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Communication

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Asymmetric Induction via Short-Lived Chiral Enolates with a Chiral C-O Axis

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Supporting Information Placeholder

ABSTRACT: A novel method for the asymmetric cyclization of alkyl aryl ethers has been developed. The reactions were assumed to proceed via short-lived chiral enolate intermediates with a chiral C-O axis to give cyclic ethers with tetrasubstituted carbon in up to 99% ee. The half-life of racemization of the chiral enolate intermediate was roughly estimated to be ~1 sec at –78 °C.

We have been interested in asymmetric reactions that proceed via enolate intermediates with intrinsic axial chirality.[1,2] In 1991, we developed an asymmetric induction via enolate intermediate **A** with a chiral C-C axis (Figure 1a).[3] The half-life of racemization of the axially chiral enolate **A** at the reaction temperature (–20 °C) was estimated to be ~24 days based on the racemization behavior of the corresponding enol methyl ether **1**.[2b,3] In 2000, we developed an asymmetric induction via enolate intermediate **B** with a chiral C-N axis (Figure 1b).[1a] The half-life of racemization of the axially chiral enolate **B** at the reaction temperature (–78 °C) was determined to be 22 h based on a measurement of the time-dependent

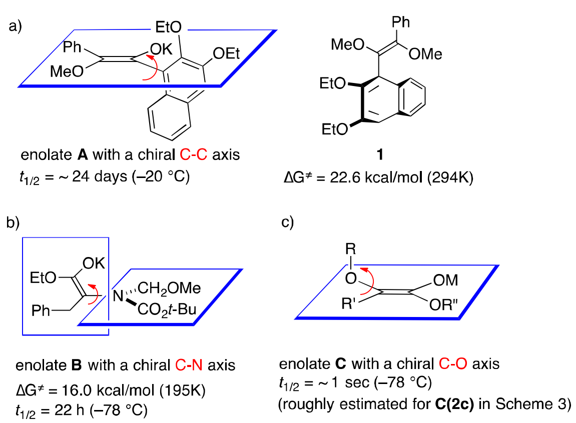
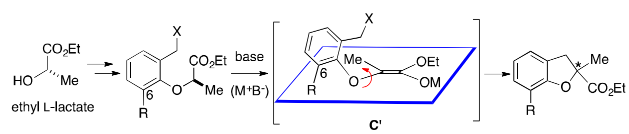


Figure 1. Enolates with a) a chiral C-C axis, **A**, b) a chiral C-N axis, **B**, and c) a chiral C-O axis, **C** (this work), respectively, as intermediates for asymmetric reactions.

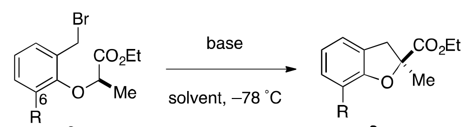
racemization of enolate **B**. Enolates **A** and **B** have sufficient configurational stability for the asymmetric reactions to take place at the reaction temperatures before they undergo significant racemization. On the other hand, asymmetric induction via chiral enolate intermediates with a chiral C-O axis such as **C** (Figure 1c) was expected to be difficult because of their extremely short half-lives of racemization. Here, we report the first example of asymmetric induction via short-lived chiral enolate intermediates with a chiral C-O axis.[4]

Scheme 1. Strategy for Asymmetric Alkylation via Chiral Enolates with a Chiral C-O Axis



