DOI: 10.1002/adsc.200900580

Organocatalytic Asymmetric Synthesis of Protected α,β-Diamino Acids

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Received: August 23, 2009; Published online: November 12, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900580.

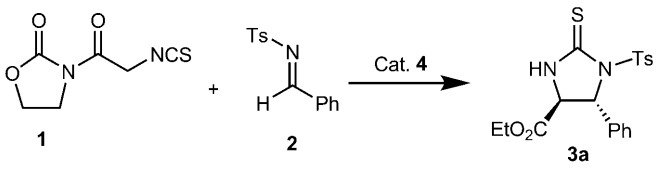
Abstract: In the presence of the readily available quinine-derived catalyst **4d**, highly diastereo- and enantioselective Mannich reactions of tosyl-protected imines and α-isothiocyanato imides proceeded to afford the protected α,β-diamino acids, useful building blocks for natural products and biologically active compounds, in good to excellent yields.

Keywords: asymmetric catalysis; α,β-diamino acids; Mannich reaction; organocatalysis; quinine derivatives

Amino acids, such as α-amino acids,[1] β-amino acids[2] and β-hydroxy-α-amino acids,[3] are frequently found in many biologically active peptides and natural products. They have attracted intensive investigation from numerous research groups. However, α,β-diamino acids,[4] which are also versatile intermediates in academic and industrial fields, as well as some other types of amino acids, were less well studied, especially with regard to their asymmetric syntheses. Although some of the methodologies have realized asymmetric versions by employing chiral ligand/metal complexes, it still remains a big challenge to develop a more efficient, economical and operationally simple strategy, and at the same time avoiding toxic metals and expensive chiral ligands.[5] Herein, we report a catalytic asymmetric synthetic protocol for the synthesis of the protected α,β-diamino acids by the Mannich reactions of tosyl-protected imines and α-isothiocyanato imides with a cheap and readily available quinine derivative as catalyst under the mild reaction conditions.[6]

PMP- and Boc-protected phenylimines were first examined for this transformation in the presence of 10 mol% catalyst **4e**. However, no reactions occurred. This was probably due to the reduced electrophilicities of the imines toward α-isothiocynato imide **1**.[7] When more reactive tosyl-protected phenylimine **2** was employed, to our delight, the reaction proceeded smoothly to give the desired product in 92% yield, though no enantioselectivity was achieved (Table 1, entry 5). Encouraged by this promising result, three new bifunctional catalysts **4k**, **4l** and **4m** were designed and synthesized for the reaction (Figure 1). Unfortunately, they could not promote this transformation.[7] Another ten catalysts were then screened

Table 1. Catalyst screening.[a]



1 2 3a

Entry	4	t [h]	Yield [%][b]	dr[c]	ee [%][d]
1	**4a**	5	73	95:5	43
2	**4b**	5	92	95:5	85
3	**4c**	24	81	91:9	40
4	**4d**	4	99	95:5	>99
5	**4e**	5	92	–	0
6	**4f**	6	91	95:5	−48
7	**4g**	24	78	87:13	−50
8	**4h**	24	50	95:5	−40
9	**4i**	10	95	67:33	−24
10[e]	**4b**	10	88	89:11	70

[a] Reaction was performed at room temperature (23 °C) on a 0.1 mmol scale in toluene (0.1 M) using 1.2 equiv. of **2** and 10 mol% **4**. *Reaction conditions:* see Experimental Section.
[b] Combined yield of both diastereoisomers.
[c] Determined by ^{1}H NMR on the crude mixture.
[d] Determined by chiral HPLC of the major isomer.
[e] Reaction was performed at 0–4 °C.

