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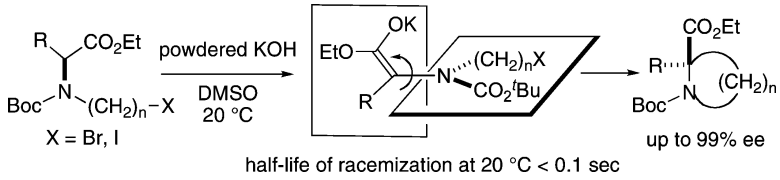

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Powdered KOH in DMSO: An Efficient Base for Asymmetric Cyclization via Memory of Chirality at Ambient Temperature

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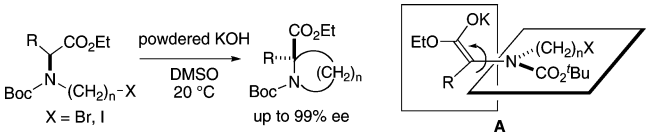
Abstract: Enolate chemistry has been extensively used for stereoselective C−C bond formation, in which metal amide bases are frequently employed in strictly anhydrous solvents at low temperatures. However, we found that asymmetric intramolecular C−C bond formation via axially chiral enolate intermediates proceeded in up to 99% ee at 20 °C using powdered KOH in dry or wet DMSO as a base. The enantioselectivity was even higher than that of the corresponding reactions with potassium hexamethyldisilazide in DMF at −60 °C. The racemization barrier of the axially chiral enolate intermediate was estimated to be ∼15.5 kcal/mol. On the basis of the barrier, the chiral enolate intermediate was supposed to undergo cyclization within $\sim 10^{-3}$ sec at 20 °C after it is generated to give the product in ≥99% ee. Thus, enolates generated with powdered KOH in DMSO were expected to be extremely reactive.

Introduction

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 asymmetric alkylation of α-amino acid derivatives without the aid of external chiral sources such as chiral auxiliaries or chiral catalysts, that is, memory of chirality.[2−4] Inter- and intramolecular alkylation of α-amino acid derivatives proceeded in up to 98% ee via axially chiral enolate intermediates, where enolate formation was performed typically at −78 to −60 °C to maintain enantiomeric purity of the chiral enolates.[4,5] However, we found that asymmetric cyclization via axially chiral enolate intermediate **A** proceeded in up to 99% ee at 20 °C using powdered KOH in DMSO as a base (Scheme 1). Surprisingly, some of the asymmetric cyclization reactions with KOH/DMSO at 20 °C proceeded with greater enantioselectivity than those with KHMDS in DMF at −60 °C. Another intriguing feature is that four-membered cyclization proceeded faster than the corresponding six-membered cyclization.

Scheme 1. Asymmetric Cyclization at Ambient Temperature via Axially Chiral Enolate Intermediate **A**



Results and Discussion

We have developed a method for the straightforward synthesis of cyclic amino acids with a tetrasubstituted stereocenter from readily available α-amino acids via memory of chirality.[3i,4c,e] Treatment of *N*-ω-bromoalkyl-*N*-*tert*-butoxycarbonyl(Boc)-α-amino acid derivatives with KHMDS in DMF at −60 °C gave cyclic amino acid derivatives in up to 98% ee with retention of configuration.[4c] The asymmetric cyclization was thought to proceed through an axially chiral enolate intermediate **A** (X = Br). We had believed that asymmetric reactions via memory of chirality would not take place highly enantioselectively at ambient temperature because the axially chiral enolate intermediates suffer from temperature-dependent racemization. For example, α-methylation of *N*-Boc-*N*-methoxymethyl(MOM)-α-amino acid derivatives proceeded in up to 93% ee at −78 °C via axially chiral enolate intermediate **B**, which has a half-life

(1) For reviews, see (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597.

