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Direct-Type Aldol Reactions of Fluorenylidene-Protected/Activated Glycine Esters with Aldehydes for the Synthesis of β-Hydroxy-α-amino Acid Derivatives

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Celebrating 150 years of German–Japanese relations

The synthesis of β-hydroxy-α-amino acid has been widely documented in the literature.[1] Indeed, this moiety can be found in numerous natural products such as vancomycin[2] and lactacystin.[3] One of the most rapid routes to these products involves an aldol condensation between an N-protected glycine and an aldehyde. Miller and co-workers[4] reported aldol condensation of a glycine Schiff base with aldehydes using a chiral phase-transfer catalyst. More recently, Shibasaki and co-workers[5] reported the successful direct asymmetric aldol reaction[6] between a glycine Schiff base and several aliphatic aldehydes with moderate diastereo- and enantioselectivities. In the same year, Maruoka and co-workers[7] described the same reaction using a phase-transfer catalyst giving the corresponding aldol adduct with high diastereo- and enantioselectivities. Other groups also reported similar aldol condensations using glycine Schiff bases.[8] As alternative nucleophilic species, 5-alkoxyoxazole,[9] α-isocyano acetates,[10] and α-isothiocyanatoimides[11] were used for this type of reaction.[12] Moreover, enzymatic accesses have been found but show some substrate limitations.[13]

Recently, our group showed that aminoalkanes could be protected and activated at the same time by using a 9-fluorenylidene group.[14] This group allows a strong activation of the α-position of the nitrogen atom via stabilization of the 14 π electron system.[15] Based on that idea, we have developed an efficient synthesis of diamine compounds by Mannich-type reactions of N-protected imines, such as *N-tert*-butoxycarbonyl (Boc) or *N*-diphenylphosphinoyl (Dpp) imines. Those results encouraged us to investigate the direct-type aldol reactions of fluorenylidene-protected glycine Schiff bases. Herein, we describe the development of highly stereoselective aldol reactions using a catalytic amount of functionalized base.

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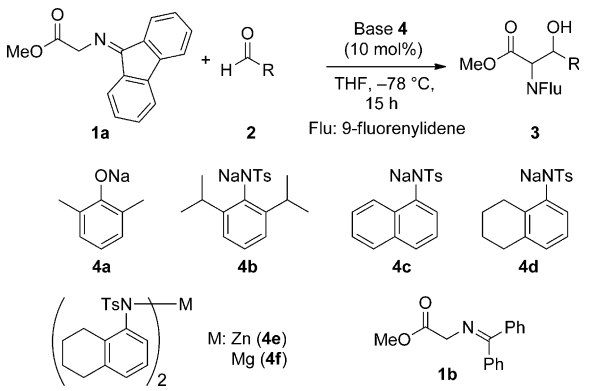
We started our investigation by using fluorenylidene glycine methyl ester (**1a**)[16] and a typical aliphatic aldehyde, cyclohexanecarboxyaldehyde (**2a**) in THF in the presence of 10 mol% base catalyst (Scheme 1). The results are summarized in Table 1. In this reaction system, the reaction at lower temperature was found to be quite effective, and an interesting diastereoselectivity was observed when sodium 2,6-dimethylphenoxide was used as a base catalyst (Table 1,



Scheme 1. Catalytic aldol reaction of Flu-protected glycine ester **1a**.

Table 1. Optimization of reaction conditions.[a]

Entry	Base **4**	*anti*/*syn*[b]	Yield [%][c]
1	**4a**	78/22	45
2	**4b**	79/21	69
3	**4c**	87/13	82
4	**4d**	90/10	85
5	**4e**	n.d.	5
6	**4f**	96/4	95
7[d]	**4f**	96/4	72
8[e]	**4f**	96/4	96
9[f]	**4f**	96/4	96
10[g]	**4f**	–	NR

[a] The reaction was performed using **1a** and cyclohexanecarboxyaldehyde (**2a**, 1.1 equiv) in THF at −78 °C for 15 h in the presence of base **4** (10 mol%). [b] Determined by ^{1}H NMR analysis of the crude mixture. n.d. = not determined. [c] Yield of isolated product. [d] The reaction was performed in Et_2O. [e] Catalyst loading of 5 mol% was used. [f] Catalyst loading of 2 mol% was used. [g] The reaction was performed using the glycine Schiff base **1b** instead of **1a**.

entry 1). In the reaction, the choice of the base appears to be crucial for the reactivity and the selectivity, and sodium *N*-aryltosylamide gave promising results (entries 2–4). Among them, the amides bearing naphthalene ring systems performed best, and sodium *N*-5,6,7,8-tetrahydro-1-naphthyltosylamide showed the high diastereomeric ratio of *anti*/*syn* = 90:10. We then investigated the effect of the metal moiety in the amide catalyst and found that magnesium salts showed the best stereoselectivity (entry 6). It was confirmed that Et_2O also worked as an acceptable solvent, but the yield was a little lower (entry 7). Further, reduction of the catalyst amount was conducted, and just 2 mol% Mg catalyst gave the desired product in high yield without any loss of diastereoselectivity (entry 9). The effect of the fluorenylidene group is very important, and the typical glycine Schiff base **1b** derived from benzophenone did not work at all under the reaction conditions (entry 10). It should be noted that the use of fluorenylidene group enhanced the reactivity of the glycine ester dramatically in the aldol reaction.

