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ARTICLE TYPE

Asymmetric aldol reaction via memory of chirality†

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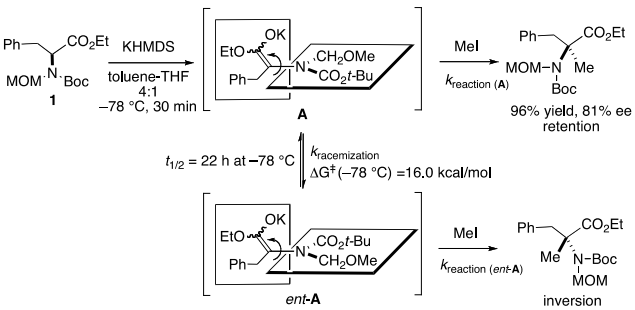
Asymmetric aldol reactions of α-amino acid derivatives via memory of chirality were developed. Chiral oxazolidones with contiguous tetra- and trisubstituted chiral centers were obtained in 78-94% ee by the asymmetric aldol reaction followed by intramolecular acylation.

We have studied asymmetric induction via memory of chirality.[1,2] This strategy enables a direct construction of α-amino acid derivatives with chiral tetrasubstituted carbon from readily available α-amino acids without the aid of external chiral sources such as chiral catalysts or chiral auxiliaries. We have reported several asymmetric intramolecular transformations via memory of chirality such as alkylation,[3] conjugate addition,[4] and Dieckmann condensation.[5] On the other hand, intermolecular transformation via memory of chirality has been limited only to simple alkylation and allylation.[6] The relative difficulties in developing intermolecular asymmetric transformation by this strategy originates in the nature of intermediary enolates. Since the intermediary chiral enolates are prone to undergo time-dependent racemization, relatively slow intermolecular processes appear to be more difficult than the corresponding intramolecular ones. Here, we report the first example of asymmetric intermolecular aldol reactions between α-amino acid derivatives and aromatic aldehydes via memory of chirality through careful investigation of the balance between the racemization behaviour of intermediary chiral enolates and their reactivity toward aldehydes.[7]

We have reported that α-methylation of an amino acid derivative via memory of chirality (Scheme 1).[6a] The asymmetric transformation was proposed to proceed via axially chiral enolate **A**. The half-life of racemization of **A** was measured to be 22 h at the reaction temperature (–78 °C), which corresponds to the racemization barrier of the chiral enolate to be 16.0 kcal/mol. Since the reaction rate of enolate **A** ($k_{\text{reaction (A)}}$) with electrophiles is same as that of enolate *ent*-**A** ($k_{\text{reaction (}ent\text{-A)}}$), the ratio between **A** and *ent*-**A** directly correlates with the ee of the product. The ratio between $k_{\text{reaction (A)}}$ and $k_{\text{racemization}}$ critically affects overall efficiency of the asymmetric transformation. Choice of a solvent mixture (toluene:THF=4:1) is the key for the high yield and asymmetric induction. Use of the major volume of toluene is effective for slowing the racemization of enolate **A**,[8] probably due to the formation of higher-order aggregates of the enolate. On the other hand, use of the minor volume of THF seems to be effective for increasing the reactivity of the enolate to promote smooth alkylation.[9] Based on the backgrounds on the nature of the intermediary chiral enolates, we envisaged to develop asymmetric aldol reactions through careful consideration of the balance between k_{reaction} of the aldol reaction and $k_{\text{racemization}}$ of the chiral enolate intermediate.



Scheme 1 A reaction path of asymmetric methylation via axially chiral enolate **A**.

