity (87% yield, 13∶1 *dr*) of the product was obtained, but the enantioselectivity was considerably decreased to 78% *ee* (entry 15). These results implied that the (*S*)-axial chirality might mismatch with quinine in the control of enantioselectivity (entry 15 vs. 14).

Having established the optimal conditions, we then investigated reaction generality for imine substrates (Table 2). A wide scope of aromatic aldimines were

Table 1 Evaluation of chiral catalysts and optimization of conditions[a]



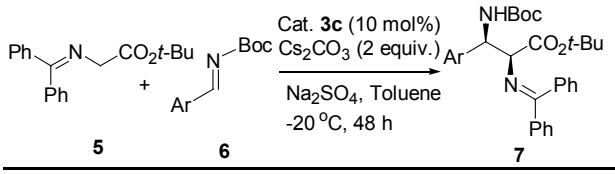
Entry	Cat.	Temp./℃	Solvent	Yield[b]/%	*dr*[c]	*ee*[d]/%
1	**1**	0	$PhCH_3$	83	10∶1	9
2	**2**	0	$PhCH_3$	94	13∶1	0
3	**3a**	0	$PhCH_3$	73	5∶1	64
4	**3b**	0	$PhCH_3$	66	6∶1	55
5	**3c**	0	$PhCH_3$	84	8∶1	67
6	**4a**	0	$PhCH_3$	79	14∶1	16
7	**4b**	0	$PhCH_3$	65	14∶1	13
8	**4c**	0	$PhCH_3$	82	11∶1	32
9	**3c**	0	CH_2Cl_2	92	19∶1	16
10	**3c**	0	Et_2O	99	10∶1	0
11	**3c**	0	THF	87	13∶1	8
12	**3c**	0	PhF	69	15∶1	55
13	**3c**	0	PhCl	70	14∶1	60
14	**3c**	–20	$PhCH_3$	79	13∶1	86
15	**3c'**	–20[e]	$PhCH_3$	87	13∶1	78

[a] Unless indicated otherwise, reactions of **5** (0.10 mmol), **6a** (0.12 mmol), catalyst (0.01 mmol), Cs_2CO_3 (0.20 mmol) and Na_2SO_4 (100 mg) were carried out in a solvent (1 mL) for 48 h. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis. [e] Catalyst **3c'** was used in the reaction. The (*S*)-BINOL skeleton was used in the synthesis of the epimer **3c** of the catalyst **3c**.

able to smoothly undergo the Mannich reaction to give rise to *α*,*β*-diamino acid derivatives in high yields while both diastereo- and enantioselectivities have an apparent correlation with the aryl substituent of aldimines (entries 1—13). Obviously, the presence of electronically withdrawing or neutral substituents at *ortho* or *para*-position of the benzene ring basically provided higher enantioselectivity than those bearing electron-donating substituents (entries 1—2 and 4—6 vs. 7). In contrast, the introduction of either an electronically rich or deficient *meta*-substituent at the benzene ring of aldimines was nicely tolerated to give excellent levels of enantioselectivity (entries 3 and 8—9). Moreover, the disubstituted aldimine also underwent the Mannich reaction in a perfect yield and with 90% *ee* (entry 10). Addition-

ally, the protocol was also amenable to 2-thiophenyl, 2-furyl and 1-naphthyl imines, leading to the generation of desired products in excellent yields ranging from 93% to 99% and with high enantioselectivity of up to 94% *ee* (entries 11—13). However, the Mannich reaction of aliphatic imines with *tert*-butyl glycinate **5** was unable to give satisfactory enantioselectivities.[13] The relative configurations and absolute configuration of the same products **7** were assigned by comparing the data with those in the literatures by ^{1}H NMR, HPLC and optical rotation,[4c,4e] and other products were assigned by analogy.

Table 2 Substrate scope for imines[a]



5 **6** **7**

Entry	Ar	Yield[b]/%	*dr*[c]	*ee*[d]/%
1	**6b** (C_6H_5)	99	>20 : 1	93
2	**6c** (2-FC_6H_4)	99	19 : 1	96
3	**6d** (3-FC_6H_4)	99	19 : 1	92
4	**6e** (4-FC_6H_4)	99	20 : 1	94
5	**6f** (4-ClC_6H_4)	99	>20 : 1	94
6	**6g** (4-BrC_6H_4)	90	>20 : 1	92
7	**6h** (4-MeC_6H_4)	99	15 : 1	88
8	**6i** (3-MeC_6H_4)	99	17 : 1	94
9	**6j** (3-$MeOC_6H_4$)	64	>20 : 1	93
10	**6k** (3,4-$Cl_2C_6H_3$)	99	13 : 1	90
11	**6l** (2-thiophenyl)	99	10 : 1	92
12	**6m** (2-furyl)	93	14 : 1	94
13	**6n** (1-naphthyl)	99	6 : 1	90

[a] Unless indicated otherwise, reactions of **5** (0.10 mmol), **6** (0.12 mmol), catalyst **3c** (0.01 mmol), Cs_2CO_3 (0.20 mmol) and Na_2SO_4 (100 mg) were carried out in toluene (1 mL) for 48 h. [b] Isolated yield. [c] Determined by H NMR analysis. [d] Determined by HPLC analysis.

Conclusions

In conclusion, we have developed a family of quinine-based ammonium salts featured by the incorporation of an additional axial chirality, capable of efficiently promoting the Mannich-type reaction of a glycine Schiff base with *N*-Boc imines. In particular, the ammonium salt derived from (*R*)-BINOL and quinine was found to be the most efficient catalyst, rendering the Mannich reaction to give *α*,*β*-diamino ester derivatives in up to 99% yield and with high diastereo- and enantioselectivities (up to >20 : 1 *dr* and 96% *ee*). More importantly, the finding that the axial chirality plays a crucial role in the control of stereoselectivity might provide a possible clue for the design of new chiral phase transfer catalysts.

Acknowledgement

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(Zhao, X.)