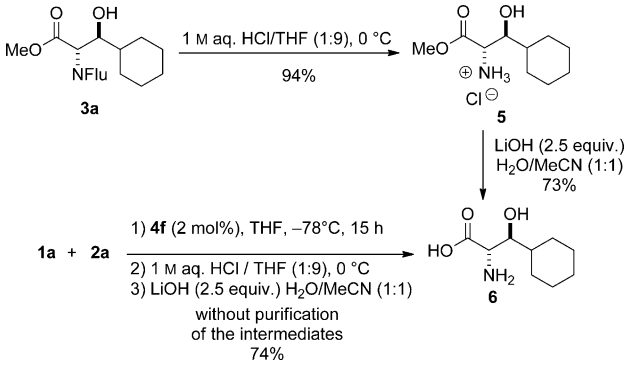
With optimum reaction conditions in hand, we next investigated the scope of aldehydes (Table 2). Typical aliphatic aldehydes, *n*-hexanylaldehyde (**2b**), isobutylaldehyde (**2c**), and isopentylaldehyde (**2d**), worked well, similarly to **2a**, and high yields and high diastereoselectivities were obtained (entries 1–3). The reaction was not sensitive to substitutions at the α-position of the aldehyde. Aliphatic aldehydes bearing an aromatic ring were also found to be effective, and good to high yields and high selectivities were observed (entries 4–6). Interestingly, easily enolizable aldehydes, phenylacetoaldehyde (**2e**) and diphenylacetoaldehyde (**2g**), gave the desired products in good yields without significant side reactions. However, use of aromatic and α,β-unsaturated aldehydes was not fruitful, and the desired aldol products were obtained in low to good yields with quite disappointing selectivities (entries 7–10). That is presumably because a retro-aldol process from the aldol product in the reaction system seemed to be significant when conjugated aldehydes were employed.

Table 2. Aldehyde scope.[a]

Entry	R	*anti*/*syn*	Yield [%]
1	*n*-C_5H_{11} (**2b**)	89/11	91
2	*i*Pr (**2c**)	94/6	88
3	$(CH_3)_2CHCH_2$ (**2d**)	92/8	90
4	$PhCH_2$ (**2e**)	95/5	85
5	$PhCH_2CH_2$ (**2f**)	95/5	87
6	Ph_2CH (**2g**)	94/6	74
7	Ph (**2h**)	55/45	35
8	*o*-$O_2NC_6H_4$ (**2i**)	54/46	79
9	(*E*)-PhCH=CH (**2j**)	–	NR
10	(*E*)-CH_3CH=CH (**2k**)	52/48	53

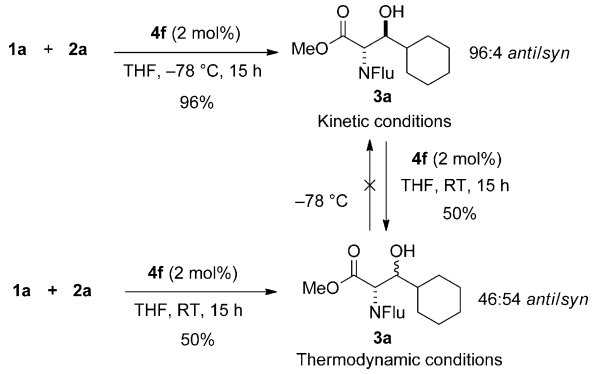
[a] The reaction was performed using **1a** and **2** (1.1 equiv) in THF at −78 °C for 15 h in the presence of **4f** (2 mol%). [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Yield of isolated product.

The products could be easily converted to the corresponding β-hydroxy-α-amino acid by removal of the fluorenylidene group and hydrolysis of the ester (Scheme 2). Acid hydrolysis of the aldol adduct **3a** gave the corresponding β-hydroxy-α-amino ester HCl salt **5** in 94% yield, and following basic hydrolysis, the desired β-hydroxy-α-amino acid **6**[17] was obtained. This sequence could also be performed without any purification of the intermediates.



Scheme 2. Modification of the product.

During the investigations of this aldol reaction, we could easily observe the retro-aldol process. When we carried out the reaction at room temperature, the desired aldol product **3a** was obtained in moderate yield with very low diastereoselectivity (Scheme 3). When we put the product **3a** with low diastereomeric ratio under the reaction conditions at −78 °C, no change in the diastereomeric ratio was observed. On the other hand, when we put **3a** with high diastereomeric ratio under the reaction conditions at room temperature, the ratio dramatically decreased, with some loss of the product. These results indicate that the aldol reaction proceeded at −78 °C under kinetic control to afford the desired product in high diastereoselectivity, and the diastereomeric ratio of the product decreased at high reaction temperature to lead to a low diastereomeric ratio under thermodynamic control via the retro-aldol process.



