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Asymmetric Cyclization via Memory of Chirality: A Concise Access to Cyclic Amino Acids with a Quaternary Stereocenter

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Cyclic amino acids are of increasing interest in the life-science industry.[1] Incorporation of these compounds into peptides induces conformational constraint, and it provides an important tool for studying the relationships between peptide conformation and biological activity and for probing biological processes including protein folding.[2] Cyclic amino acids are useful building blocks for natural product synthesis[3] and are also key structural units of catalysts for enantioselective synthesis.[4] Cyclic amino acids with a quaternary stereocenter constitute a new class of nonnatural amino acids with an even more constrained conformation. The lack of availability of these unusual amino acids from natural sources necessitates the development of efficient methods for their synthesis.[5] The simplest and ideal access to these molecules seems to involve direct intramolecular alkylation of α-amino acid derivatives as shown in Scheme 1. However, such a route has rarely been examined, probably because of the anticipated production of racemic products due to a loss of chirality during the enolization step. In a pioneering work in this field by Stoodley, the intramolecular reaction of an axially chiral enolate with an electrophilic diazo group gave 1,4,5-triazabicyclo-3-nonenes with retention of configuration.[6] Recently, enantioselective *β*-lactam synthesis has been reported on the basis of the memory effect of chirality of the parent amino acids, albeit with a moderate enantiomeric excess.[7] We report here a simple and efficient method for asymmetric cyclization of amino acid derivatives according to the strategy in Scheme 1. This provides a novel access to a variety of aza-cyclic amino acids with a quaternary stereocenter of high enantiomeric purity.

To preserve chirality during enolate formation and subsequent C−C bond formation, the choice of the protecting group on the nitrogen of α-amino acids is critical.[8,9] According to our previous results on the intermolecular alkylation of α-amino acid derivatives, where the *N*-*tert*-butoxycarbonyl (Boc) group is essential for the generation of a chiral nonracemic enolate intermediate,[8] *N*-Boc-*N*-(3-bromopropyl)-phenylalanine derivative **1** was designed as a substrate for asymmetric cyclization. Substrate **1** was readily prepared from (*S*)-phenylalanine ethyl ester through *N*-alkylation with 3-bromo-1-propanol, introduction of a Boc group to the nitrogen, and conversion of the hydroxy group into bromine in 63% overall yield without loss of enantiomeric purity (>99% ee).

The conditions for enantioselective cyclization of **1** were examined (Table 1). Treatment of **1** with potassium hexamethyldisilazide (KHMDS) in THF at −78 °C gave α-benzylproline **2** in 89% ee and 92% yield. Whereas the corresponding reaction in toluene gave **2** in 47% ee, the reaction of **1** in DMF gave **2** in 98% ee and 94% yield with retention of configuration (entries 2 and 3). Lithium amide bases such as lithium hexamethyldisilazide or lithium 2,2,6,6-tetramethylpiperidide gave worse results (entries 4 and 5).

Asymmetric cyclization via enantioselective intramolecular C−C bond formation was examined with various amino acid derivatives (Table 2). Treatment of tyrosine derivative **3** simply with KHMDS in DMF at −60 °C for 30 min gave α-(4-ethoxyphenyl)methyl-

Scheme 1. Strategy for Asymmetric Cyclization

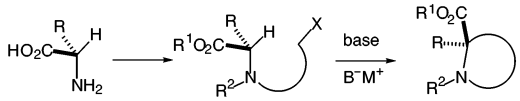
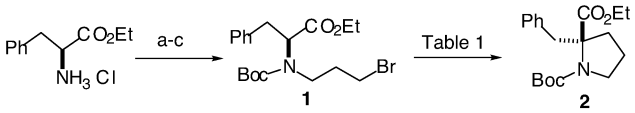


Table 1. Asymmetric Cyclization of **1**

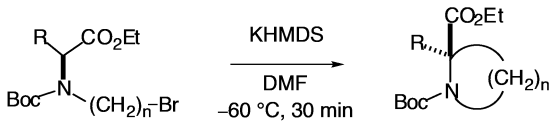


(a) 3-bromo-1-propanol, K_2CO_3, DMF, (b) $(Boc)_2O$, *i*-Pr_2NEt, (c) CBr_4, PPh_3 (63% overall)

entry	base[a]	solvent	temp, time	**2**, yield (%)	**2**[b], ee[c](%)
1	KHMDS[d]	THF	−78 °C, 30 min	92	89
2	KHMDS[d]	toluene	−78 °C, 2 h	92	47
3	KHMDS[d]	DMF	−60 °C, 30 min	94	98
4	LHMDS[e]	DMF	−60 °C, 30 min	60	77
5	LTMP[f]	DMF	−60 °C, 30 min	∼0	

[a] 1.2 equiv of base was used. [b] The (*S*)-isomer was obtained in every entry. See the Supporting Information. [c] Determined by HPLC analysis. [d] Potassium hexamethyldisilazide. [e] Lithium hexamethyldisilazide. [f] Lithium 2,2,6,6-tetramethylpiperidide.

