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Enantioselective α-allylation of a phenylalanine derivative under the control of aggregation of a chiral nonracemic enolate

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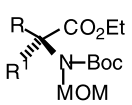
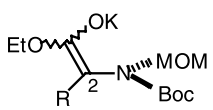
Abstract—α-Allylation of **3** took place upon treatment with KHMDS followed by allylic halides in 82–87% ee in the absence of external chiral sources. A chiral nonracemic enolate with intramolecular aggregation (**D**) is expected to be an intermediate.

Previous studies from our laboratory have demonstrated asymmetric induction based on the dynamic chirality of enolates.[1,2] α-Alkylation of some α-amino acid derivatives proceeds enantioselectively without the aid of external chiral sources such as chiral auxiliaries or chiral catalysts.[1,2b–d,3,4] For example, *N*-Boc-*N*-MOM-amino acid derivatives (**1**) undergo α-methylation to give **2** in 76∼93% ee upon treatment with potassium hexamethyldisilazide (KHMDS) followed by methyl iodide. Chiral nonracemic enolate intermediate **A** with dynamic axial chirality along the C(2)–N axis ($t_{1/2}$ = 22 h at −78°C) was proposed as a crucial intermediate for this asymmetric induction.[1] This method, however, is not sufficient for α-allylation due to low enantioselectivity (23∼69% ee). We further investigated the asymmetric synthesis of α-allylated α-amino acids because they are versatile components of functional peptides.[5,6] We describe here a new strategy for the control of stereochemistry of the reactions of enolates with electrophiles by controlling their aggregation. An improved enantioselectivity was observed in α-allylation of phenylalanine derivative with a phenol group (**3**).

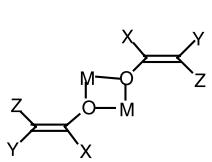




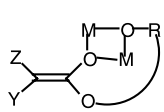
1 : R^1 = H MOM = CH_2OMe
2 : R^1 = Me Boc = CO_2 *t*-Bu

A

We often encounter comparable or even better stereoselectivity in the reactions of enolates with bulkier electrophiles rather than that with a small electrophile, methyl iodide.[7] The lower enantioselectivity observed in the α-allylation of **1** implies that an intermediate in α-allylation may be different from that in α-methylation. We assumed the existence of a few different aggregates of a chiral enolate in the reaction of **1**. If it is possible to control the aggregation of the enolate, both α-methylation and α-allylation would take place via a common aggregate intermediate, and this could lead to an improvement in the enantioselectivity of α-allylation. Enolates generally form aggregates consisting of an oxygen–metal bond framework (**B**).[8] They usually exist as a mixture of different aggregates in solution. The complexity of the aggregates is due, at least in part, to the *intermolecular* association of enolate subunits. We anticipated that the formation of stable *intramolecular* aggregate (**C**) enforced by the coordination of pseudo-enolate subunit (R-OM) would simplify the aggregate intermediate and affect the stereoselectivity of the reaction. Based on this hypothesis, a phenylalanine derivative with a phenol group (**3**) (Table 1) was designed, which is expected to form aggregate **D** upon treatment with a base.



B



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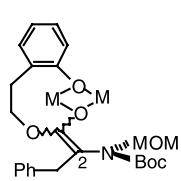

D

Keywords: aggregate; chiral enolate; dynamic chirality; allylation; amino acid.

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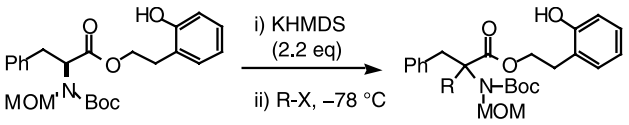
Table 1. Asymmetric α-alkylation of **3**



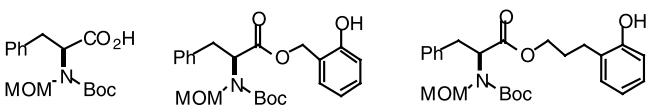
3 **4**

Entry	R-X	Solvent	Yield (%)	Ee (%)[a]
1	MeI	Toluene:THF = 4:1	81	88[b] (81)[c]
2	MeI	THF	83	75[b] (35)[c]
3	CH_2=$CHCH_2I$	Toluene:THF = 4:1	71	82 (55)[c]
4	$(CH_3)_2C$=$CHCH_2Br$	Toluene:THF = 4:1	47	87 (69)[c]
5	*trans*-PhCH=$CHCH_2I$	Toluene:THF = 4:1	89	83 (48)[c]

[a] Ee was determined by HPLC analysis with a chiral stationary phase.
[b] (*S*)-Isomer.
[c] % Ee of the corresponding product from **1**.