Scheme 3. Consideration of the reaction process.

Finally, the structure of **4f** was investigated by NMR studies. In THF-d_8, the tosyl amide and **4f** showed very different

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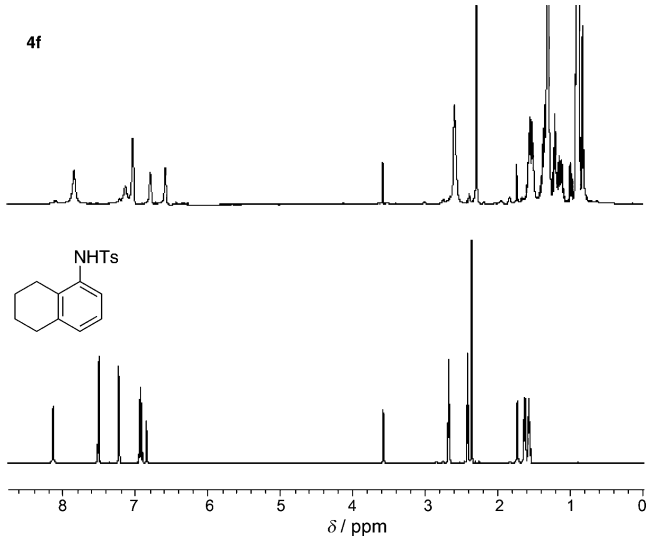

Figure 1. ^{1}H NMR analysis of **4f** and the corresponding tosylamide.

^{1}H NMR spectra (Figure 1). The disappearence of the NH peak suggested deprotonation of the tosyl amide NH by di-*n*-butylmagnesium. On the other hand, ^{13}C NMR analysis indicated that **4f** formed an oligomeric structure, which was a bit too complex to be determined.

In summary, we have developed highly diastereoselective direct-type aldol reactions of glycine Schiff bases bearing a fluorenylidene moiety as a protecting/activating group of the amino group using only a catalytic amount of base. The desired reactions proceeded smoothly at low temperature using the Mg catalyst, and the aldol products were obtained in high yields with high diastereoselectivities when aliphatic aldehydes were employed. The activating group was easily removed to give the corresponding free amino acid. It was revealed that reaction temperature was important and the diastereoselectivity was determined under kinetic control. Further investigation to improve the reaction system and application to other asymmetric catalyses are now ongoing.

Experimental Section

General Procedure

In a well-dried 10 mL reaction tube, the tosyl amide (2.4 mg, 0.0080 mmol, 0.040 equiv) was dissolved in anhydrous THF (1.0 mL) and cooled to −78 °C. *n*Bu_2Mg in heptane (0.0040 mmol, 0.020 equiv) was then added dropwise to the mixture, and the mixture was stirred at room temperature. After 30 min stirring, the reaction tube was cooled again to −78 °C, and a solution of *N*-fluorenylidene glycine ester **1a** (50 mg, 0.20 mmol, 1.0 equiv) and aldehyde **2** (0.22 mmol, 1.1 equiv) in dry THF (1.0 mL) were introduced. After 15 h, the reaction was quenched by addition of sat. NH_4Cl (1.0 mL) and extracted with Et_2O (5.0 mL × 3). The combined organic layers were then dried over Na_2SO_4 and concentrated under vacuum. Finally the crude material was purified by column chromatography (deactivated silica gel (10% of water)) using a mixture of Et_2O/hexane to give the corresponding aldol product.

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Keywords: aldol reaction · amino acids · base catalyst · fluorenylidene · magnesium

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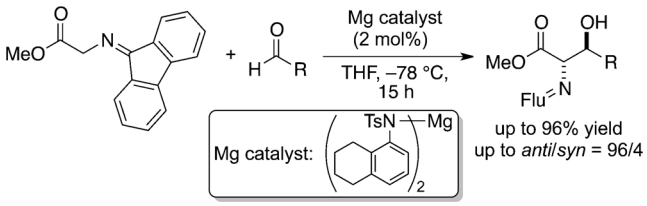

Two birds with one stone: Magnesium-base-catalyzed highly diastereoselective direct-type aldol reaction of glycine Schiff base bearing a fluorenylidene moiety as a protecting and activating group was developed. The desired reactions proceeded smoothly at low temperature, and the aldol products were obtained in high yield with high diastereoselectivity.

Aldol Reactions

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Direct-Type Aldol Reactions of Fluorenylidene-Protected/Activated Glycine Esters with Aldehydes for the Synthesis of β-Hydroxy-α-amino Acid Derivatives