To realize asymmetric induction via rapidly racemizing chiral enolates with a chiral C-O axis, we chose the five-membered cyclization of chiral alkyl aryl ethers (Scheme 1), in which the chiral enolate intermediate is expected to undergo intramolecular alkylation immediately after it is generated. We anticipated that the choice of the R group at C(6) might be critical for the asymmetric induction, since this could increase the rotational barrier around the chiral C-O axis.[5] We initiated the study with alkyl aryl ethers **2** (Table 1). Substrates **2** were readily prepared in optically pure form from readily available and inexpensive L-ethyl lactate and the corresponding phenols by Mitsunobu etherification. Treatment of **2a** (R=H) with potassium hexamethyldisilazide (KHMDS) in THF at –78 ˚C gave **3a** (R=H) in 61% yield as a racemate (Table 1, entry 1). Other conditions that used various bases (KHMDS, NaHMDS, and LiHMDS) and solvents (DMF and toluene) also gave **3a** as a racemate (data not shown). We then investigated substrates **2** with a substituent (R≠H) at C(6). Treatment of **2b** (R=Me) with KHMDS in THF at –78 ˚C gave **3b** in 62% yield and 56% ee (entry 2). The reaction in toluene or DMF/THF (2:1) resulted in a decrease in ee (28% ee) or both ee and yield (38% ee, 38% yield), respectively (entries 3 and 4). While the asymmetric cyclization of **2b** with LiHMDS in THF resulted in the recovery of **2b** (entry 5), that with NaHMDS gave **3b** in 66% yield and 84% ee (entry 6). The corresponding reaction at –90 ˚C slightly improved the ee (87% ee), but diminished the yield (37%, entry 7).[6] Treatment of **2c** (R=*i*-Pr) with NaHMDS in THF at –78 ˚C gave **3c** in 82% yield and 99% ee (Table 1, entry 8). These results indicated that the bulkiness of the substituent R at C(6) critically affects the efficiency of the asymmetric cyclization. Asymmetric cyclization of **2d** (R=$SiMe_3$) and **2e** (R=Ph) proceeded in a highly enantioselective manner to give **3d** in 97% ee (70% yield) and **3e** in 94% ee (60% yield), respectively (entries 9 and 10). Substrate **2f** (R=Br) underwent asymmetric cyclization with high enantioselectivity (96% ee), but in a low yield (20%) (entry 11). Although dihydrobenzofuran **3a** (R=H) was obtained as a racemate by the present method, it could be alternatively obtained in 97% ee by protodesilylation of **3d** (Scheme 2). Similarly, **3f** was obtained in an acceptable yield by

Table 1. Asymmetric Five-Membered Cyclization of Alkyl Aryl Ethers 2[a]

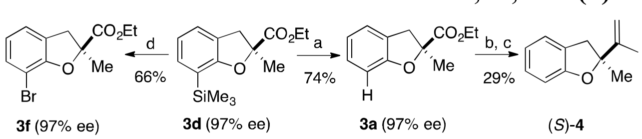


2 3

entry	substrate: R	base,[b] solvent	product, yield (%)	ee (%)[c], abs. config[d]
1	**2a**: H	KHMDS, THF	**3a**, 61	0
2	**2b**: Me	KHMDS, THF	**3b**, 62	56, *S*
3	**2b**: Me	KHMDS, toluene	**3b**, 60	28, *S*
4	**2b**: Me	KHMDS, DMF/THF (2:1)	**3b**, 38	38, *S*
5	**2b**: Me	LiHMDS, THF	**3b**, trace	–[e], –[e]
6	**2b**: Me	NaHMDS, THF	**3b**, 66	84, *S*
7[f]	**2b**: Me	NaHMDS, THF	**3b**, 37	87, *S*
8	**2c**: *i*-Pr	NaHMDS, THF	**3c**, 82	99, *S*
9	**2d**: Me_3Si	NaHMDS, THF	**3d**, 70	97, *S*
10	**2e**: Ph	NaHMDS, THF	**3e**, 60	94, –[e]
11	**2f**: Br	NaHMDS, THF	**3f**, 20	96, *S*

[a] Reactions were run at a substrate concentration of 0.1 M. [b] 1.1~2.0 Equivalents of the base was used. For the experimental details, see Supporting Information. [c] Ee's were determined by HPLC analysis with a chiral stationary phase; see Supporting Information. [d] The absolute configuration of **3d** was determined by chemical correlation with known compound (*S*)-**4**. The absolute configurations of **3b**, **3c** and **3f** were deduced based on their CD spectra. See Supporting Information. [e] Not determined. [f] Run at –90 ˚C.

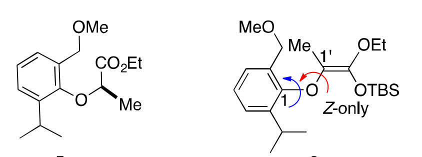
Scheme 2. Transformation of 3d into 3a, 3f, and (*S*)-4



a) TFA, CH_2Cl_2, 0 °C: b) MeMgI, Et_2O, (61%): c) $POCl_3$, pyridine (48%): d) $Me_3BnN^+Br_3^-$, $ZnCl_2$, AcOH, rt

the bromodesilylation of **3d**. The absolute configuration of **3d** was determined to be *S* by its chemical correlation with (*S*)-**4** (Scheme 2).[7] Dihydrobenzofuran **4** prepared from **3d** showed, $[\alpha]_D^{20} = -78$ (*c* 0.15, $CHCl_3$) {lit[7] (*S*)-**4**: $[\alpha]_D^{20} = -83$ (*c* 0.23, $CHCl_3$)}. The absolute configurations of **3b**, **3c**, and **3f** were deduced to be *S* by the comparison of their CD spectra with that of **3d**. These results indicate that the present five-membered cyclization proceeded with retention of configuration.