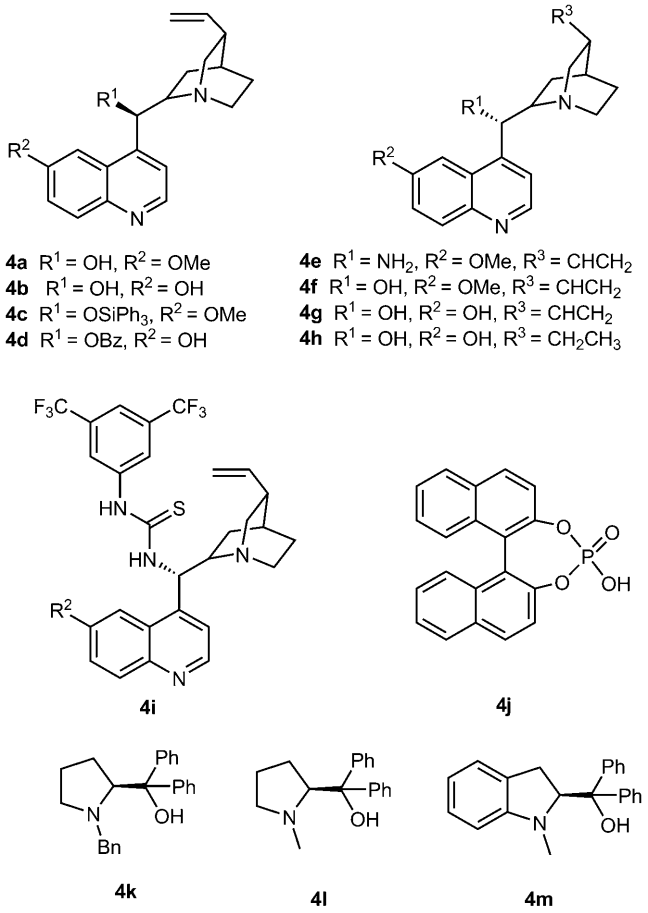


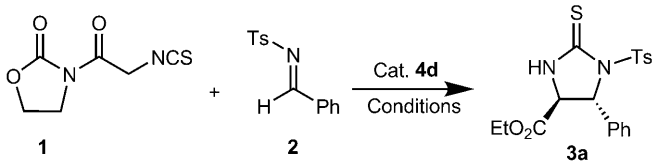
Figure 1. Structures of catalysts screened.

and we observed that *Cinchona* alkaloid derivatives catalyzed the reaction giving low levels of asymmetric induction (entries 1, 3 and 4–8), while simple BINOL-derived phosphoric acid **4j** could not induce any reaction.[7] When the more acidic catalyst **4b** (comparing to **4a**) was examined, the enantioselectivity was significantly increased to 85% *ee* (entry 2, 95:5 *dr* and 92% yield).[8] Decreasing the reaction temperature to 0–4 °C led to the diminished diastereo- and enantioselectivity (entry 10, 70% *ee* and 89:11 *dr*). Protection of the 9-hydroxy group on catalyst **4b** with a benzoyl group dramatically improved the catalytic efficiency, thus achieving excellent stereoselective control (entry 4, >99% *ee* and 95:5 *dr*).[9]

The effect of catalyst loading, solvent and reactant concentration for this transformation was further investigated (Table 2). Catalyst **4d** proved powerful enough to afford product **3a** in excellent yield (98%), enantio- (98%) and good diastereoselectivity (90:10 *dr*), even with a low catalyst loading (1.0 mol% in entry 5). Various non-polar solvents were well tolerated, with *m*-xylene giving the best result in the presence of 2.5 mol% catalyst **4d** at room temperature (entry 10, in 99% yield, >99% *ee* and 95:5 *dr*).

With the optimal reaction conditions in hand, the scope of tosyl-protected imines was explored as shown in Table 3. Aromatic, heteroaromatic and aliphatic Ts-protected imines were good substrates for this reaction, affording the desired adducts in high yields and stereoselectivities. Ts-protected 3 or 4-substituted and non-subsituted phenylimines were strong-

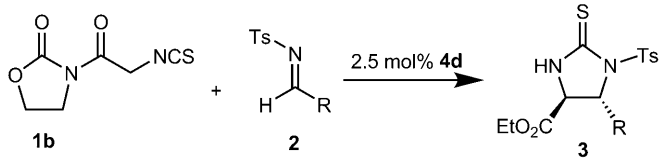
Table 2. Optimization of reaction conditions.



