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Highly Enantio- and Diastereoselective Mannich Reactions of Chiral Ni(II) Glycinates with Amino Sulfones. Efficient Asymmetric Synthesis of Aromatic α,β-Diamino Acids

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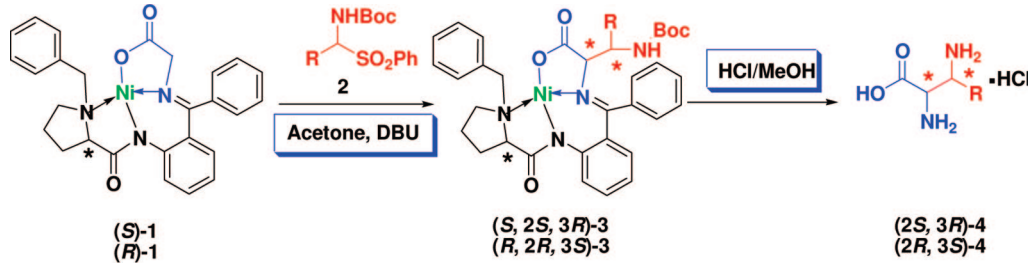
Received September 4, 2008



This paper describes a practical, enantio- and diastereoselective Mannich reaction between a chiral Ni(II) complex of glycine **1** and α-amino sulfones **2**, involving the creation of a carbon−carbon bond and two stereogenic centers in a single operation; it represents an attractive route to the synthesis α,β-diamino acids.

Introduction

α,β-Diamino acids are versatile building blocks in organic synthesis and medicinal and peptide/peptidomimetic chemistry.[1,2] Furthermore, they are also useful in wide applications, as chiral auxiliaries and ligands for asymmetric synthesis.[3] Accordingly, the development of efficient methods in their preparation has been a mainstay in organic synthesis.[4] Jørgensen et al. report an indirect method using a chiral copper complex-promoted aza-Henry reaction of nitro compounds with α-imino esters.[5] This approach requires an additional reduction step, to convert the nitro moiety to an amino group. Willis et al. meanwhile described a direct catalytic Mannich reaction that leads to *anti*-α,β-diamino acids.[6] However, the removal of the *para*-toluenesulfonate (tosyl) protecting group requires harsh reaction conditions. A chiral phase-transfer catalyst was recently disclosed by Shibasaki et al. to achieve highly diastereoselective access to *syn*-α,β-diamino acids,[7a] and Ooi et al. also reported the asymmetric synthesis of α,β-diamino acid derivatives under asymmetric phase transfer conditions.[7b] Hayashi et al. have reported asymmetric gold(I)-catalyzed reactions of methyl isocyanoacetate with imines as potentially useful access to erythro-α,β-diamino acids.[8] However, these approaches rely on the use of relatively exotic and therefore expensive catalysts that might limit their broad synthetic applications. Finally, Soloshonok et al. has reported a single example of highly diastereoselective aza-aldol reaction of chiral Ni(II) complex

† These authors contributed equally to this work.

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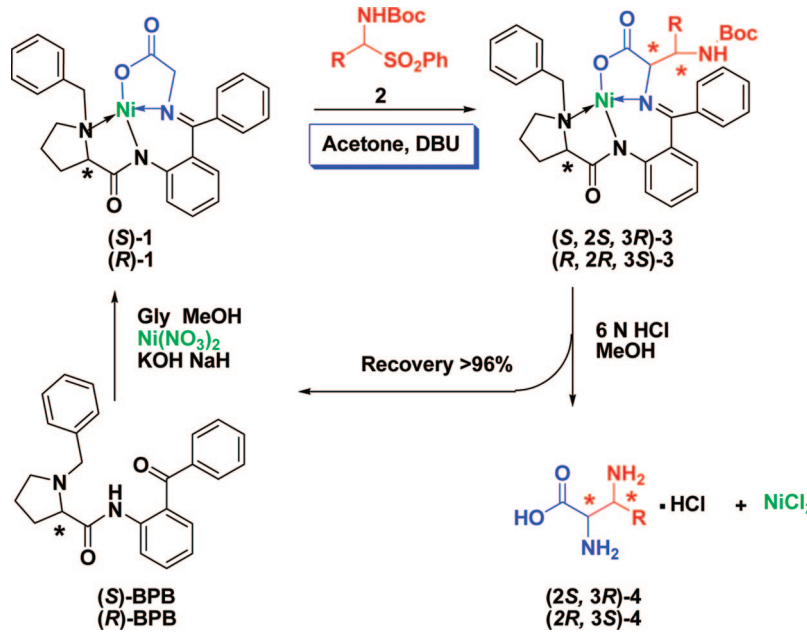
10.1021/jo8019169 CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/10/2008

SCHEME 1. Stereoselective Synthesis of Enantioenriched α,β-Diamino Acids via Chiral Ni(II) Complexes with Sulfones



of glycine (*S*)-**1** with extremely electrophonic trifluoroacetaldimine as a plausible method for preparation of 3-perfluoroalkyl-2,3-diamino acids.[9] Thus, various methodological and structural shortcomings of the literature approaches render these methods of limited synthetic application, in particular for preparation of the target diamino acids on relatively large scale. In this paper, we disclose a strategy for the practical synthesis of highly enantio- and diastereoselective α,β-diamino acids, with high efficiency. Significantly, the process developed in this work features rare synthetic methods for operational convenience[10] and is based on readily available and inexpensive starting materials.

