Amino Acid Synthesis

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The Fluorenone Imines of Glycine Esters and Their Phosphonic Acid Analogues**

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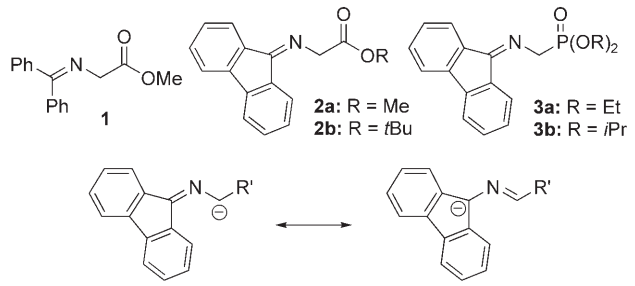
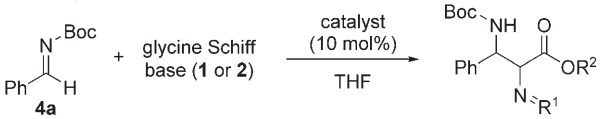
Glycine derivatives are useful starting materials for the synthesis of α-amino acids. For example, benzophenone imines of glycine esters, compounds of type **1** introduced by O'Donnell and Eckrich in 1978,[1] have been employed in numerous syntheses of α-amino acids.[2,3] Herein we report alternatives to **1**; namely, fluorenone imines **2** of glycine esters and their phosphonic acid analogues **3**. α Anions of these fluorenone imines are stabilized by resonance involving the 14π electrons of the aromatic fluorene moiety. Therefore, higher stability than that of other glycine Schiff bases, including **1**, is expected (Scheme 1).



Scheme 1. Fluorenone imines **2** of glycine esters, phosphonic acid ester analogues **3**, and resonance structures of the α anions of such compounds.

Mannich-type reactions of glycine ester derivatives with imines provide an efficient route to α,β-diamino acid derivatives.[4,5] Therefore, we investigated the use of **2** as a substrate in Mannich-type reactions with imines. The reaction of the methyl ester **2a** with imine **4a** was selected as the model reaction, and several catalysts and reaction conditions were tested (Table 1). First, amines were tested as catalysts. It was found that 1,1,3,3-tetramethylguanidine gave the best results in terms of reactivity and selectivity (Table 1, entries 1–6). The benzophenone imine **1** of glycine methyl ester reacted sluggishly under the same reaction conditions (Table 1, entry 7). Moreover, the diastereoselectivity was improved by using sterically encumbered **2b**, which contains a *tert*-butyl ester: The *syn* adduct[6] was obtained exclusively (Table 1, entry 8). LiOPMP (PMP = *p*-methoxyphenyl) was also an effective catalyst, with the desired adduct formed in excellent yield and with excellent diastereoselectivity (*syn*/*anti* > 99:1) in a shorter reaction time (Table 1, entry 9).

Table 1: Optimization of the reaction conditions.

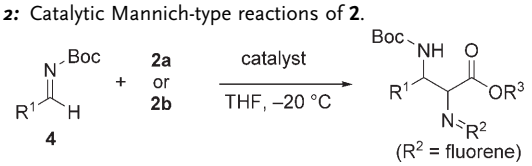


Entry	Gly	Catalyst	*T* [°C]	*t* [h]	Yield [%]	*syn*/*anti*[c]
1	**2a**	Et_3N	RT	36	quant.	14:1
2	**2a**	iPr_2NEt	RT	36	83	5:1
3	**2a**	DBU[a]	RT	0.5	quant.	2:1
4	**2a**	DBU	−20	0.5	quant.	2:1
5	**2a**	TMG[b]	RT	0.5	quant.	5:1
6	**2a**	TMG	−20	0.5	72	9:1
7	**1**	TMG	−20	16	trace	–
8	**2b**	TMG	−20	1	98	> 99:1
9	**2a**	LiOPMP	−20	0.5	quant.	> 99:1

[a] 1,8-Diazabicyclo[5.4.0]undec-7-ene. [b] 1,1,3,3-Tetramethylguanidine. [c] Determined by HPLC analysis.

We examined the scope of this Mannich-type reaction with respect to the imine substrate **4** (Table 2). Imines derived from aromatic aldehydes reacted smoothly in the presence of 1,1,3,3-tetramethylguanidine (10 mol%) to afford the desired α,β-diamino acid derivatives in excellent yields with *syn* diastereoselectivity (Table 2, entries 1–4). Although the reaction of an imine derived from an aliphatic aldehyde proceeded with lower diastereoselectivity under the same

Table 2: Catalytic Mannich-type reactions of **2**.