We chose *N*-*tert*-butoxycarbonyl (Boc)-*N*-methoxymethyl(MOM)-amino acid derivative **1** as the substrate for the development of asymmetric aldol reactions, because the racemization behaviour of chiral enolate **A** generated from **1** has been well studied.[6a,8] Asymmetric aldol reaction of **1** was first examined according to the protocol for asymmetric α-methylation shown in Scheme 1. Treatment of **1** with 1.1 equivalents of potassium hexamethyldisilazide (KHMDS) in toluene-THF (4:1) for 30 min to generate axially chiral enolate **A**,[6a] followed by addition of 3.0 equivalents of benzaldehyde (procedure I in Table 1) gave oxazolidone derivative **2** in 85% yield and only 32% ee after intramolecular acylation of the resulting potassium aldolate with the Boc moiety (entry 1). In order to avoid partial racemization of the chiral enolate during the aldol reaction and to gain insights into the asymmetric induction at the early stage of the aldol reaction, another reaction procedure was employed. A solution of **1** was added to a pre-cooled solution

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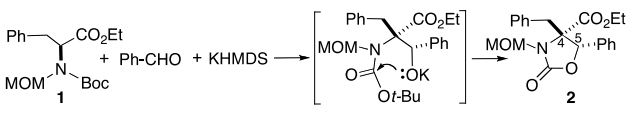
† Electronic Supplementary Information (ESI) available: Experimental procedures, caharacterization data, copies of ^{1}H NMR and ^{13}C NMR. CCDC-867310 for **10**. See DOI: 10.1039/b000000x/

of benzaldehyde (3.0 equiv.) and KHMDS (1.1 equiv.) (procedure II) in toluene-THF (4:1) at –78 °C, and the resulting solution was stirred for only 10 min to give **2** in 2% yield and 99% ee (entry 2). Treatment of **1** under the identical conditions to those in entry 2 except for the temperature (–30 °C) gave **2** in a slightly increased yield (7%) and a slightly decreased ee (96%) (entry 3). The reaction with the prolonged reaction time (4 h) at the same temperature (–30 °C) gave **2** in 96% yield in a decreased ee (71% ee) (entry 4). Comparison of the results between entries 3 and 4 indicates partial racemization of the intermediary chiral enolate during its reaction with benzaldehyde. According to our observation on racemization behaviour of the enolate,[8,9] pure toluene was employed as a solvent in order to minimize racemization of the chiral enolate. Product **2** was obtained in a increased ee (80% ee) by the reaction of **1** in toluene even after the longer reaction time (6 h) than that employed for the corresponding reaction in toluene-THF (4:1) (71% ee after 4 h) (entries 4 *vs.* 5). In order to further increase both the yield and the ee of the reaction, another procedure was examined. Three equivalents of KHMDS were added to a pre-cooled solution of benzaldehyde (5.0 equiv.) and **1** (procedure III) in toluene at –30 °C, and the resulting solution was stirred for 6 h to give **2** in 86% yield and 83% ee (entry 6). While decrease in the reaction temperature to –50 °C increased the ee of the aldol reaction to 87% ee, that diminished the yield to 65% (entries 6 *vs.* 7). Ethereal solvents were employed in combination with toluene in order to improve the yield by increasing the reactivity of the enolate (entries 8-10 *vs.* 7). While the addition of either THF, *i*-Pr_2O, or *t*-BuOMe is effective in increasing the yield of the reaction (86%~quant), that slightly decreased the enantioselectivity of the aldol process (78~84% ee). The corresponding reactions at –60 °C increased the ee to 86~92% ee (entries 11 and 12). Based on these results, we chose the conditions employed in entries 10 and 12, procedure III in toluene- *t*-BuOMe (2:1), as the optimum ones. The corresponding *tert*-butyl and benzyl esters of **1** were treated under the reaction conditions employed for entry 10 gave the corresponding *tert*-butyl and benzyl esters of **2** in 89% ee (31% yield) and 82% ee (quant), respectively (entries 13 and 14).