The Ni(II) complex of the chiral Schiff base of glycine has been widely used to synthesize enantiopure α-amino acids via aldol,[11] Michael addition,[12] and C-alkylation reactions.[13] The notable merits of the Ni(II) complex's methods are (1) the provision of high enantio- and/or diastereocontrol, (2) the use of readily available and cost-effective substances, (3) mild reaction conditions and simple reaction procedures, (4) high reaction yields with good reproducibility, and (5) easy recovery of chiral ligands. These unique properties render it an attractive strategy for practical synthesis in industrial settings.[14] Accordingly, we proposed the use of the chiral Ni(II) complex as a stereocontroller for the asymmetric synthesis of α,β-diamino acids. Remarkably, we demonstrated that the Mannich reaction between a chiral Ni(II) complex of glycine **1** and α-amino sulfones **2** served as an efficient approach to α,β-diamino acids, with the creation of a new carbon−carbon bond and two adjacent stereogenic centers in a single operation (Scheme 1). This is an example of highly stereoselective Mannich reactions with an in situ generation of carbamate-protected imines by chiral Ni(II) complex. As demonstrated, robust and readily obtained Boc/Cbz-α-amino sulfones **2**[15] with wide ranges of structural diversity can efficiently participate in the process with high enantio- and diastereoselectivity, thus significantly expanding the scope of the reactions. Furthermore, the use of readily manipulated Boc/Cbz protecting groups enables the use of these highly enantioenriched amino acid products in further synthetic elaborations.

Results and Discussion

Mannich Reactions between (*S*)-Ni(II) Complex 1 and *N*-(*tert*-Butoxycarbonyl)-(−)-(phenylsulfonyl)benzylamine 2a Using Various Bases and Solvents. On the basis of the successful synthesis of α-amino-β-hydroxy acids,[11] we selected chiral (*S*)-Ni(II) complex of glycine **1** with (*S*)-*o*-[*N*-(*N*-

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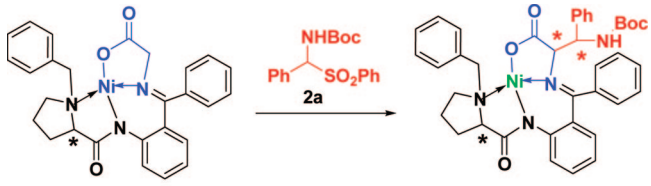
TABLE 1. Optimization of the Reaction Conditions[a]



(*S*)-**1** (*S*, 2*S*, 3*R*)-**3a**

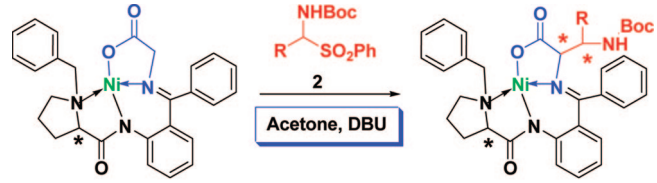
entry	base	solvent	temp °C	yield %	*syn*:*anti*[b]	de %[c]
1	DBU	CH_2Cl_2	23	86	81:19	>99
2	NaH	CH_2Cl_2	23	91	65:35	91
3	*t*BuOK	CH_2Cl_2	23	91	64:36	90
4	NaOH	CH_2Cl_2	23	92	71:29	87
5	DBU	CH_3CN	23	93	90:10	>99
6	DBU	acetone	23	93	92:8	>99
7	DBU	THF	23	92	80:20	98
8	DBU	DMF	23	85	83:17	>99
9	DBU	CH_2Cl_2	40	80	76:24	>99
10	DBU	CH_2Cl_2	0	85	87:13	>99
11	DBU	CH_2Cl_2	−20	80	87:13	>99
12	DBU	CH_2Cl_2	−40	92	90:10	>99
13	DBU	CH_2Cl_2	−60	96	92:8	>99

[a] Reactions were run with 0.20 mmol of (*S*)-**1**, 0.21 mmol of **2a** in 10 mL of solvent with 0.24 mmol base for 4 h. [b] Determined by HPLC analysis. [c] Determined by SFC analysis (see Supporting Information for details).

benzylprolyl)amino]benzophenone as a chiral equivalent nucleophilic partner and chose to study the union of (*S*)-**1** and the α-amino sulfone **2a** derived from benzaldehyde as a model substrate for optimizing reaction conditions. The results are summarized in Table 1. In the initial study, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) was selected as a base[9] and the reaction was conducted in dichloromethane. Gratifyingly, the process delivered the Mannich adduct (*S*,2*S*,3*R*)-**3a** in high enantioselectivity 99% de (Table 1, entry 1). We used 1.2 equiv of DBU as base for this Mannich reaction; 1 equiv of DBU was used to generate in situ the corresponding imines, and the other 0.2 equiv of DBU was used for purely catalytic purposes.[9] A variety of alternative bases were investigated accordingly. It was found that a moderate diastereoselectivity (entries 2−4) was observed with the use of NaH, *t*-BuOK, and NaOH. Screening of solvents (entries 5−8) revealed that, while dichloromethane and acetonitrile afforded good results, the best combination of yield and enantioselectivity was realized with acetone (Table 1, entry 6). The representative results collected in entries 1−8 show that the diastereoselectivity greatly depends on the conditions applied, while the thermodynamically controlled stemochemical outcome could be only slightly influenced by the nature of both base and solvent used. Further optimization studies established that with the reaction with the base DBU and dichloromethane at various temperatures, from 40 to −60 °C (entries 9−13), in all cases good yields and excellent enantioselectivities were achieved. Lowering the reaction temperature led to significant improvement in the diastereoselectivity. From the viewpoint of practical applications, we chose DBU as a base and acetone as a solvent, both at ambient temperature, to probe the generality of the Mannich process (Table 1, entry 6).

Mannich Reactions between (*S*)-Ni(II) Complex 1 and α-Amino Sulfones 2. After the reaction conditions were optimized, the generality of the reaction was investigated, and the results, summarized in Table 2, show that the reaction has broad applicability. Examination of the results reveals that the process served as a general approach to *syn*-α,*β*-diamino acids.

