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Stereochemical Diversity in Asymmetric Cyclization via Memory of Chirality

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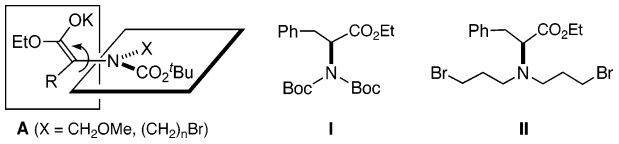
The enantioselective construction of a chiral tetrasubstituted stereocenter is one of the most challenging tasks in current synthetic organic chemistry.[1] We have developed a direct method for the enantioselective construction of α,α-disubstituted α-amino acids from α-amino acids via memory of chirality.[2,3] Under these conditions, α-methylation of *N*-*tert*-butoxycarbonyl(Boc)-*N*-methoxymethyl(MOM)-α-amino acid derivatives takes place in up to 93% ee without the aid of external chiral sources such as chiral auxiliaries or chiral catalysts.[4] This protocol has been applied to the asymmetric cyclization for straightforward synthesis of cyclic amino acids with a tetrasubstituted stereocenter from α-amino acids.[5] We further developed a method for the asymmetric construction of highly substituted nitrogen heterocycles via the intramolecular conjugate addition of chiral enolates generated from α-amino acids.[6] We report here stereochemical diversity in asymmetric cyclization as shown in Scheme 1. This provides a novel access to both enantiomers of nitrogen heterocycles with a tetrasubstituted stereocenter of high enantiomeric purity from readily available L-α-amino acids.

A chiral nonracemic enolate **A** with a chiral C−N axis has been proposed as the crucial intermediate for the asymmetric transformation via memory of chirality.[2,4−6] Experimental evidence for **A** involves the observation that α-alkylation of **I** and **II** gave racemic products, respectively, under the standard conditions for asymmetric alkylation via memory of chirality because the enolates generated from these derivatives cannot be axially chiral along the C−N axis.[4,5]



A (X = CH_2OMe, $(CH_2)_nBr$) **I** **II**

We have reported that treatment of **1** with potassium hexamethyldisilazide (KHMDS) in DMF at −60 °C gave **2** in 98% ee with retention of configuration (Table 1, entry 1).[5] A rationale for the stereochemical course is shown in Scheme 2. A conformation search of **1** gives two stable conformers **A** and **B**.[5] Deprotonation of conformer **A** with KHMDS, where the C(α)−H bond is eclipsed with the N−C($CH_2CH_2CH_2Br$) bond, via transition state **X** would give an enantiomerically enriched enolate **C** with a chiral C−N axis, 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 because of the steric interaction between KHMDS and the Boc group. This hypothesis is consistent with the observed solvent effects, since deprotonation of **B** via chelation of the Boc-carbonyl group with potassium cation (transition state **Y**) becomes more significant in less coordinative solvents, resulting in decreased enantioselectivity (entries 1−3). This observation prompted us to investigate another hypothesis that enforcing chelation by the use of a lithium cation should make

Scheme 1. Stereochemical Diversity in Asymmetric Cyclization

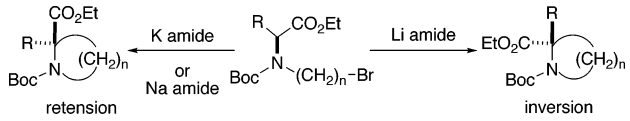
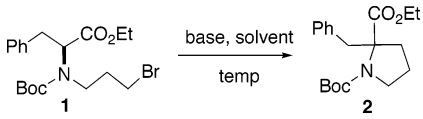