The optimized conditions were applied to asymmetric aldol reactions of **1** with various aromatic aldehydes (Table 2). A mixture of **1** and an aldehyde in toluene-*t*-BuOMe (2:1) was treated with KHMDS at –60 °C or –50 °C to give a chiral oxazolidone with contiguous tetra- and trisubstituted chiral centers in diastereomerically pure form through the asymmetric aldol reaction followed by intramolecular acylation of the resulting potassium aldolate. *para*-Substituted benzaldehydes gave oxazolidones **3**-**6** by the reactions with **1** in 64-95% yield and 78-88% ee (entries 2-5). *ortho*-Methoxybenzaldehyde underwent the aldol-acylation reaction to give oxazolidone **7** in 67% yield and 89% ee (entry 6). Reaction of **1** with 2-naphthaldehyde gave oxazolidone **8** in high enantioselectivity (89% ee) and a low yield (44%) (entry 7). Although a single diastereomer was obtained in each run after purification by column chromatography, the involvement of the minor diastereomer in the crude mixture can not be excluded, especially when the yield was low. The attempted reactions of **1** with aliphatic aldehydes did not afford the significant amounts of aldolates or the corresponding oxazolidones.

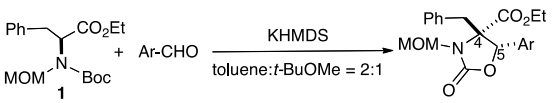
Table 1 Optimization of asymmetric aldiol reactions via memory of chirality.

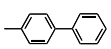


entry	procedure[a]	solvent	temp (°C)	time	yield (%)[b,c]	ee[d] (%)
1	I	toluene:THF=4:1	–78	2.5 h	85	32
2	II	toluene:THF=4:1	–78	10 min	2	99
3	II	toluene:THF=4:1	–30	10 min	7	96
4	II	toluene:THF=4:1	–30	4 h	96	71
5	II	toluene	–30	6 h	57	80
6	III	toluene	–30	6 h	86	83
7	III	toluene	–50	10 h	65	87
8	III	toluene:THF=2:1	–50	12 h	86	78
9	III	toluene:*i*-Pr_2O=2:1	–50	12 h	95	84
10	III	toluene:*t*-BuOMe=2:1	–50	12 h	quant	81
11	III	toluene:*i*-Pr_2O=2:1	–60	12 h	70	86
12	III	toluene:*t*-BuOMe=2:1	–60	12 h	69	92
13[e]	III	toluene:*t*-BuOMe=2:1	–50	12 h	31[f]	89
14[g]	III	toluene:*t*-BuOMe=2:1	–50	12 h	quant[h]	82

[a] I: **1** was tretated with KHMDS (1.1 equiv.) for 30 min, then with benzaldehyde (3.0 equiv.) for 2 h. II: A solution of **1** was added to a solution of benzaldehyde (3.0 equiv.) and KHMDS (1.1 equiv.). III: KHMDS (3.0 equiv.) was added to a solution of benzaldehyde (5.0 equiv.) and **1**. [b] A single diastereomer was obtained in each run. [c] The relative configuration was determined by NOE studies (see ESI) as well as an X-ray analysis of the derivative of **2** (see text). [d] (4*S*,5*S*)-Isomer was obtained in each run. For determination of the absolute configuration, see text. [e] The corresponding *tert*-butyl ester was employed as a substrate. [f] The yield of the corresponding *tert*-butyl ester. [g] The corresponding benzyl ester was employed as a substrate. [h] The yield of the correspondin benzyl ester.

Table 2 Asymmtric aldiol reactions of **1** with aromatic aldehydes.[a]



Entry	Ar	temp (°C)	time (h)	product[b,c]	yield (%)	ee (%)
1		–60	6	**2**[d]	69	92
2		–60	12	**3**[e]	67	88
3		–60	6	**4**[e]	66	88
4		–50	6	**5**[e]	64	78
5		–50	12	**6**[e]	95	80
6		–50	12	**7**[e]	67	89
7		–60	6	**8**[e]	44	89

[a] KHMDS (3.0 equiv.) was added to a solution of an aldehyde (5.0 equiv.) and **1**. [b] A single diastereomer was obtained in each run. [c] Relative configuration of **2**-**6** and **8** was determined by NOE studies, see ESI. Relative configuration of **7** was tentatively assigned by analogy. [d] (4*S*,5*S*). [e] The absolute configuration was tentatively assigned by analogy to **2**.