TABLE 2. Asymmetric Mannich Reactions of (*S*)-Ni(II) Complex 1 with α-Amino Sulfones 2[a]



(*S*)-**1** (*S*, 2*S*, 3*R*)-**3**

entry	product	R group	yield %	*syn*:*anti*[b]	de %[c]
1	(*S*,2*S*,3*R*)-**3a**	Ph	93	92:8	>99
2	(*S*,2*S*,3*R*)-**3b**	2-Me-C_6H_4	92	91:9	91
3	(*S*,2*S*,3*R*)-**3c**	3-Me-C_6H_4	93	92:8	96
4	(*S*,2*S*,3*R*)-**3d**	4-Me-C_6H_4	91	93:7	>99
5	(*S*,2*S*,3*R*)-**3e**	4-MeO-C_6H_4	90	92:8	94
6	(*S*,2*S*,3*R*)-**3f**	4-NO_2-C_6H_4	91	93:7	79
7	(*S*,2*S*,3*R*)-**3g**	4-F-C_6H_4	94	94:6	87
8	(*S*,2*S*,3*R*)-**3h**	4-Cl-C_6H_4	93	93:7	73
9	(*S*,2*S*,3*R*)-**3i**	4-Br-C_6H_4	94	94:6	91
10	(*S*,2*S*,3*R*)-**3j**	2-furyl	91	90:10	>99
11	(*S*,2*S*,3*R*)-**3k**	3-thiophenyl	92	91:9	92
12	(*S*,2*S*,3*R*)-**3l**	2-naphthyl	90	92:8	>98
13	(*S*,2*S*,3*R*)-**3m**	2-quinoline	90	90:10	88
14	(*S*,2*S*,3*R*)-**3n**	cyclohexyl	25	90:10	77
15	(*S*,2*S*,3*R*)-**3o**	*i*-Pr	16	91:9	>99
16	(*S*,2*S*,3*R*)-**3p**	Et	17	90:10	94

[a] Reactions were run with 0.20 mmol of (*S*)-**1**, 0.21 mmol of **2** in 10 mL of acetone with 0.24 mmol DBU for 4 h under ambient conditions. [b] Determined by HPLC analysis. [c] Determined by SFC analysis (see Supporting Information for details).

The system was inert to the steric effect. The three regioisomeric α-amino sulfones **2** effectively participated in the Mannich reactions while achieving equally high levels of yield and selectivity (entries 1−4). In general, functionalized aryl imines are excellent substrates for the reaction, regardless of the electronic effect. The aromatic system bearing electron-donating and -withdrawing groups could be tolerated (entries 5−9); moreover, the process could be applied to heterocyclic compounds (entries 10−13). The less reactive aliphatic substrates also engaged in the reaction with good to high de values, in spite of low yields (entries 14−16). The aliphatic products were obtained with lower yields than the aryl ones, which may be consistent with the view that the aryl substituents reduce the electron density on the carbon atom of the α-amino sulfones, enhancing its reactivity, while aliphatic substituents weaken the effect. The *syn*-diastereomer was obtained as the major product, based on a single X-ray crystal structural analysis (Figure S1 in the Supporting Information).

Mannich Reactions between (*R*)-Ni(II) Complex 1 and α-Amino Sulfones 2. The successful preparation of (*S*)-amino acids by the electronic *si* side attack of the Ni(II) complex of (*S*)-**1** enolate double bond using simple halides was widely published by Belokon et al.;[16] however, the preparation of (*R*)-amino acids through the Ni(II) complex of (*R*)-**1** has been rarely reported. Table 3 summarizes the asymmetric Mannich reactions of substrate (*R*)-**1** with different α-amino sulfones **2**, under optimized conditions at hand (Table 1, entry 6). All reactions were conducted under the same reaction conditions, and all resulted in a virtually quantitative yield and high diastereoselelctivity (entries 1−13). The three regioisomeric α-amino sulfones **2** generated from tolualdehyde all provided the Mannich

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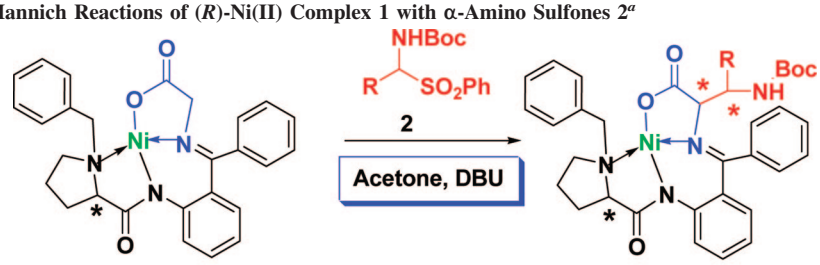
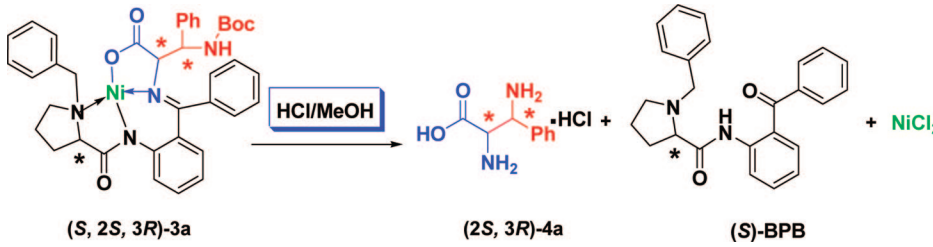
TABLE 3. Asymmetric Mannich Reactions of (*R*)-Ni(II) Complex 1 with α-Amino Sulfones 2[a]