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Scheme 2. α-Methylation via Axially Chiral Enolate Intermediate **B**

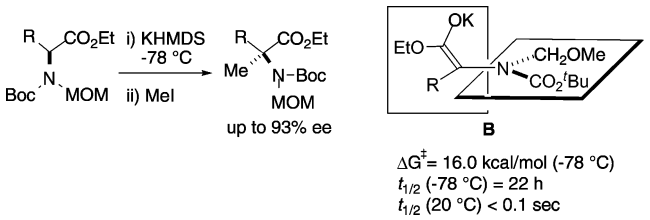
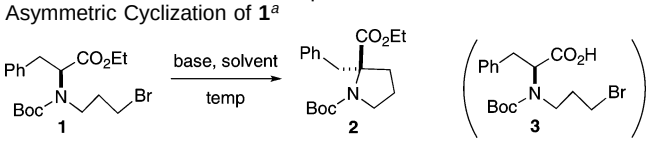


Table 1. Effects of Bases, Temperature, and Solvents on Asymmetric Cyclization of **1**[a]



entry	base (mol equiv)	solvent[b]	temp, time(h)	**2**, yield[c] (%)	**2**, ee[d] (%)
1[e]	KHMDS(1.2)	DMF	−60 °C, 0.5	94	98
2	KHMDS(1.2)	DMF	0 °C, 0.2	97	93
3	*t*-BuOK(1.5)	DMF	0∼20 °C, 1	67	87
4	KH(2.0)	DMF	0 °C, 0.2	76	89
5	KOH[f,g](3.0)	DMF	20 °C, 2	89	98
6	KOH[f,g](3.0)	DMSO	20 °C, 2	91	99
7	KOH[f,h](3.0)	DMSO	20 °C, 2	90	99
8	LiOH[f](3.0)	DMSO	20 °C, 17	∼0 (75)	
9	NaOH[f](3.0)	DMSO	20 °C, 2	81	97
10	CsOH[f](3.0)	DMSO	20 °C, 2	64	99
11	KOH[f,g](3.0)	1% H_2O in DMSO	20 °C, 2	98	99
12	KOH[f,g](3.0)	10% H_2O in DMSO	20 °C, 1	76	97
13	KOH[f,g](3.0)	20% H_2O in DMSO	20 °C, 1	12	93
14	KOH[f,g](3.0)	CH_2Cl_2	20 °C, 2	∼0 (97)	
15	KOH[f,g](3.0)	THF	20 °C, 2	45 (45)	71
16	KOH[f,g](3.0)	EtOH	20 °C, 23	∼0[i] (8)	

[a] Reactions in entries 1−2 and reactions in 3−15 were carried out with a substrate concentration of 0.08 and 0.1 M, respectively. [b] DMF, distilled from P_2O_5 at reduced pressure; DMSO, anhydrous DMSO (H_2O < 0.005%) from Aldrich, CH_2Cl_2, dehydrated CH_2Cl_2 (H_2O < 0.002%) from Kanto Kagaku; THF, distilled from sodium ketyl of benzophenone; EtOH, 99.5% ethanol from nakalai tesque. [c] Numbers in the parentheses indicate the percent recovery of **1**. [d] ee of the corresponding *N*-benzoate determined by HPLC analysis. The (*S*)-isomer was obtained in each run. For the determination of the absolute configuration, see ref 4c. [e] Data quoted from ref 4c. [f] Powdered metal hydroxide was used. [g] Prepared from commercial 85% KOH pellets from Nakalai Tesque. [h] Prepared from commercial >99% KOH pellets from Kojundo Chemical Laboratory, Co., Ltd. [i] Carboxylic acid **3** was obtained in 55% yield.

of racemization of 22 h at −78 °C,[4a] whereas that at 20 °C was calculated to be less than 0.1 s from the racemization barrier (Scheme 2).[6] Accordingly, it did not seem feasible to develop highly enantioselective *intermolecular reactions* via the memory of chirality at ambient temperature. On the other hand, it seemed possible to develop highly enantioselective *intramolecular reactions* at ambient temperature if the chiral enolate intermediates react very rapidly within the time-scale of their racemization.