Entry	Gly	R^1	Catalyst (mol%)	*t* [h]	Yield [%]	*syn*/*anti*[a]
1	**2b**	Ph (**4a**)	TMG (10)	1	98	> 99:1
2	**2b**	*p*-$MeOC_6H_4$	TMG (10)	16	91	> 99:1
3	**2b**	*p*-FC_6H_4	TMG (10)	16	96	14:1
4	**2b**	2-furyl	TMG (10)	1	99	28:1
5	**2b**	$Ph(CH_2)_2$	TMG (10)	16	84	4:1
6[b]	**2a**	$Ph(CH_2)_2$	LiOPMP (2)	0.5	98	9:1
7[b]	**2a**	*c*-C_6H_{11}	LiOPMP (2)	0.5	quant.	12:1

[a] Determined by HPLC and/or NMR spectroscopic analysis. [b] Imine **4**: 2 equivalents.

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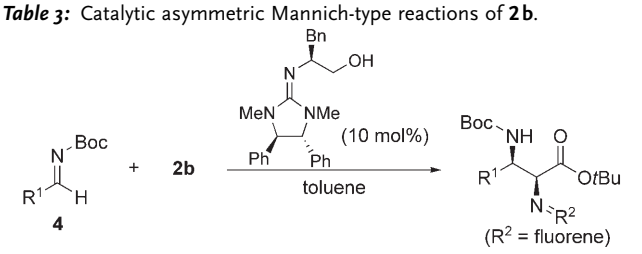
conditions (Table 2, entry 5), higher yields and *syn* diastereoselectivity were observed when LiOPMP (2 mol%) was employed as the catalyst (Table 2, entries 6 and 7).

A chiral guanidine catalyst[7] (10 mol%) successfully induced asymmetry when aromatic, heteroaromatic, and aliphatic imines **4** were treated with the glycine Schiff base **2b** in toluene at −45 or −60 °C to afford optically active α,β-diamino acid derivatives in high yields with high *syn* selectivities and high enantioselectivities (Table 3).

Table 3: Catalytic asymmetric Mannich-type reactions of **2b**.



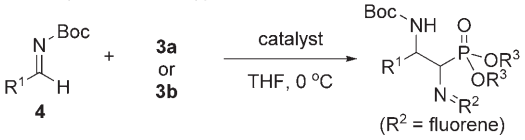
Entry	R^1	T [°C]	t [h]	Yield [%]	*syn*/*anti*[a]	*ee* (*syn*) [%][b]
1	Ph	−45	12	quant.	>99:1	96 (2*S*,3*R*)
2	Ph	−60	12	quant.	>99:1	95 (2*S*,3*R*)
3	*p*-$MeOC_6H_4$	−45	48	76	36:1	90
4	2-furyl	−45	36	88	9:1	98
5[c]	$Ph(CH_2)_2$	−45	24	87	29:1	92
6[c]	*c*-C_6H_{11}	−45	48	84	11:1	96

[a] Determined by ^{1}H NMR spectroscopic analysis and/or HPLC analysis. [b] Determined by HPLC analysis on a chiral phase; for the absolute configuration, see the Supporting Information. [c] Imine **4**: 2 equivalents. Bn = benzyl.

Next, we investigated Mannich-type reactions of the fluorenone imines **3** of aminomethylphosphonic acid esters. α,β-Diaminophosphonic acids, regarded as analogues of α,β-diamino acids, are of great interest in medicinal and bioorganic chemistry.[8] Mannich-type reactions of phosphonic acid analogues of glycine Schiff bases with imines are potentially useful for the synthesis of these compounds; however, to the best of our knowledge, only one such Mannich-type reaction has been reported to date.[9,10] A stoichiometric amount of a base was used, and no catalytic version of the reaction has been developed, presumably because the α hydrogen atoms in phosphonic acid analogues of glycine Schiff bases are less acidic than those in glycine Schiff bases.[11]

First, the reaction of **3a** with imine **4a** was investigated (Table 4). Amines were not effective as catalysts in this reaction; stronger bases, such as LiOPMP and NaO*t*Bu, gave better results (Table 4, entries 1–4). The reaction was significantly more efficient with the substrate **3b**, which reacted with **4a** in THF at 0 °C in the presence of NaO*t*Bu (2 mol%) to afford the desired adduct in 95% yield with perfect *syn* selectivity within 10 min (Table 4, entry 5).[6] Aromatic and aliphatic imines reacted smoothly under these conditions to provide the corresponding α,β-diaminophosphonic acid esters in excellent yields and with excellent *syn* selectivities (Table 4, entries 6–14). This transformation is the first example of the mediation of a reaction of phosphonic acid analogues of glycine Schiff bases by a catalytic amount of a base.