entry	product	R group	yield %	*syn:anti*[b]	de %[c]
1	(*R*,2*R*,3*S*)-**3a**	Ph	94	92:8	>99
2	(*R*,2*R*,3*S*)-**3b**	2-Me-C_6H_4	93	90:10	90
3	(*R*,2*R*,3*S*)-**3c**	3-Me-C_6H_4	93	91:9	89
4	(*R*,2*R*,3*S*)-**3d**	4-Me-C_6H_4	94	93:7	>99
5	(*R*,2*R*,3*S*)-**3e**	4-MeO-C_6H_4	95	92:8	79
6	(*R*,2*R*,3*S*)-**3f**	4-NO_2-C_6H_4	86	93:7	89
7	(*R*,2*R*,3*S*)-**3g**	4-F-C_6H_4	92	93:7	88
8	(*R*,2*R*,3*S*)-**3h**	4-Cl-C_6H_4	94	94:6	84
9	(*R*,2*R*,3*S*)-**3i**	4-Br-C_6H_4	95	94:6	86
10	(*R*,2*R*,3*S*)-**3j**	2-furyl	92	91:9	80
11	(*R*,2*R*,3*S*)-**3k**	3-thiophenyl	90	90:10	81
12	(*R*,2*R*,3*S*)-**3l**	2-naphthyl	87	91:9	88
13	(*R*,2*R*,3*S*)-**3m**	2-quinoline	86	90:10	94
14	(*R*,2*R*,3*S*)-**3n**	cyclohexyl	23	92:8	>99
15	(*R*,2*R*,3*S*)-**3o**	*i*-Pr	18	90:10	94
16	(*R*,2*R*,3*S*)-**3p**	Et	19	91:9	88

[a] Reactions were run with 0.20 mmol of (*R*)-**1**, 0.21 mmol of **2** in 10 mL of acetone with 0.24 mmol DBU for 4 h under ambient conditions. [b] Determined by HPLC analysis. [c] Determined by SFC analysis (see Supporting Information for details).

SCHEME 2. Decomposition of Ni(II) Complex to Release Amino Acids and Recovery of the Ligand (*S*)-BPB



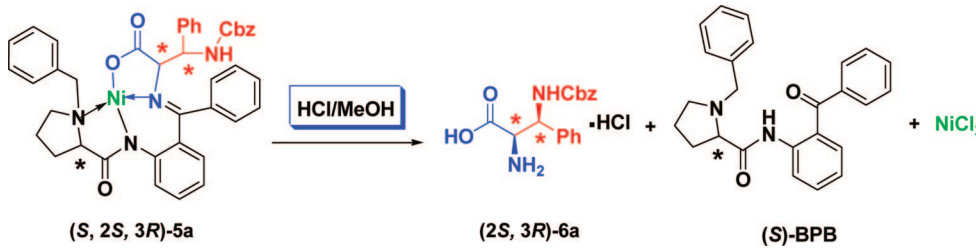
adducts with equally high levels of yield and selectivity to the parent system (entries 1−4). In general, functionalized aryl imines are excellent substrates for the reaction, with examples of electron-donating and -withdrawing groups and a number of halo-substituted examples all performing well (entries 5−9). The use of 2-furyl-, 3-thiophenyl-, 2-naphthyl-, and 2-quinoline imines demonstrates that heteroaromatic imines can be successfully employed (entries 10−13). The cyclohexyl-derived imine delivered the Mannich adduct at 23% yield with >99% de, although the smaller *i*-propyl- and ethyl-derived imines showed reduced yields (entries 14−16). In all cases, the *syn*-diastereomer was obtained as the major product. The relative stereochemistry (*syn*/*anti*) of the Mannich products was determined by X-ray analysis of (*R*,2*R*,3*S*)-**3a**, and the absolute configuration is shown in Figure S1 in the Supporting Information.

Decomposition of Products (*S*,2*S*,3*R*)-3a and (*S*,2*S*,3*R*)-5a, Isolation of 2,3-Diamino-3-phenylpropanoic Acid (2*S*,3*R*)-4a·HCl and N$^{\beta}$-Cbz-2,3-Diamino-3-phenylpropanoic Acid (2*S*,3*R*)-6a·HCl, and Recovery of the Ligand (*S*)-BPB. It was shown that the chiral ligand BPB (Scheme 2) was easily recovered in quantitative yield and could be reused by using a simple procedure. The decomposition of compound (*S*,2*S*,3*R*)-**3a** under standard conditions by heating a suspension of (*S*,2*S*,3*R*)-**3a** in methanol/6 N HCl afforded the target amino acid 2,3-diamino-3-phenylpropanoic acid (2*S*,3*R*)-**4a**·HCl in 96% yield, and meanwhile (*S*)-BPB was recovered quantitatively (Scheme 2). Moreover, we demonstrated that the method can be scaled in gram-scale synthesis (5 g).

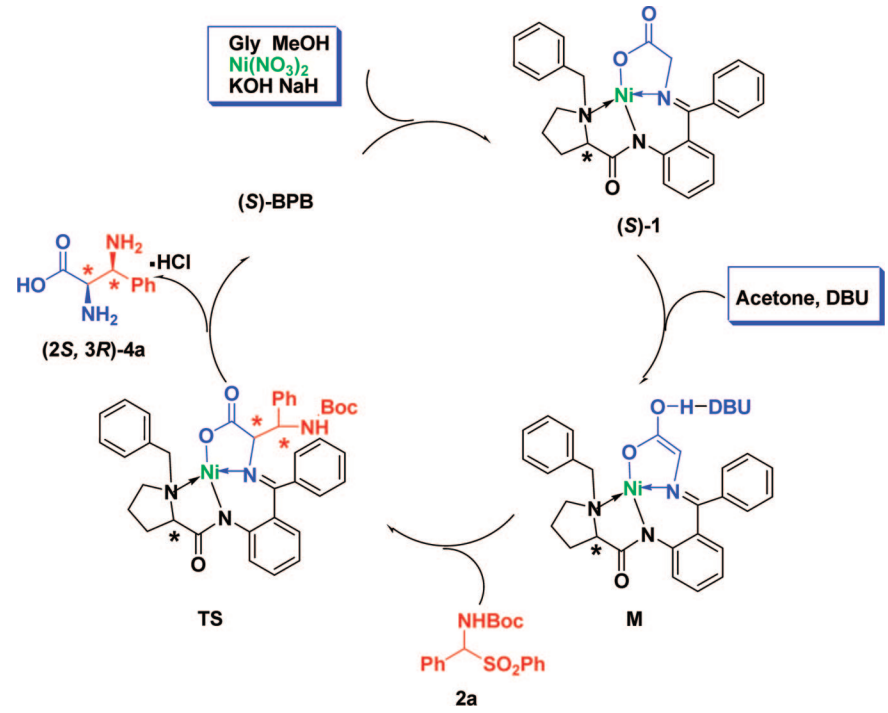
Finally and importantly, it was also shown that the process could be applied to Cbz-α-amino sulfone as a donor for this asymmetric Mannich reaction (Scheme 3). The resulting product (*S*,2*S*,3*R*)-**5a** was readily converted to N$^{\beta}$-Cbz-2,3-diamino-3-phenylpropanoic acid (2*S*,3*R*)-**6a**·HCl. The orthogonally protected amino acid protecting group in (2*S*,3*R*)-**6a**·HCl enabled ready manipulation in further synthetic elaborations.