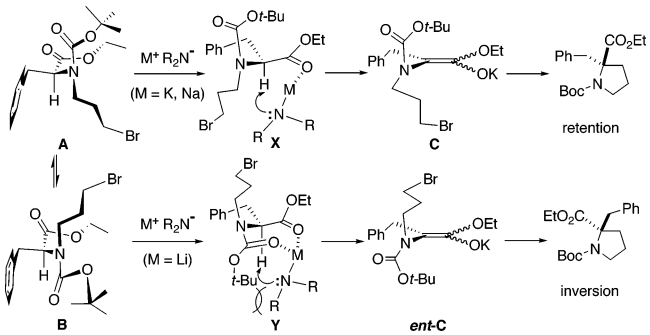
Table 1. Effects of Base and Solvent on the Stereochemical Course for the Asymmetric Cyclization of **1**



entry	base[a]	solvent	temp, time (h)	**2**, yield (%)	**2**, ee[b] (%)
1[c]	KHMDS[d]	DMF	−60 °C, 0.5	94	98 (*S*)
2[c]	KHMDS[d]	THF	−78 °C, 0.5	92	89 (*S*)
3[c]	KHMDS[d]	toluene	−78 °C, 2	92	47 (*S*)
4[c]	LHMDS[e]	DMF	−60 °C, 0.5	60	77 (*S*)
5	LHMDS[e]	THF	−60 °C, 1	10	14 (*R*)
6	LTMP[f]	THF	−60 °C, 1	73	41 (*R*)
7	LTMP[f]	THF	20 °C, 0.5	93	91 (*R*)
8	LTMP[f]	toluene	20 °C, 0.5	90	77 (*R*)
9	LDA	THF	20 °C, 0.5	69	82 (*R*)

[a] Reactions were run using 1.2 equiv of base. [b] Determined by HPLC analysis. The letter in parentheses indicates the absolute configuration. For determination of the absolute configuration, see ref 5. [c] Data quoted from ref 5. [d] Potassium hexamethyldisilazide. [e] Lithium hexamethyldisilazide. [f] Lithium 2,2,6,6-tetramethylpiperidide.

Scheme 2. A Hypothetical Scheme for Stereochemical Course of Asymmetric Cyclization



transition state **Y** dominant and give the product with inversion of configuration. According to this hypothesis, we investigated the asymmetric cyclization of **1** with lithium amide bases (entries 4−9). Treatment of **1** with LHMDS in DMF gave (*S*)-**2** with retention of configuration in decreased enantioselectivity (entry 1 vs 4). The use of LHMDS in a less coordinative solvent (THF) gave (*R*)-**2** with inversion of configuration in 14% ee (entry 4 vs 5). Upon treatment of **1** with LTMP in THF at −60 °C, (*R*)-**2** was obtained in 41% ee (entry 6). Surprisingly, the corresponding reaction at 20 °C gave (*R*)-**2** in 91% ee and in 93% yield (entry 7).[7] Against our expectation, the use of toluene instead of THF did not increase the enantioselectivity (entry 7 vs 8).[8] Use of LDA also gave (*R*)-**2** in

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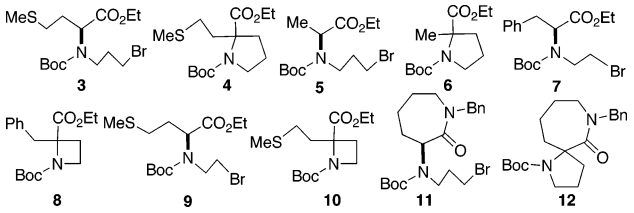
Table 2. Enantiodivergent Asymmetric Cyclization[a]

entry	substrate	base, solvent, temp	product	yield (%)	ee (%)[b]
1[c]	**1**	KHMDS, DMF, −60 °C	**2**	94	98 (*S*)
2	**1**	LTMP, THF, 20 °C	**2**	93	91 (*R*)
3[c]	**3**	KHMDS, DMF, −60 °C	**4**	92	97 (*S*)
4	**3**	LTMP, THF, −20 °C	**4**	92	81 (*R*)
5[c]	**5**	KHMDS, DMF, −60 °C	**6**	91	95 (*R*)
6	**5**	LTMP, THF, 20 °C	**6**	91	87 (*S*)
7[c]	**7**	KHMDS, DMF, −60 °C	**8**	61	95 (*R*)
8	**7**	LTMP, THF, −20 °C	**8**	69	90 (*S*)
9	**9**	KHMDS, DMF, −60 °C	**10**	98	97 (*S*)
10	**9**	LTMP, THF, 0 °C	**10**	66	83 (*R*)
11	**11**	NaHMDS, THF, 20 °C	**12**	72	99 (*R*)[d]
12	**11**	LHMDS, toluene, 0 °C	**12**	66	94 (*S*)[d]

[a] For experimental procedure, see Supporting Information. [b] The ee was determined by HPLC analysis. The letter in parentheses indicates the absolute configuration. For the determination of the absolute configuration, see Supporting Information. [c] Data quoted from reference 5. [d] Notation based on central chirality.