Table 2. Enantioselective Synthesis of Aza-cyclic Amino Acid Derivatives with a Quaternary Stereocenter[a]



entry	substrate	*n*	R	product	yield (%)	ee (%)[b]
1	**1**[c]	3	$PhCH_2$	**2**	94	98 (*S*)
2	**3**	3	4-EtO-C_6H_4-CH_2	**4**	95	97
3	**5**	3	$MeSCH_2CH_2$	**6**	92	97
4	**7**	3	Me_2CH	**8**	78	94
5	**9**	3	CH_3	**10**	91	95 (*R*)
6	**11**	2	$PhCH_2$	**12**	61	95
7	**13**[c]	4	$PhCH_2$	**14**	84	97
8	**15**[c]	5	$PhCH_2$	**16**	31[e]	83 (*S*)
9[d]	**15**[c]	5	$PhCH_2$	**16**	61[f]	72 (*S*)

[a] A solution of substrate (0.25 mmol) in dry DMF (2.4 mL) was treated with 1.2 mol equiv of KHMDS (0.50 M in THF) for 30 min at −60 °C, unless otherwise mentioned. [b] The ee was determined by HPLC analysis. The letter in the parentheses indicates the absolute configuration. See the Supporting Information. [c] >99% ee. [d] The reaction was run for 2 h. [e] **15** (70% ee) was recovered in 52% yield. [f] **15** (54% ee) was recovered in 17% yield.

proline derivative **4** in 97% ee and 95% yield (entry 2). Methionine and valine derivative **5** and **7** gave α-substituted prolines **6** and **8** in 97% and 94% ee, respectively, by the same treatment (entries 3 and 4). Cyclization of alanine derivatives **9** via intramolecular alkylation also proceeded in a highly enantioselective manner (95% ee, entry 5). This is in contrast to the corresponding intermolecular

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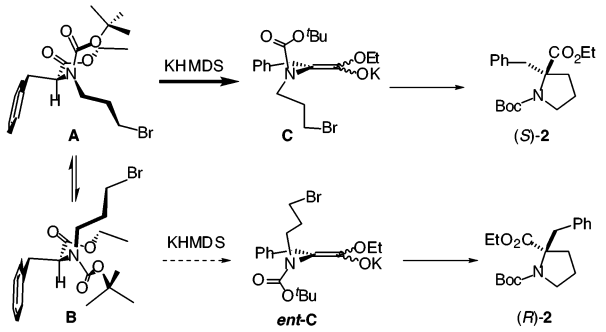
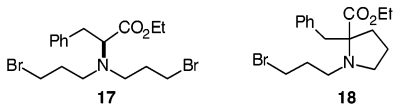
Scheme 2. A Possible Mechanism for Asymmetric Cyclization



reaction where the enantioselectivity in α-alkylation of an alanine derivative is much lower than that with phenylalanine, tyrosine, and valine derivatives.[10] The enantioselective construction of four-, six-, and seven-membered cyclic amino acids is also achieved by this protocol. Treatment of **11**, **13**, or **15** with KHMDS in DMF at −60 °C for 30 min gave azetidine (**12**), piperidine (**14**), or azepane derivative (**16**) in 95%, 97%, or 83% ee, respectively (entries 6−8). The stereochemical course of the cyclization of **1**, **9**, and **15** was retention in each case.

A possible mechanism for the asymmetric cyclization is shown in Scheme 2. A conformational search of **1** gives two stable conformers **A** and **B**.[11] Deprotonation of conformer **A** with KHMDS, where the C(α)−H bond is eclipsed with the N−C(CH_2-CH_2CH_2Br) bond, would give an enantiomerically enriched enolate **C** with a chiral C−N axis,[8b] which undergoes intramolecular alkylation to give **2** with a total retention of configuration. Deprotonation of conformer **B**, where the C(α)−H bond is eclipsed with the N−C(Boc) bond, to give *ent*-**C** seems unfavorable due to the steric interaction between KHMDS and the Boc group. This hypothesis is consistent with the observed solvent effects, because deprotonation of **B** via chelation of the Boc-carbonyl group with potassium cation becomes more significant in a less coordinative solvent such as toluene, resulting in decreased enantioselectivity (Table 1, entries 1−3). An alternative mechanism may be a concerted S_Ei process. Although we cannot exclude this possibility at this time, we prefer the mechanism involving a chiral enolate intermediate shown in Scheme 2 for several reasons. Enantioselectivity in seven-membered ring formation depends on the reaction time (Table 2, entries 8 and 9). This seems to be due to partial racemization of a chiral enolate intermediate during relatively slow seven-membered-ring cyclization. The ee of the recovered **15** indicates time-dependent racemization of the intermediary enolate (Table 1, footnotes e and f).[12]

Support for this mechanism was obtained by the reaction of **17**. Upon cyclization by the standard procedure, **17** gave *racemic*-**18**. This indicates the critical importance of a chiral enolate intermediate for the asymmetric induction, because the enolate generated from **17** cannot be axially chiral along the C−N axis.