Quantum Chemical Calculations. Theoretical calculations have been carried out to understand the reaction mechanism and the high enantio- and diastereoselectivity. We chose reactions with (*S*)-Ni(II) complex and α-amino sulfones as our investigated subjects. According to our calculations, the reaction involves four fundamental steps (Scheme 4): (1) the enolization of (*S*)-Ni(II) complex **1**, promoted by DBU with a hydrogen bond to form intermediate **M**; (2) Ni(II)-enolate reacts with imine obtained from α-amino sulfone **2a**, to give

SCHEME 3. Synthesis of N$^{\beta}$-Cbz-2,3-Diamino-3-Phenylpropanoic Acid·HCl



SCHEME 4. Proposed Cycle for (*S*)-Ni(II) Complex Mannich Reaction



transition states of *syn*-**TS** and *anti*-**TS**; (3) the release of (2*S*,3*R*)-**4a**·HCl adduct; and (4) the regeneration of (*S*)-Ni(II) complex **1**.

The intriguing effect of the DBU motivated us to study its function; as addressed in the Experimental Section, reactions employing DBU obtained the Mannich adduct (2*S*,3*R*)-**4a**·HCl with very high enantioselectivity 99% de (Table1, entries 1, 5, and 6). It is thought that the nitrogen of DBU connected with the oxygen of complex **1** by hydrogen bonding to promote the enolization of complex **1**. We then put them together to optimize the minima; fortunately, our computational results indicated that the hydrogen bond (O···H···N) really exists and that it makes the intermediary species **M** 9.46 kcal/mol more stable than the potential energy of the sum of **1** and DBU.

What's more, four transition states—(*S*,2*S*,3*R*)-*syn*-**TS**, (*S*,2*R*,3*S*)-*syn*-**TS**, (*S*,2*S*,3*S*)-*anti*-**TS**, and (*S*,2*R*,3*R*)-*anti*-**TS**—were obtained (Figure 1), and the frequency calculations showed that all of them were true transition states with only one imaginary frequency corresponding to the vibration for the formation of the carbon−carbon bond. It was found that *anti*-**TS**s are less favorable than *syn*-**TS**s, due to the large steric repulsion between *tert*-butyl of imine and Ni-enolate; the *re* facial attacking (*S*,2*S*,3*R*)-*syn*-**TS** is 1.16 kcal/mol of lower less energy than the *si* facial alternative (*S*,2*R*,3*S*)-*syn*-**TS**, while (*S*,2*R*,3*R*)-*anti*-**TS** is 1.97 kcal/mol more stable than (*S*,2*S*,3*S*)-*anti*-**TS**. In conclusion, the steric repulsion is expected to be the essential factor contributing to the instability of *anti*-**TS**s. The computed energy parameters of these transition states are given in Table 4.

A final step was the release of *syn*-**4a** and *anti*-**4a** and regeneration of (*S*)-Ni(II) complex **1**.

Finally, the computed energy profile for the proposed mechanism is presented in Figure 2. It can be seen that pathways of *syn*-**TS**s are more favorable than those of *anti*-**TS**s, with lower activation energies. Furthermore, the transition state (*S*,2*R*,3*S*)-*syn*-**TS** is structurally less favorable than the alternative (*S*,2*S*,3*R*)-*syn*-**TS**, due to steric hindrance; thus, (*S*,2*S*,3*R*)-*syn*-**TS** is found to be 1.16 kcal/mol more stable than (*S*,2*R*,3*S*)-*syn*-**TS**, and correction between them for the solvent effect with polarizable continuum models provides a small difference in the activation of free energies of 0.94 kcal/mol in favor of the (*S*,2*S*,3*R*)-*syn*-**TS** structure. In addition, the computations reveal that the (*S*,2*S*,3*R*)-*syn*-**3a** structure produces 1.84 kcal/mol less energy than (*S*,2*R*,3*S*)-*syn*-**3a** in the gas phase; when the solvent effect is considered, there is also a small decrease in free energy to −34.74 kcal/mol. Apparently, the results indicate that the reaction to produce (*S*,2*S*,3*R*)-*syn*-**3a** is the most favorable process among these four pathways when both thermodynamic and kinetic factors are considered. The activation energy of this reaction is calculated to be approximately 22.6 kcal/mol in