We chose the transformation of **1** into **2** as an intramolecular reaction via memory of chirality and examined the temperature dependence of its enantioselectivity. Treatment of **1** with KHMDS at −60 °C in DMF gave **2** in 98% ee,[4c] whereas, at 0 °C, **2** was formed in only slightly diminished enantioselectivity of 93% ee (Table 1, entries 1 vs 2). This finding prompted us to further investigate bases and solvents for asymmetric reactions near ambient temperature. Bases that contained a potassium cation were screened for the reactions in DMF (entries 3−5). When **1** was treated with potassium *tert*-butoxide or potassium hydride in DMF at 0∼20 °C, **2** was obtained in 87 or 89% ee, respectively (entries 3 and 4). To our surprise, the treatment of **1** with powdered KOH (prepared by grinding commercial 85% KOH pellets with a mortar in a glove box, see Supporting Information) in DMF at 20 °C gave **2** in 98% ee (entry 5). We further found that powdered KOH in DMSO (KOH/DMSO) was an excellent base for the transformation and gave **2** in 99% ee and 91% yield (entry 6). KOH/DMSO was a suspension even after vigorous stirring at 20 °C for 5 min at the concentration (0.3 M) employed for the reaction. No difference in the efficiency of asymmetric cyclization was observed between powdered KOH prepared from commercial 85% KOH pellets and that from commercial >99% KOH pellets (entries 6 vs 7). Powdered LiOH was not effective as a base, whereas powdered NaOH and powdered CsOH showed reactivity similar to powdered KOH (entries 8−10). The solvent effects in KOH-promoted asymmetric cyclization were investigated (entries 11−16). Whereas the existence of 1% water in DMSO did not affect the efficiency of the asymmetric transformation (entries 6 vs 11), an increase in the amount of water in DMSO decreased both yield and enantioselectivity of the cyclization (entries 12 and 13). Powdered KOH in CH_2Cl_2 was totally unreactive as a base, and powdered KOH in THF was much less effective than KOH/DMSO for the transformation of **1** into **2** (entries 14 and 15). Powdered KOH in EtOH (KOH/EtOH) did not promote cyclization but rather promoted hydrolysis to give carboxylic acid **3** as a major product in 55% yield (entry 16). The difference in reactivity between KOH/DMSO and KOH/EtOH could be ascribed to the difference in the pKa's of H_2O in these solvents. The pKa's of H_2O in H_2O and in DMSO are known to be 16 and 31, respectively.[7] This means that KOH in DMSO is a strong base, which can abstract the α proton of esters (pKa 18∼30[7,8]), whereas KOH in protic solvents is not.

These newly developed mild reaction conditions (KOH/DMSO/20 °C) were applied to asymmetric four-, five-, and six-membered cyclization of phenylalanine, valine, and methionine derivatives. The results are summarized in Table 2. Asymmetric cyclization of phenylalanine derivative **4** with KOH/DMSO proceeded within 2 h at 20 °C to give azetidine **5** with a tetrasubstituted carbon center in 99% ee and 82% yield with retention of configuration (entry 1). Similarly, four-membered cyclization of valine and methionine derivatives **6** and **8** gave azetidines **7** and **9**, respectively, in 99% ee (entries 2 and 3). Five-membered cyclization of **1**, **10**, and **12** with KOH/DMSO proceeded smoothly to give pyrrolidines **2**, **11**, and **13**, respectively, in 98∼99% ee and 91∼94% yield (entries 4−6). We previously reported that asymmetric four-membered cyclization of **4** and **8** and five-membered cyclization of **1**, **10**, and **12** took place in 94∼98% ee upon treatment with KHMDS in DMF at −60 °C (brackets in entries 1 and 3−6).[3i,4c] Surprisingly, asymmetric four- and five-membered cyclizations with KOH/DMSO at 20 °C proceeded with higher enantioselectivity than those with KHMDS in DMF at −60 °C. This could be ascribed to the high reactivity of the axially chiral enolate intermediate **A** generated with KOH/DMSO, which immediately undergoes cyclization before suffering from noticeable racem-

(6) The racemization barrier at 20 °C was roughly estimated from that at −78 °C based on the assumption that $\Delta S^{\ddagger}$ of the unimolecular racemization process (bond rotation along the chiral C−N axis) is nearly zero.

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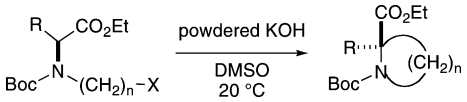
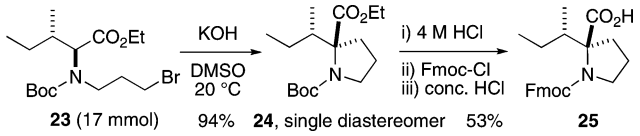
Table 2. Asymmetric Cyclization of α-Amino Acid Derivatives with KOH/DMSO at Ambient Temperature[a]