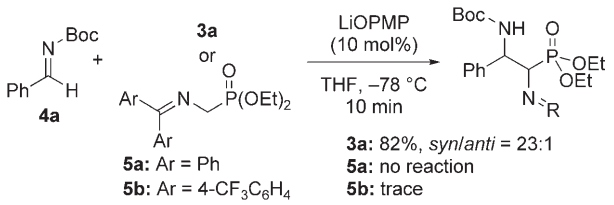
Table 4: Catalytic Mannich-type reactions of fluorenone imines **3**.



Entry	**3**	R^1	Catalyst (mol%)	t [h]	Yield [%]	*syn*/*anti*[a]
1[b]	**3a**	Ph (**4a**)	Et_3N (10)	24	<5	–
2[b]	**3a**	Ph	DBU (10)	24	97	2:1
3	**3a**	Ph	LiOPMP (10)	1/6	quant.	11:1
4	**3a**	Ph	NaO*t*Bu (10)	1/6	94	13:1
5	**3b**	Ph	NaO*t*Bu (2)	1/6	95	>99:1
6	**3b**	*p*-$MeOC_6H_4$	NaO*t*Bu (2)	1/6	quant.	13:1
7	**3b**	*p*-FC_6H_4	NaO*t*Bu (2)	1/6	97	27:1
8	**3b**	*m*-MeC_6H_4	NaO*t*Bu (2)	1/6	96	21:1
9	**3b**	*o*-MeC_6H_4	NaO*t*Bu (2)	1/6	99	>99:1
10	**3b**	*m*-$(CH_2{=}CH)C_6H_4$	NaO*t*Bu (2)	1/6	quant.	>99:1
11	**3b**	2-furyl	NaO*t*Bu (2)	1/6	quant.	23:1
12	**3b**	2-thienyl	NaO*t*Bu (2)	1/6	quant.	33:1
13	**3b**	$Ph(CH_2)_2$	NaO*t*Bu (2)	1/6	88	>99:1
14	**3b**	*c*-C_6H_{11}	NaO*t*Bu (2)	1/6	quant.	>99:1

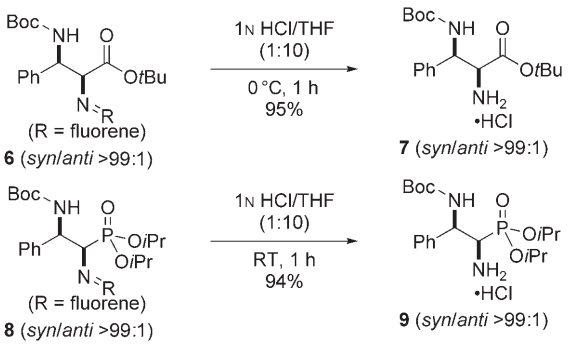
[a] Determined by NMR spectroscopic analysis. [b] *N*,*N*-Dimethylformamide was used as the solvent at room temperature.

The high reactivity of the fluorenone imines was confirmed by the following comparative experiments: Whereas **3a** reacted with **4a** smoothly even at −78 °C, almost no conversion was observed when the related benzophenone imines **5a**,**b** were used under identical conditions (Scheme 2).



Scheme 2. Comparative experiments. Boc = *tert*-butoxycarbonyl.

The fluorenone imine moiety was hydrolyzed readily under mildly acidic conditions (Scheme 3). Thus, the adduct **6** was treated with 1N HCl/THF (1:10) at room temperature for 1 h to give the deprotected product **7** in 95% yield. Similarly, the adduct **8** was deprotected to afford **9** in 94% yield. The



Scheme 3. Cleavage of the fluorenone imine.

Boc moiety was inert under these conditions, and no epimerization was observed.

In summary, we have developed fluorenone imine derivatives of glycine esters and phosphonic acid analogues of these compounds as substrates for Mannich-type reactions with imines. The reactions proceeded smoothly in the presence of a catalytic amount of a base to afford the corresponding α,β-diamino acid and phosphonic acid derivatives in excellent yields and with excellent *syn* diastereoselectivities. A catalytic asymmetric version of this reaction was also demonstrated. Notably, the fluorenone imines are much more reactive than benzophenone imines of glycine esters, which have often been used in α-amino acid syntheses. Further investigations of the fluorenone imines in other reactions are in progress.

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[11] To the best of our knowledge, catalytic processes involving phosphonic acid analogues of glycine Schiff bases are unprecedented, not only in Mannich-type reactions, but in general. We also observed efficient catalysis by alkaline earth metals in some reactions of these phosphonic acids.