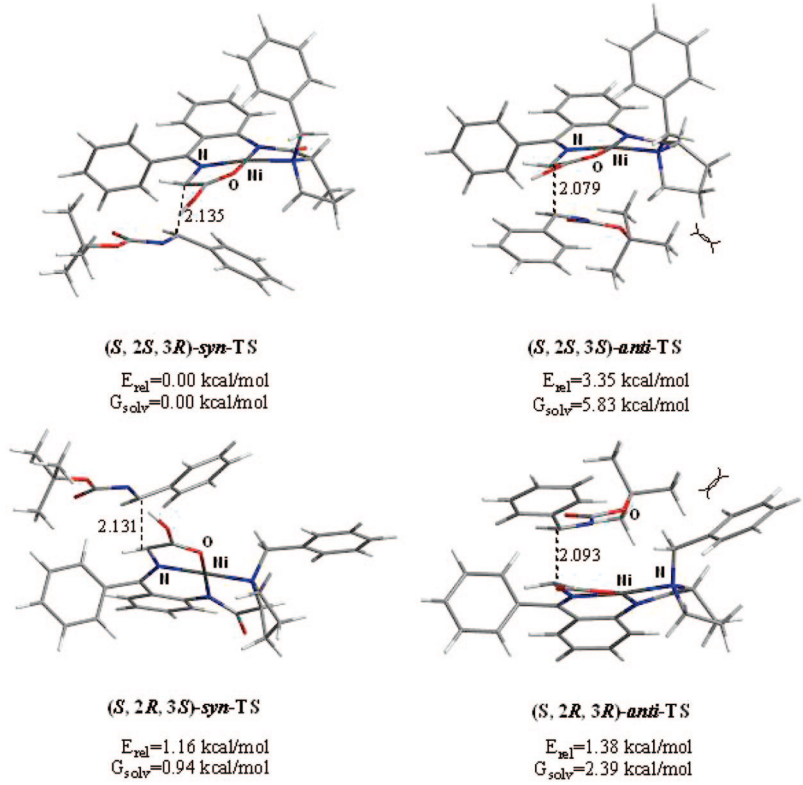


FIGURE 1. Optimized geometries and their relative energies of four transition states.

TABLE 4. Calculated Total Energies, Thermal Correction Energies, Free Energies, and Their Relative Energies to the Same Reactant (E_{tot}, E_{corr}, G_{tot}, ΔE_{tot}, ΔE_{corr}, and ΔG_{tot}), and Relative Solvent-Corrected Free Energies (ΔG_{solv})

	E^a (au)	$E_{corr}{}^b$ (au)	G^a (au)	ΔE^a (kcal/mol)	$\Delta E_{corr}{}^b$ (kcal/mol)	ΔG^a (kcal/mol)	$\Delta G_{solv}{}^c$ (kcal/mol)
R	−3598.992664	−3598.259356	−3598.298111	0.00	0.00	0.00	0.00
(*S*,2*S*,3*R*)-*syn*-**TS**	−3598.956646	−3598.224889	−3598.255385	22.60	21.61	26.81	24.22
(*S*,2*S*,3*R*)-*syn*-**3a**	−3599.046005	−3598.310144	−3598.341348	−33.47	−31.83	−27.13	−34.74
(*S*,2*R*,3*S*)-*syn*-**TS**	−3598.954805	−3598.222807	−3598.253753	23.76	22.92	27.84	25.16
(*S*,2*R*,3*S*)-*syn*-**3a**	−3599.043076	−3598.306964	−3598.338238	−31.63	−29.83	−25.18	−32.78
(*S*,2*S*,3*S*)-*anti*-**TS**	−3598.951307	−3598.218876	−3598.246989	25.95	25.39	32.08	30.05
(*S*,2*S*,3*S*)-*anti*-**3a**	−3599.039758	−3598.303805	−3598.334977	−29.55	−27.85	−23.13	−29.21
(*S*,2*R*,3*R*)-*anti*-**TS**	−3598.954448	−3598.222098	−3598.249700	23.98	23.37	30.38	26.61
(*S*,2*R*,3*R*)-*anti*-**3a**	−3599.037109	−3598.301061	−3598.332149	−27.89	−26.13	−21.36	−28.87

[a] Total energies and free energies of optimized structures were calculated by the HF/6-31G(d) method. [b] Thermal correction energies (E_{corr}, 298 K) were computed from the results of frequency calculations by the HF/6-31G(d) method with scale factor of 0.9135. [c] Solvent-corrected relative activation free energies (ΔG_{solv}) were calculated with electrostatic contributions according to the polarizable continuum (PCM) models, with $\epsilon = 20.7$ to mimic the CH_3COCH_3 medium.

the gas phase and 24.2 kcal/mol in acetone, which are in good accord with experimental results.

With the solvent-corrected computational activation energies for the Mannich reaction, it was important to compute the de values of the *syn* adducts from the aforementioned theoretical activation energies and compare them with experimental data. Since the Mannich reactions are subject to the Curtin−Hammett principle, the (*S*,2*S*,3*R*)-**3a**/(*S*,2*R*,3*S*)-**3a** product ratio can, therefore, be estimated by eq 1 and used to infer the ratio of (2*S*,3*R*)-**4a**/(2*R*,3*S*)-**4a**, in which $G_{(S,2S,3R)}$ and $G_{(S,2R,3S)}$ are the free energies that lead to the (*S*,2*S*,3*R*)-**3a** and (*S*,2*R*,3*S*)-**3a** products. Moreover, ΔG_{solv} is defined as $\Delta G_{solv} = \Delta G + \delta AG_{solv}$, where δAG_{solv} is the relative free energy difference of $G_{(S,2S,3R)\text{-solv}}$ and $G_{(S,2R,3S)\text{-solv}}$ with the PCM model. The relative free energies G_{solv} for the (*S*,2*S*,3*R*)-s*yn*-**TS** and (*S*,2*R*,3*S*)-*syn*-**TS** transition states are presented in Table 4. According to eq 1 and the solvent-corrected data of ΔG_{solv}, the (*S*,2*S*,3*R*)-**3a**/(*S*,2*R*,3*S*)-**3a** ratio for the Mannich *syn* adducts is calculated to be 97:3, which is in excellent agreement with the experimental enantioselectivities (>99%).