entry	substrate	n	R	X	time[b] (h)	product	yield(%)	ee[c] (%)
1	**4**	2	$PhCH_2$	Br	2	**5**	82	99 (*R*) [95[d]]
2	**6**	2	Me_2CH	Br	3	**7**	79	99
3	**8**	2	$MeSCH_2CH_2$	Br	1	**9**	85	99 (*S*) [97[e]]
4	**1**	3	$PhCH_2$	Br	2	**2**	91	99 (*S*) [98[d]]
5	**10**	3	Me_2CH	Br	2	**11**	94	98 [94[d]]
6	**12**	3	$MeSCH_2CH_2$	Br	2	**13**	91	98 (*S*) [97[d]]
7	**14**	4	$PhCH_2$	Br	12	**15**	73	90 [97[d]]
8	**16**	4	Me_2CH	Br	17	**17**	74	94
9	**18**	4	$MeSCH_2CH_2$	Br	4	**19**	86	88
10	**20**	4	$PhCH_2$	I	2	**15**	97	97
11	**21**	4	Me_2CH	I	8	**17**	90	98
12	**22**	4	$MeSCH_2CH_2$	I	3	**19**	89	97

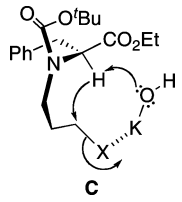
[a] A mixture of a substrate (0.25 mmol) and powdered KOH (prepared from 85% commercial KOH pellets from Nacalai Tesque, 0.75 mmol) in dry DMSO (anhydrous DMSO (H_2O < 0.005%) from Aldrich, 2.5 mL) was stirred vigorously at 20 °C for the time indicated in the table. [b] Time required for the consumption of the starting material checked by TLC. [c] ee of the corresponding *N*-benzoate determined by HPLC analysis. A letter in the parenthesis indicates the absolute configuration. For the determination of the absolute configuration, see refs 3i and 4c. Numbers in the brackets indicate percent ee of the product obtained by the reaction with KHMDS in DMF at −60 °C. [d] Data quoted from ref 4c. [e] Data quoted from reference 3i.

Scheme 3. Asymmetric Synthesis of Fmoc-Cyclic Amino Acid **25**



ization (vide infra). In contrast to the four- and five-membered cyclization, six-membered cyclization of **14** with KOH/DMSO at 20 °C gave piperidine **15** with enantioselectivity lower than that observed in the reaction of **14** with KHMDS in DMF at −60 °C (entry 7). The enantioselectivity (88∼94% ee) observed in the six-membered cyclization of bromides **14**, **16**, and **18** (entries 7−9) was improved by use of the corresponding iodides. Treatment of **20**, **21**, and **22** with KOH/DMSO for 2−8 h at 20 °C gave piperidines **15**, **17**, and **19**, respectively, in 97∼98% ee and 89∼97% yield (entries 10−12). An increase in enantioselectivity of cyclization of the iodides could be ascribed to their inreased rates of cyclization. The similar effects of leaving groups on asymmetric alkylation via memory of chirality have been reported by Carlier and co-workers.[9] This protocol was applied to the medium-scale synthesis of Fmoc-cyclic amino acid **25**, which is expected to be a useful building block for conformationally restricted peptides of biological interest (Scheme 3).[10] Isoleucine derivative **23** (17 mmol) was treated with KOH/DMSO[11] at 20 °C for 2 h to give **24** as a single diastereomer in 94% yield, which was then converted into **25** in 53% yield.

We then investigated the mechanistic aspects of asymmetric cyclization promoted by KOH/DMSO.[12] We previously proposed that axially chiral enolate **A** (X = Br) is the key intermediate for asymmetric cyclization with KHMDS in DMF.[4c] Whereas a mechanism via intermediate **A** is also expected for asymmetric cyclization with KOH/DMSO, an alternative route may involve a concerted S_Ei process, as shown in **C**. To investigate the validity of **A** and **C**, cyclization of **26** with two identical substituents on the nitrogen was examined because the enolate generated from **26** cannot be axially chiral along the C−N axis (Scheme 4). Treatment of **26** with KOH/DMSO at 20 °C for 5 h gave racemic **27** in 27% yield together with 44% recovery of **26**. This indicates that asymmetric cyclization with KOH/DMSO also proceeds via axially chiral enolate intermediate **A**.