Phenol derivative **3** (98% ee) was prepared by condensation of *N*-Boc-*N*-MOM-phenylalanine (**5**) and 2-(2-benzyloxyphenyl)ethanol in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide followed by hydrogenolysis in 80% yield. Compound **5** was readily obtained from Boc-phenylalanine benzyl ester in 73% yield via the introduction of a MOM group to the nitrogen (KHMDS, MOMCl, −78°C) followed by hydrogenolysis of the benzyl ester. α-Alkylation of **3** was examined and the results are shown in Table 1. Treatment of **3** with 2.2 equiv. of KHMDS in toluene–THF (4:1) followed by methyl iodide at −78°C gave **4** (R = Me) in 88% ee (entry 1). The stereochemical course of the α-methylation was determined to be retention,[9] which parallels that of **1**.[1] α-Allylation of **3** proceeded with improved selectivity of 82∼87% ee compared to that of **1** (entries 3–5).[10] The degree of asymmetric induction of α-alkylation of **3** was comparable with several electrophiles (entries 1, 3–5). The solvent effect in α-methylation was not significant, in contrast to the results with **1** (entry 2). These results indicate, although speculative, that the reactive intermediate in these reactions might be a single aggregate species of a chiral nonracemic enolate, which may be shown as **D** (M = K).

To investigate the effects of the chain length of a linker between the phenol and ester carbonyl, analogues with shorter **6** and longer linkers **7** were prepared. α-Methylation and α-allylation of **7** took place in 80% ee (71% yield) and 72% ee (51% yield), respectively, under conditions identical to those for **3**. On the other hand, treatment of **6** with KHMDS followed by methyl iodide or allyl iodide gave a complex mixture, probably due to decomposition via cleavage of the benzyl ester. While the asymmetric induction in the reaction of **7** was improved, **3** was the most suitable substrate for this purpose.



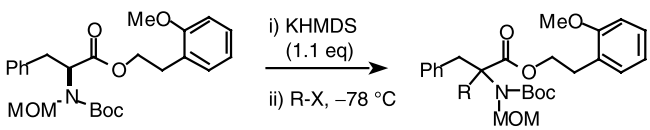
5 **6** **7**

To elucidate the effect of a phenolic OH group of **3**, reactions of anisole derivative **8** were examined (Table 2). In both α-methylation and α-allylation, the enantioselectivity was comparable to that observed with **1** (entries 1 and 3). The solvent-dependency of the enantioselectivity in α-methylation was also similar to that with **1** (entries 1 and 2). The behavior of **8** in asymmetric α-alkylation is closer to that of ethyl ester **1** than to that of phenol derivative **3**. The presence of the phenolic OH group in **3** is significant for asymmetric induction, which indicates that potassium phenoxide contributes to the intramolecular aggregation of the enolate intermediate probably as a pseudo-enolate subunit.

Asymmetric α-alkylation of **3** is assumed to proceed via chiral nonracemic enolate intermediate (**D**) with dynamic axial chirality along the C(2)–N axis, by analogy to our previous study with **1**.[1] We then investigated the behavior of the enolate intermediate generated from **3** and KHMDS toward racemization. When **3** was treated with KHMDS in toluene–THF (4:1) at −78°C for 30 min and then at −40°C for 30 min, the reaction of the resulting enolate with methyl iodide at −78°C gave **4** in 68% ee (cf. 88% ee after 30 min of base treatment at −78°C, Table 1, entry 1). The half-life of racemization of the chiral enolate is roughly estimated to be ∼80 min at −40°C, assuming first-order kinetics for racemization.[1] On the other hand, the same treatment of **1** gave **2** in 5% ee (cf. 81% ee after 30 min of base treatment at −78°C),[1] which corresponds to a half-life of racemization of ∼7 min at −40°C. Thus, the formation of an intramolecular aggregate enhances the stability of the chiral enolate against racemization.[11]

In conclusion, α-allylation of phenylalanine derivative **3** proceeded with high enantioselectivity in the absence of external chiral sources. The formation of an intramolecular aggregate of a chiral nonracemic enolate seems essential for asymmetric induction, and is also effective for preserving the enantiomeric purity of the chiral enolate intermediate (i.e. enhancement of the memory effect of chirality). We expect that this protocol may have potential applicability to the control of the reactivity and selectivity of enolate intermediates.