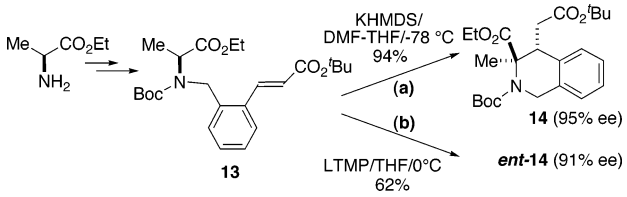


82% ee (entry 9), which is consistent with the hypothesis.

The conditions for enantiodivergent cyclization have been applied to various amino acid derivatives (Table 2). Five-membered cyclization of **1**, **3**, and **5** with KHMDS in DMF at −60 °C gave **2**, **4**, and **6** in 98, 97, and 95% ee, respectively, with retention of configuration (entries 1, 3, and 5). On the other hand, use of LTMP in THF gave the cyclization products in 81∼91% ee with inversion of configuration (entries 2, 4, and 6). Similar phenomena were observed in four-membered cyclization. Treatment of **7** with KHMDS in DMF at −60 °C gave **8** in 95% ee with retention of configuration (entry 7), while that with LTMP at −20 °C gave **8** in 90% ee with inversion of configuration (entry 8). Four-membered cyclization of methionine-derived analogue **9** showed similar stereochemical results (entries 9 and 10). Five-membered spirocyclization showed somewhat different stereochemical behavior. Treatment of **11** with KHMDS in DMF at −60 °C did not give **12**, due to the predominant β−elimination of HBr. Upon treatment of **11** with NaHMDS in THF at 20 °C, (*R*)-**12** was obtained with retention of configuration in 99% ee (entry 11). On the other hand, treatment of **11** with LHMDS in toluene at 0 °C gave (*S*)-**12** in 94% ee with inversion of configuration (entry 12).

The present protocol for enantiodivergent cyclization was applied to intramolecuar conjugate addition of chiral enolates. We have reported that treatment of **13** with KHMDS in DMF−THF (1:1) at −78 °C gave **14** as a single diastereomer in 95% ee (Scheme 3, (a)).[6] The absolute configuration of **14** was tentatively assigned based on the stereochemical course of asymmetric intramolecuar conjugate addition via memory of chirality. Upon treatment with LTMP in THF at 0 °C, **13** gave *ent*-**14** as a single diastereomer in 91% ee. Thus, both enantioners of tetrahydroisoquinoline derivatives with contiguous quarternary-tertiary stereocenters were readily prepared from L-alanine.

Scheme 3. Enantiodivergent Intramolecular Conjugate Addition of Chiral Enolates.



In conclusion, we have developed an enantiodivergent asymmetric cyclization of *N*-Boc-*N*-ω-bromoalkyl-α-amino acid derivatives. With potassium or sodium amide bases in DMF or THF, cyclization proceeds with retention of configuration, while inversion of configuration was observed with lithium amide bases in THF or toluene. Since high enantioselectivity was obtained in each transformation, these methods provide a concise entry to both enantiomers of cyclic amino acids with a tetrasubstituted stereocenter from natural L-amino acids.[9]

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Supporting Information Available: Experimental procedures and HPLC charts in Table 2; preparation and characterization of **9**, **11**, and **13**; characterization of **10**, **12**, and **14**; determination of the absolute configuration of **4**, **8**, **10**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) These unusual temperature effects were generally observed in the five-membered cyclization of **1**, **3**, and **5** with LTMP in THF, while the usual temperature-dependency was observed in five-membered spirocyclization of **11** with LHMDS.

(8) This could be ascribed to the difference in the aggregation state of LTMP in THF from toluene. For the discussion of the aggregate structure of LTMP, see Hall, P. L.; Gilchrist, J. M.; Harrison, A. T.; Fuller, D. J.; Column, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575−9585.

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