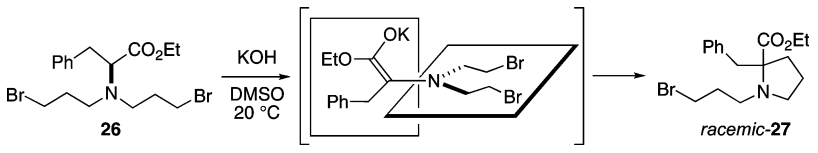


C

The racemization behavior of **A** was investigated next. We previously determined the barrier to racemization of the axially chiral enolate **B** by periodic quenching of the enolate with methyl iodide (Scheme 2).[4a] However, this protocol cannot be applied to enolate **A** because it undergoes cyclization immediately after it is generated. **28**, an analogue of **1**, was used to estimate the racemization barrier of the axially chiral enolate **A** because the enolate **C** generated from **28** would not undergo cyclization (Figure 1). The barrier to racemization of a potassium enolate generated from **28** and KHMDS in DMF−THF (1:1) at −78 °C was determined through the periodic quenching of the enolate with methyl iodide.[13] Experiments were performed twice at the strictly controlled temperature. The decrease in ee ($\ln ee^0/ee^t$) as a function of time for the base treatment of **28** was plotted (Figure 1, ee^0 and each of ee^t are the average of two runs). The barrier was calculated from the slope, $2k = 1.99 \times 10^{-3}$ min^{-1} ($r = 0.995$), to be 15.5 kcal/mol at −78 °C. On the basis of the assumption that asymmetric cyclization of **1** with KOH/DMSO proceeds via enolate **A** (X = Br, $n = 3$) whose racemization barrier is comparable to **C**, enolate **A** is expected to undergo cyclization at 20 °C within $\sim 10^{-3}$ sec after it is generated to give product **2** in 99% ee ($t_{99/100}$ at 20 °C = 3.0×10^{-4} sec, calculated from $\Delta G^{\ddagger}$ (15.5 kcal/mol)).[6] Because the asymmetric cyclization reactions in Table 2 are also assumed to proceed via axially chiral enolates **A**, enolates generated with KOH/DMSO in these reactions are expected to undergo rapid cyclization within $\sim 10^{-2}$ sec at 20 °C to give products in ≥88% ee ($t_{88/100}$ at 20 °C = 3.8×10^{-3} sec, calculated from $\Delta G^{\ddagger}$ (15.5 kcal/mol)).[6] The extremely high reactivity of the enolates generated with KOH/DMSO could be ascribed to their amine-free structure.[14,15]

Another interesting observation in asymmetric cyclization with KOH/DMSO is that the four-membered cyclization pro-

Scheme 4. Cyclization of **26** with Powdered KOH in DMSO via an Achiral Enolate Intermediate