The absolute configuration of **2** was determined by an X-ray analysis of its derivative **10** (Figure 1). Hydrolysis of **2** (85% ee) obtained by the reactions in Table 1 followed by condensation of

the resulting acid with (*S*)-1-(1-naphthyl)ethylamine gave **9** in 86% yield as a diastereomerically pure form after column chromatography. Treatment of **9** with trifluoroacetic acid gave **10** in 85% yield via Pictet-Spengler cyclization, in which the MOM group serves as a formaldehyde equivalent.[10] An X-ray structure of a single crystal of **10** is shown in Figure 1. This indicates that asymmetric aldol reaction of **1** took place in inversion of configuration at the newly generated tetrasubstituted carbon center. Asymmetric aldol reactions of tyrosine derivative **11** and leucine derivative **13** with benzaldehyde took place by the treatment according to the protocol in Table 2 gave oxazolidones **12** and **14** in 85% ee (95% yield) and 94% ee (83% yield), respectively.

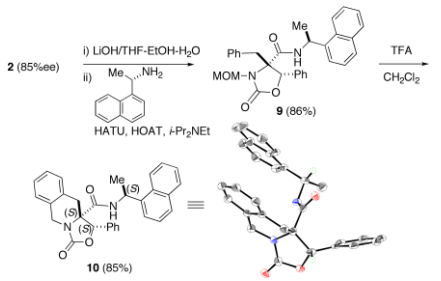
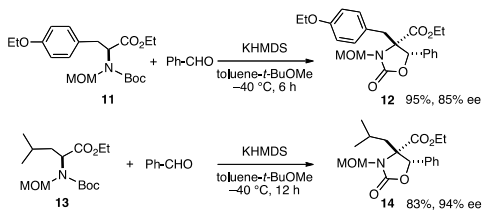


Figure 1 Transformation of **2** into **10** and an X-ray structure of **10**.



Scheme 2 Asymmetric aldol-acylation reactions of **11** and **13**.

The following phenomena appear to be intriguing from mechanistic viewpoints and enolate chemistry. (1) While methylation of **1** proceeds in retention of configuration, its aldol reaction took place in inversion of configuration. These reactions seem to proceed via a common chiral enolate intermediate (at least for the reactions of entry 1 in Table 1 and Scheme 1). Thus, the reacting enantioface of the axially chiral enolate is reverse to each other depending on the electrophile (alkyl halide or aldehyde). (2) While the enolate generated from **1** by the procedure I (entry 1 in Table 1 and Scheme 1) has been known to be a 2:1 *Z/E* mixture,[6a] its aldol reaction with benzaldehyde gave a diastereomerically pure product in 85% yield. Some of other related aldol reactions also gave diastereomerically pure products in good yields. We are not ready to propose the rationale for these phenomena, yet. Mechanistic investigations are currently underway in our laboratory.

In conclusion, we have developed an intermolecular asymmetric aldol reaction of α-amino acid derivatives via memory of chirality for the first time.[7] Although asymmetric aldol reactions have extensively developed,[11,12] the present method has unique characteristics in which asymmetric induction is controlled solely by the enolate chirality in the absence of chiral catalysts or chiral auxiliaries. Chiral oxazolidone derivatives with contiguous tetra- and trisubstituted chiral centers can be obtained from readily available α-amino acids by the present method in a highly diastereoselective and enantioselective manner. Chiral oxazolidones have been known to be useful chiral auxiliaries,[11] and recently disclosed to be a novel class of antibiotics.[13] Oxazolidones obtained by the present method are structural equivalents to β-hydroxy-α-amino acids with a tetrasubstituted carbon center,[14] which are the frequently observed structural subunits in biologically active natural products.[15]

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9 While the reaction in pure THF gave the α-methylated product in 93% yield and 35% ee (reference 6c), the corresponding reaction in pure toluene gave the α-methylated product in 47% yield and 75% ee. This could be ascribed to be higher reactivity of the enolate in THF and registance of the enolate against racemization in toluene.

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