$$\frac{[(S,2S,3R\text{-}\mathbf{3a}]}{[(S,2R,3S\text{-}\mathbf{3a}]} = \frac{\exp(-\Delta G_{(S,2S,3R)}/RT)}{\exp(-\Delta G_{(S,2R,3S)}/RT)} = \exp[-(G_{(S,2S,3R)} - G_{(S,2R,3S)}/RT)] = \exp[-(\Delta G_{solv}/RT)] \quad (1)$$

Conclusions

In conclusion, we have developed a practical and highly efficient enantio- and diastereoselective route to *syn*-configured α,*β*-diamino acids using a direct asymmetric Mannich reaction. A broad range of aryl-, heteroaryl-, and alkyl-derived imines can all be employed under operationally simple and safe conditions. The absolute configuration of one of the products was determined, and a model for the intermediate was proposed. Further studies will focus on mechanistic aspects such as compatibility of aliphatic imines and further applications of other

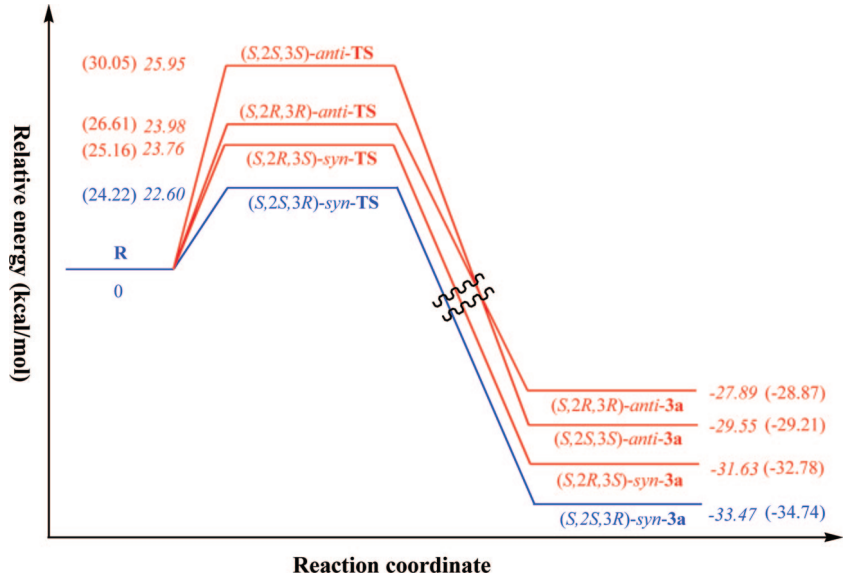


FIGURE 2. Energy profiles of pathways of (*S*)-Ni(II) complex Mannich reaction with *syn*-**TS**s and *anti*-**TS**s. The potential energy of the reactant (**R**) is set to zero. The most favorable reaction pathway to (*S*,2*S*,3*R*)-*syn*-**3a** adducts is shown in blue, and the others are in red. Activation energies are shown in italics, and in parentheses are the calculated solvent-corrected activation free energies with the SCRF method based on the polarizable continuum models (PCM) with $\epsilon = 20.7$ to mimic the CH_3COCH_3 medium.

chiral Ni(II) complexes in important carbon−carbon bond-forming reactions. The results thereof will be reported in due course.

Experimental Section

General Procedures for the Synthesis of (*S*,2*S*,3*R*)-3a. The Ni(II) complex of glycine **1** (100 mg, 0.201 mmol) was dissolved in acetone (10 mL). The α-amino sulfone derived from benzaldehyde **2a** (73 mg, 0.211 mmol) and DBU (37 μL, 0.241 mmol) were added under ambient conditions. The reaction mixture was then stirred at room temperature for 4 h. The crude reaction mixture was concentrated and then washed three times with water and brine, and the combined aqueous phase was extracted with dichloromethane (three times). The combined organic layers were dried with Na_2SO_4, concentrated, and purified by flash column chromatography (petroleum ether/ethyl acetate) to give (*S*,2*S*,3*R*)-**3a** as a red solid.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-Amino-3-*tert*-butoxycarbonylamino-3-phenylpropanoic Acid Schiff Base Complex 3a: Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 93%; mp 242−243 °C; $[\alpha]^{22}_D = +2154$ (*c* 0.35 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 6.6 Hz, 2H), 7.62−7.51 (m, 6H), 7.36−7.13 (m, 8H), 6.78−6.70 (m, 2H), 6.45 (d, J = 8.7 Hz, 1H), 4.71−4.69 (m, 1H), 4.23−4.18 (m 2H), 3.43 (t, J = 12.9 Hz, 1H), 3.24−3.21 (m, 1H), 2.85−2.82 (m, 1H), 2.22−2.20 (m, 2H), 1.92−1.80 (m, 2H), 1.27 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 177.7, 173.0, 153.8, 143.2, 138.3, 133.8, 133.7, 133.1, 132.8, 131.4, 129.8, 129.7, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 128.0, 126.3, 125.6, 123.2, 120.5, 79.2, 77.3, 77.0, 76.7, 73.1, 70.1, 63.4, 57.1, 55.2, 30.4, 28.1, 22.8 ppm; IR (KBr) 704, 1163, 1252, 1493, 1635, 1664 (C═N), 1716 (C═O), 2976, 3396 cm^{-1}; MS (EI, *m*/*z*) 702 $[M]^+$; HRMS (EI) calcd for $C_{39}H_{40}N_4NiO_5$ $[M]^+$ 702.2352, found 702.2358.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-Amino-3-benzylcarbonylamino-3-phenylpropanoic Acid Schiff Base Complex 5a: Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 93%; mp 118−120 °C; $[\alpha]^{22}_D = +1996$ (*c* 0.53 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31(d, J = 8.1 Hz, 1H), 7.97 (d, J = 7.8 Hz, 2H), 7.60−7.52 (m, 6H), 7.37−7.13 (m, 13H), 6.86−6.68 (m, 3H), 4.96 (d, J = 12.6 Hz, 1H), 4.87−4.70 (m 2H), 4.26−4.11 (m, 2H), 3.41 (d, J = 12.9 Hz, 1H), 3.23 (t, J = 17.7 Hz, 1H), 2.87−2.84 (m, 1H), 2.21−2.16 (m, 2H), 1.92−1.86 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3, 177.7, 173.2, 154.5, 143.3, 138.0, 136.5, 133.9, 133.7, 133.1, 132.9, 131.4, 130.1, 129.6, 129.1, 128.9, 128.8, 128.7, 128.5, 128.3, 127.8, 127.2, 126.4, 125.6, 123.2, 120.6, 77.3, 77.0, 76.7, 72.6, 70.2, 66.4, 63.5, 57.2, 55.3, 30.5, 22.9 ppm; MS (ESI, *m*/*z*) 737 $[M + H]^+$, 759 $[M + Na]^+$; HRMS (ESI) calcd for $C_{42}H_{38}N_4NiO_5$ $[M + Na]^+$ 759.2093, found 759.2089.