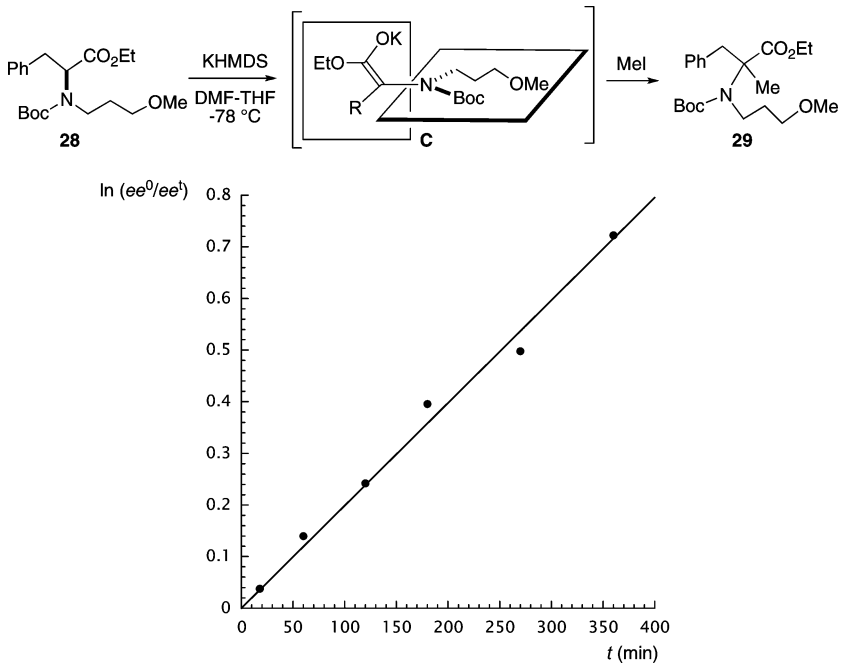


Figure 1. Plot of ln (ee^0/ee^t) versus time (t) for the base treatment of **28**. ee^0 = the ee value of **29** obtained by the reaction of the enolate immediately after its generation from **28** and KHMDS with methyl iodide. ee^t = the ee value of **29** obtained by the treatment of **28** with KHMDS for the time indicated followed by addition of methyl iodide. Experiments were performed twice at the strictly controlled temperature. ee^0 and each of ee^t are the average of two runs. The barrier to racemization was determined to be 15.5 kcal/mol at −78 °C from the slope, $2k = 1.99 \times 10^{-3}$ min^{-1} ($r = 0.995$). See the Supporting Information for the experimental detail for the determination of the racemization barrier.

ceeds faster than the six-membered one. This tendency was generally observed in the asymmetric cyclization of amino acid derivatives prepared from phenylalanine, valine, and methionine (Table 2, entries 1−3 vs 7−9). As a typical example, the progress of the four-membered cyclization of **4** and six-membered cyclization of **14** was monitored (Figure 2). The four-membered cyclization of **4** was 2∼3 times faster than the six-membered cyclization of **14**. The rate-determining step for the cyclization with KOH/DMSO must be the enolate-formation step because the half-lives of racemization of the chiral enolate intermediates generated from **4** and **14** are supposed to be much

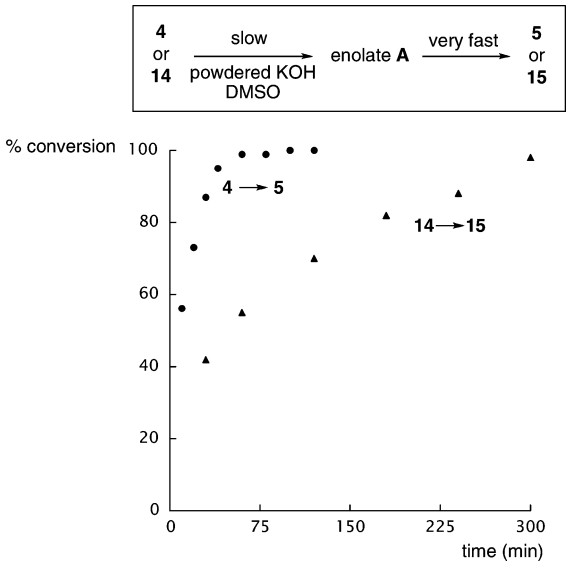


Figure 2. Plot of percent conversion of four-membered cyclization of **4** and six-membered cyclization of **14** versus time (min).

shorter (<0.1 s)[16] than the time required for the reactions to be complete (2∼12 h). Thus, axially chiral enolates **A** (X = Br, n = 2 or 4) would form gradually, and once formed, would immediately undergo asymmetric cyclization. Because enolates **A** suffer from time-dependent racemization, ee's of the products would correlate with the rate of cyclization of enolate intermediates; that is, the faster the cyclization, the higher the enantioselectivity. On the basis of this assumption, the four-membered cyclization of enolates **A** (X = Br, n = 2) (99% ee, Table 2, entries 1−3) is expected to proceed faster than the corresponding six-membered cyclization of enolates **A** (X = Br, n = 4) (∼88−

(9) (a) MacQuarrie-Hunter, S.; Carlier, P. R. *Org. Lett*. **2005**, *7*, 5305−5308. (b) Carlier, P. R.; Lam, P. C.-H.; DeGuzman, J. C.; Zhao, H. *Tetrahedron: Asymmetry* **2005**, *16*, 2998−3002.

(10) For recent reviews on the importance and preparation of cyclic amino acids with a tetrasubstituted stereocenter, see (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.

(11) Commercial (not dry) DMSO was used without further purification.

(12) One might suppose that the active base in these reactions is a dimsyl anion generated in a small quantity from KOH and DMSO (pKa's of H_2O and DMSO in DMSO are 31 and 35, respectively; ref 7). However, this seems not feasible because the dimsyl anion prepared from KH in DMSO showed a different reactivity in the reaction of **1**. Treatment of **1** with 3.0 mol equiv of potassium dimsylate in DMSO at 20 °C for 2 h gave **2** in 99% ee and 68% yield together with the corresponding carboxylic acid of **2** in 25% yield.