Table 2. Asymmetric α-alkylation of **8**



8 **9**

Entry	R-X	Solvent	Yield (%)	Ee (%)[a]
1	MeI	Toluene:THF = 4:1	95	77 (81)[b]
2	MeI	THF	88	51 (35)[b]
3	CH_2=$CHCH_2I$	Toluene:THF = 4:1	90	58 (55)[b]

[a] Ee was determined by HPLC analysis with a chiral stationary phase.
[b] % Ee of the corresponding product from **1**.

Acknowledgements

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References

1. Chirality whose properties are time- and temperature-dependent is referred to as dynamic chirality: Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2155.
2. (a) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694; (b) Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809; (c) Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373; (d) Kawabata, T.; Chen, J.; Suzuki, H.; Nagae, Y.; Kinoshita, T.; Chancharunee, S.; Fuji, K. *Org. Lett.* **2000**, *2*, 3883.
3. For examples of asymmetric synthesis of α,α-disubstituted α-amino acid derivatives utilizing intrinsic chirality of parent α-amino acids, see: (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390; (b) Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 11612; (c) Ferey, V.; Toupet, L.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 430; (d) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460.
4. For related asymmetric α-substitution of α-amino acid derivatives without using external chiral sources, see: (a) Seebach, D.; Wasmuth, D. *Angew.Chem., Int. Ed. Engl.* **1981**, *20*, 971; (b) Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Chem. Commun.* **1991**, 924; (c) Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem., Soc. Perkin Trans 1* **1999**, 1067.
5. α-Allylated α-amino acids are versatile components of functional peptides, see: (a) Abell, A. D.; Gardiner, J.; Phillips, A. J.; Robinson, W. T. *Tetrahedron Lett.* **1998**, *39*, 9563; (b) Boatman, P. D.; Ogbu, C. O.; Eguchi, M.; Kim, H.; Nakanishi, H.; Cao, B.; Shea, J. P.; Kahn, M. *J. Med. Chem.* **1999**, *42*, 1367; (c) Schafmeister, C. E.; Po, J.; Verdine, G. L. *J. Am. Chem. Soc.* **2000**, *122*, 5891.
6. Recently, excellent catalytic methods for asymmetric synthesis of α-allylated α-amino acid derivatives have been developed, see: (a) Kuwano, R. Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236; (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.
7. For examples, see: (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737; (b) Kimura, K.; Murata, K.; Otsuka, K.; Ishizuka, T.; Haratake, M.; Kunieda, T.; *Tetrahedron Lett.* **1992**, *33*, 4461; (c) Tanaka, F.; Node, M.; Takana, K.; Mizuchi, M.; Hosoi, S.; Nakayama, M.; Taga, T.; Fuji, K. *J. Am. Chem. Soc.* **1995**, *117*, 12159; (d) Refs. 3b,d.
8. (a) Willard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462; (b) Seebach, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.
9. Treatment of **4** (R = Me) with 6 M HCl (reflux, 4 h) gave (*S*)-α-methyl phenylalanine, $[\alpha]_D^{21} = -18$ (*c* 0.5, H_2O). Lit. $[\alpha]_D^{20} = -22$ (*c* 1, H_2O): Kruizinga, W. H.; Bolster, J.; Kellog, R. M.; Kamphuis, J.; Boesten, W. H.; Meijer, E. M.; Schoemaker, H. E. *J. Org. Chem.* **1988**, *53*, 1826.
10. A typical experimental procedure for α-alkylation: A KHMDS solution (Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913) in THF (0.46 M, 1.43 mL, 0.66 mmol) was diluted with 3 mL of toluene. A solution of **3** (129 mg, 0.30 mmol; dried azeotropically with toluene prior to use) in toluene (2.0 mL) was added to the KHMDS solution at −78°C. After stirring for 30 min, a solution of cinnamyl iodide (110 mg, 0.45 mmol) in toluene (1.0 mL) was added. Stirring was continued for 17 h at −78°C. The mixture was poured into saturated aq NH_4Cl and extracted with ethyl acetate. The organic phase was washed with saturated aq. $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, EtOAc:hexane = 1:3) to give **4** (R = CH_2CH = CHPh) (146 mg, 89% yield). Enantiomeric excess of **4** was determined by HPLC analysis with Daicel Chiralpak AD, hexane:2-propanol = 97:3, flow 0.8 mL/min, $t_R = 82$, 89 min.
11. The enhancement of ee in α-allylation of **3** is not due to a longer half-life of the enolate intermediate to racemization. The half-life to racemization of an enolate generated from **1** and KHMDS is 22 h at −78°C, which is long enough for the chiral enolate to undergo α-allylation without significant loss of its enantiomeric purity.