In conclusion, we have shown asymmetric cyclization of *N*-Boc-*N*-ω-bromoalkyl-α-amino acid derivatives, where the chirality of the parent amino acids is preserved to a high extent during enolate formation and the subsequent C−C bond formation. Because of the simplicity of the operation and wide applicability, this method could provide useful access to nonnatural aza-cyclic amino acids with a quaternary stereocenter from natural α-amino acids.

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Supporting Information Available: Experimental procedures and characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Peterson, M.; Sauter, M.; Lonza, A.-G. *Chimia* **1999**, *53*, 608−612.
(2) (a) Degrado, W. F. *Adv. Protein Chem*. **1988**, *39*, 51−124. (b) Williams, K. A.; Deber, C. M. *Biochemistry* **1991**, *30*, 8919. (c) Yaron, A.; Naider, F. *Crit. Rev. Biochem. Mol. Biol*. **1993**, *28*, 31. (d) Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc*. **1996**, *118*, 12902−12908. (e) Goodman, M.; Shao, H. *Pure Appl. Chem*. **1996**, *68*, 1303−1308. (f) Hanessian, S.; McNaughton-Smith, G.; Lombert, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854.
(3) Sardina, F. J.; Rapoport, H. *Chem. Rev*. **1996**, *96*, 1825−1872.
(4) For recent examples: (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833. (b) Priem, G.; Pelotîer, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem*. **2003**, *68*, 3844−3848. (c) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q, Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262−5263.
(5) (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645−732. (b) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629−8659. (c) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342−351.
(6) (a) Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Chem. Commun.* **1991**, 924. (b) Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1067.
(7) (a) Gerona-Navarro, G.; Bonache, M. A.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem*. **2001**, *66*, 3538−3547. (b) Bonache, M. A.; Gerona-Navarro, G.; Martín-Martínez, M.; García-López, M. T.; López, P.; Cativiela, C.; González-Muñiz, R. *Synlett* **2003**, 1007.
(8) (a) Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc*. **1994**, *116*, 10809. (b) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed*. **2000**, *39*, 2155. (c) Kawabata, T.; Chen, J.; Suzuki, H.; Nagae, Y.; Kinoshita, T.; Chancharunee, S.; Fuji, K. *Org. Lett*. **2000**, *2*, 3883.
(9) For example, α-methylation of *N*-Boc-*N*-methyl phenylalanine derivatives proceeds in up to 82% ee, while that of the corresponding *N*-formyl-*N*-methyl derivative gives a racemic product; see ref 8a.
(10) Whereas α-methylation of *N*-Boc-*N*-methoxymethyl(MOM)-phenylalanine, -tyrosine, and -valine derivatives proceeds in 81%, 79%, and 87% ee, respectively (ref 8b), α-allylation of *N*-Boc-*N*-MOM-alanine derivative proceeds in 33% ee (unpublished data). The low ee in the reaction of an alanine derivative seems to be at least in part due to rapid racemization of the chiral enolate intermediate during intermolecular alkylation. On the other hand, the loss of enantiomeric purity of the chiral enolate is minimized during rapid five-membered intramolecular alkylation, and it gives **10** with high enantiomeric excess.
(11) The stable conformers **A** and **B** of **1** were generated by a molecular modeling search with AMBER* force field with the GB/SA solvation model for water using MacroModel V 6.0. The difference in potential energies between **A** and **B** is estimated to be 0.1 kcal/mol. A PM3 calculation with a polarized continuum model (water, $\epsilon = 78.4$) also gave stable structures similar to **A** and **B**: (a) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc*. **1990**, *112*, 6127−6129; (b) *J. Comput. Chem*. **1991**, *12*, 620.
(12) The observed solvent effects in entries 1−3 of Table 1 seem not compatible with the general features of a concerted S_Ei process. It has been reported that a higher extent of inversion of stereochemistry is observed with more polar solvents in S_E2 reactions. See: Fukuto, J. M.; Jensen, F. R. *Acc. Chem. Res*. **1983**, *16*, 177−184.

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