(13) Whereas determination of the racemization barrier of the enolate generated from **28** with KOH/DMSO is desirable, it was not possible. This is because (1) KOH/DMSO cannot be used at low temperatures suitable for the measurement of enolate racemization, and (2) KOH/DMSO cannot generate the enolate from **28** in a quantitative manner. Quantitative generation of the enolate in a much shorter period than the half-life of racemization of the enolate is indispensable for the measurement of the racemization barrier.

(14) Amine-free lithium enolates have been known to be more reactive than the enolates in the presence of a secondary amine generated in situ by abstraction of the α proton of the carbonyl group with the lithium amide base; see (a) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta*. **1985**, *68*, 1373−1393. (b) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390−5398. (c) Aebi, J. D.; Seebach, D. *Helv. Chim. Acta*. **1985**, *68*, 1507−1518.

(15) We suppose that a water molecule generated by deprotonation of the substrate with KOH may be excluded from the coordination sphere of the potassium enolate by strongly coordinating DMSO molecules.

(16) $T_{50/100}$ was roughly estimated to be 0.02 sec at 20 °C based on the racemization barrier of **C** (15.5 kcal/mol).

94% ee, Table 2, entries 7−9). Accordingly, enantioselectivities would provide a measure of the rate of cyclization of the enolate intermediates,[17] whereas the reaction time for asymmetric cyclization depends on the rate of enolate formation.[18] Higher enantioselectivity observed in the cyclization of the iodides than the corresponding bromide (Table 2, entries 7−12) is also consistent with expected higher rates of cyclization of the iodides.

In conclusion, we have developed a highly enantioselective cyclization via memory of chirality at ambient temperature. Powdered KOH in DMSO was an effective base for this purpose. Although KOH in DMSO has been used in C−O, C−N, and C−S bond formation,[19] its use in stereoselective C−C bond formation has been limited.[20] We expect that powdered KOH in DMSO would be further applicable in enolate chemistry for fine organic synthesis because it generates highly reactive enolates under mild conditions and by simple operations.

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Supporting Information Available: An experimental procedure in Table 2. Preparation of **6**, **20**, **25**−**27**, and **29**. Chracterization of **3**, **6**, **7**, and **16**−**29**. Experimental procedure for the determination of the racemization barrier of the enolate generated from **28** and KHMDS in DMF−THF (1:1) at −78 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For an additional example, seven-membered cyclization of a substrate derived from L-phenylalanine gave the product in 49% ee (25% yield) by treatment with powdered KOH in dry DMSO at 20 °C for 2 h.

(18) The rates of enolate formation from the substrates undergoing four-membered cyclization are assumed faster than those undergoing six-membered cyclization. Reasons are totally unclear. A possible explanation might be due to the slight increase in the acidity of α proton in the former substrates caused by the inductive effect of the bromo group at the *N*-2-bromoethyl substituent or due to the favorable delivery of OH^- via chelation of K^+ with the bromo group.

(19) For examples, see: (a) Pang, Y.-P.; Hong, F.; Quiram, P.; Jelacic, T.; Brimijoin, S. *J. Chem. Soc., Perkin Trans 1* **1997**, 171−176. (b) Chapman, D. R.; Reed, C. A. *Tetrahedron Lett.* **1988**, *29*, 3033−3036. (c) Goswami, B. N.; Rastogi, R. C. *Ind. J. Chem. B.* **1992**, *31B*, 703−704. (d) Ensch, C.; Hesse, M. *Helv. Chim. Acta*. **2002**, *85*, 1659−1673. (e) Andreeva, O. V.; Militsina, O. I.; Kovylyaeva, G. I.; Korochkina, M. G.; Strobykina, I. Y.; Bakaleinik, G. A.; Al'fonsov, V. A.; Kataev, V. E.; Musin, R. Z. *Russ. J. Gen. Chem.* **2007**, *77*, 469−473.

(20) For an example, see, Dechoux, L.; Ebel, M.; Jung, L.; Stambach, J. F. *Tetrahedron Lett.* **1993**, *34*, 7405−7408.