Entry	mol% (**4d**)	Solvent	M (**1**)	*t* [h]	Yield [%][a]	*dr*[b]	*ee* [%][c]
1	10	toluene	0.1	3.5	99	95:5	>99
2	7.5	toluene	0.1	4	91	93:7	>99
3	5	toluene	0.1	4	97	95:5	>99
4	2.5	toluene	0.1	5	94	95:5	>99
5	1.0	toluene	0.1	13	98	90:10	98
6	2.5	toluene	0.1	5	94	95:5	>99
7	2.5	benzene	0.1	10	74	95:5	98
8	2.5	$CHCl_3$	0.1	24	60	92:8	99
9	2.5	MTBE	0.1	8	96	95:5	96
10	2.5	*m*-xylene	0.1	5	99	96:4	>99
11	2.5	*m*-xylene	0.2	2	99	95:5	>99
12	2.5	*m*-xylene	0.05	8	99	96:4	>99

[a] Combined yield of both diastereoisomers.
[b] Determined by ^{1}H NMR of the crude reaction mixtures.
[c] Determined by chiral HPLC using chiral AD-H column or AS-H column of the major isomer.

Table 3. Substrate scope.[a]



Entry	R	*t* [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	Ph	5	90	96:4	>99
2	4-MeC_6H_4	4	99	97:3	>99
3	4-ClC_6H_4	3	97	96:4	>99
4	4-BrC_6H_4	5	92	97:3	>99
5	3-MeC_6H_4	4	98	97:3	>99
6	3-ClC_6H_4	2	99	93:7	95
7[e]	3-furyl	6	96	89:11	98
8[f]	2-MeC_6H_4	72	80	91:9	91
9[e]	2-FC_6H_4	10	91	67:33	97
10	2-thienyl	6	99	93:7	99
11[e]	2-naphthyl	5	90	95:5	97
12[e]	cinnamyl	30	97	80:20	98
13[g]	*n*-butyl	48	90	83:17	86

[a] Standard conditions, see Experimental Section.
[b] Combined yield of both diastereoisomers.
[c] Determined by ^{1}H NMR of reaction mixtures.
[d] Determined by chiral HPLC.
[e] 5 mol% **4d** was used.
[f] 10 mol% **4d** was used.
[g] 10 mol% **4d** and 20 mg 4 Å MS were employed.

ly favoured on this catalytic platform, in ≥90% yields, ≥95% *ee* and ≥93:7 *dr* (entries 1–6). For the cases of 2-substituted Ts-protected imines, higher catalyst loadings and longer reaction time were needed, probably due to their steric hindrance and thus lower diastereoselectivities were obtained. Their enantioselectivities dropped a little bit, especially for 2-methyl phenyl Ts-protected imine (entry 8, 91% *ee*). It is worthwhile to note that, even with highly unstable aliphatic Ts-protected imine substrates, the Mannich reaction could still proceed smoothly in excellent yield with acceptable diastereoselectivity and good enantioselectivity in the presence of 10 mol% catalyst **4d** and 20 mg of 4 Å molecular sieves (entry 13, 90% yield, 86% *ee* and 83:17 *dr*).

In summary, we have developed a highly efficient organocatalytic asymmetric protocol for preparation of the enantiomerically pure protected α,β-diamino acids, through the Mannich reaction between Ts-protected imines and α-isothiocyanato imide **1**, catalyzed by readily available and environmentally-friendly quinine derived catalyst **4d** under very mild conditions.

Experimental Section

Typical Procedure for the Catalytic Synthesis of α,β-Diamino Acids

To a stirred solution of catalyst **4d** (2.5 mol%) and Ts-protected imines (0.12 mmol) in 1.0 mL of *m*-xylene, was added α-isothiocyanato imide **1** (0.1 mmol). The reaction mixture was kept stirring at room temperature (23 °C) for the time given in Table 3. After the reaction was completed, solvent was removed under reduced pressure, and then dried THF was added and the mixture cooled to 0–4 °C. A THF solution of magnesium bromide ethanolate (2 mL, 3.0 equiv.), preformed from methylmagnesium bromide (0.1 mL, 3 M in DCM) and ethanol (0.1 mL) in 2 mL of THF at 0 °C, was slowly added. After 3 min, the reaction was quenched by saturated aqueous NH_4Cl. Then, the crude product was purified over silica gel chromatography with the eluent (hexane/acetone from 8:1 to 2:1) to give the corresponding protected α,β-diamino acid ethyl ester derivatives. The stereochemistry of the product was confirmed by the X-ray crystallographic analysis (CCDC 745237)[10] together with the NMR spectroscopy.

Acknowledgements

Research support from the Ministry of Education in Singapore (ARC12/07, no. T206B3225) and Nanyang Technological University (URC, RG53/07) is gratefully acknowledged.

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[7] For more details, please see the Supporting Information.

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[10] CCDC 745237 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.