General Procedures for the Synthesis of (2*S*,3*R*)-4a·HCl: The crystallized complex (*S*,2*S*,3*R*)-**3a** (1 g, 1.4 mmol) was decomposed by refluxing a suspension in a mixture of aqueous 6 N HCl (1 mL) and MeOH (15 mL) for 30 min, until the red color of the solution disappeared, as described previously. The reaction was cooled to room temperature and then evaporated to dryness. Water (20 mL) was added to the residue to form a clear solution, and this solution was then separated by column chromatography on C_{18}-reversed phase (230−400 mesh) silica gel. Pure water as an eluent was employed to remove the green $NiCl_2$ and excess HCl; MeOH/water (1/1) was then used to obtain optically pure product (2*S*,3*R*)-**4a**·HCl (246 mg, 96%): $[\alpha]^{22}_D = +37$ (*c* 0.38 g/100 mL, 6 N HCl, lit.[17] $[\alpha]^{26}_D = +39$, *c* = 0.52, H_2O). The ligand BPB that decomposed from (*S*,2*S*,3*R*)-**3a** was recovered by MeOH eluent (525 mg, 96%), and the column chromatography was washed with 100 mL of MeOH for further use.

(2*S*,3*R*)-2,3-Diamino-3-phenylpropanoic Acid 4a·HCl: Obtained as a white solid by column chromatography (MeOH/water 1:1), yield 96%; mp 187−189 °C; $[\alpha]^{22}_D = +37$ (*c* 0.38 g/100 mL, 6 N HCl); ^{1}H NMR (300 MHz, D_2O) δ 7.58−7.48 (m, 5H), 4.52 (d, J = 10.2 Hz, 1H), 3.66 (d, J = 10.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, D_2O) δ 171.9, 133.6, 132.5, 132.1, 130.5, 56.3, 56.0 ppm; MS (ESI, *m*/*z*) 181 $[M + H]^+$; HRMS (ESI) calcd for $C_9H_{12}N_2O_2$ $[M + Na]^+$ 203.0796, found 203.0797.

General Procedures for the Synthesis of (2*S*,3*R*)-6a·HCl: The crystallized complex (*S*,2*S*,3*R*)-**5a** (1 g, 1.3 mmol) was decomposed by refluxing a suspension in a mixture of aqueous 6 N HCl (1 mL) and MeOH (15 mL) for 30 min, until the red color of the solution disappeared, as described previously. The reaction was cooled to room temperature and then evaporated to dryness. Water (20 mL)

(17) Zhang, H.-H.; Hu, X.-Q.; Wang, X.; Luo, Y. C.; Xu, P.-F. *J. Org. Chem.* **2008**, *73*, 3634.

was added to the residue to form a clear solution, and this solution was then separated by column chromatography on C_{18}-reversed phase (230−400 mesh) silica gel. Pure water as an eluent was employed to remove the green $NiCl_2$ and excess HCl; MeOH/water (1/1) was then used to obtain optically pure product (2*S*,3*R*)-**6a**·HCl (397 mg, 96%). The ligand BPB that decomposed from (*S*,2*S*,3*R*)-**5a** was recovered by MeOH eluent (525 mg, 96%), and the column chromatography was washed with 100 mL of MeOH for further use.

(2*S*,3*R*)-N$^{\beta}$-Cbz-2,3-Diamino-3-phenylpropanoic Acid 6a·HCl: Obtained as a white solid by column chromatography (MeOH/water 1:1), yield 96%; mp 199−201 °C; $[\alpha]^{22}_{D} = +48$ (*c* 0.32 g/100 mL, 6 N HCl); ^{1}H NMR (300 MHz, D_2O) δ 7.47−7.35 (m, 10H), 5.14−5.13 (d, $J = 4.8$ Hz, 2H), 3.72−3.70 (d, $J = 6.3$ Hz, 1H), 3.64 (s, 1H) ppm; ^{13}C NMR (75 MHz, D_2O) δ 166.1, 154.0, 132.9, 132.1, 127.5, 127.2, 126.3, 126.1, 125.8, 125.4, 125.0, 124.5, 123.8, 64.2, 54.2, 51.7 ppm; MS (ESI, *m*/*z*) 315 $[M + H]^+$, 327 $[M + Na]^+$; HRMS (ESI) calcd for $C_{17}H_{18}N_2O_4$ $[M + H]^+$ 315.1345, found 315.1341.

Acknowledgment. We gratefully acknowledge financial support from the State Key Program of Basic Research of China (Grant 2006BAI01B02), the National Natural Science Foundation of China (Grants 20721003 and 20872153), the Basic Research Project for Talent Research Group from the Shanghai Science and Technology Commission, and the 863 Hi-Tech Program of China (Grants 2006AA020602).

Supporting Information Available: Experiment procedures and analytical and spectral characterization data for all compounds, and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO8019169