To gain insights into the mechanism of asymmetric induction, the racemization behavior of the supposed chiral enolate **C'** (Scheme 1) was investigated. We previously determined the barrier for the racemization of axially chiral enolate **B** (Figure 1b) by periodic quenching of the chiral enolate with methyl iodide.[1a,d] However, this protocol cannot be applied to enolate **C'** because it would undergo cyclization immediately after it is generated. Silyl ketene acetal **6** was used as an enolate equivalent to estimate the rotational barrier of the C-O bond as a measure of the racemization barrier of chiral enolate **C'**. Compound **5**, which has a methoxy group instead of a bromo group in **2c**, was chosen as the precursor because its enolate does not undergo cyclization, and instead, could be trapped as a silyl ketene acetal. Compound **5** was treated under conditions identical to those for the asymmetric cyclization of **2c** (entry 8 of Table 1) except for the presence of TBSOTf, to give *Z*-**6** in 79% yield. The formation of only *Z*-isomer (as determined from NOESY spectra) indicates that the enolate also has a *Z*-geometry. The two methyl groups of the isopropyl-groups of *Z*-**6** appeared as two doublets in its ^1H NMR spectrum measured at –90 °C in d_8-toluene, which suggested restricted rotation around the C-O bond. The rotational barrier was determined to be 11.5 kcal/mol by VNMR measurement {$\Delta\nu$ (28.6 Hz) and the coalescence temperature (–42 ˚C)}. It is not clear whether the rotational barrier in **6** corresponds to the rotation around the C(1')-O bond (red curved arrow) or the C(1)-O bond (blue curved arrow). However, the restricted rotation around the C-O axis in **C'** must be the origin of the present asymmetric induction because it is the only chiral element in enolate **C'**. The half-life of racemization of chiral enolate **C'** is roughly estimated to be ~1 sec at –78 ˚C, based on the assumption that the racemization barrier of chiral enolate **C'** is comparable to the rotational barrier of the C-O bond of **6**, and that $\Delta S^{\neq}$ of the unimolecular process for bond rotation is nearly zero.[8]



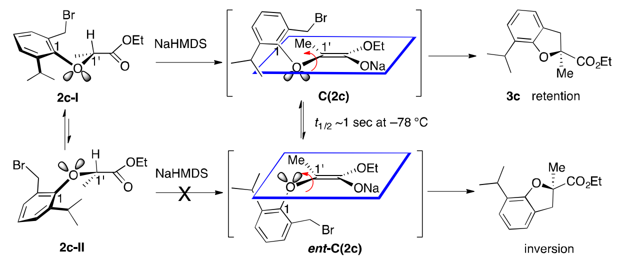
5 6

$G^{\ddagger}$ = 11.5 kcal/mol (231 K)

Figure 2. Rotational barriers of the C-O bond of silyl ketene acetals **6** and its precursor **5**.

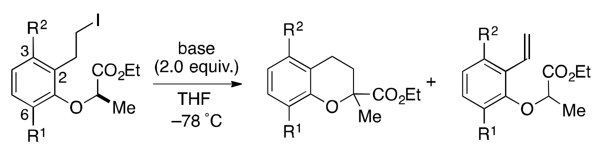
A hypothetical model for asymmetric cyclization of **2c** is shown in Scheme 3. Deprotonation of conformer **2c-I** would give enantiomerically enriched enolate **C(2c)** with a chiral C-O axis,[9] which would give **3c** with retention of configuration. On the other hand, deprotonation of conformer **2c-II** would give the product with inversion of configuration via enolate ***ent*-C(2c)**. Although deprotonation of conformer **2c-II** seems more accessible due to the steric reasons, preferential deprotonation of conformer **2c-I** might be ascribed to the conformational preference of **2c-I** over **2c-II**[10] and/or a chelating effect (CH_2Br–NaOC(OEt)=C) in the deprotonation step from **2c-I**.[11] The chiral enolate **C(2c)** is assumed to undergo intramolecular alkylation immediately after it is generated to minimize its own racemization. This merely provides hypothetical understanding without experimental proof.

Scheme 3. A Hypothetical Model for the Asymmetric Cyclization of 2c



Asymmetric six-membered cyclization was examined. According to the results of asymmetric five-membered cyclization (Table 1, entries 6 and 8), **7b** (R^1=Me) was treated under the optimum conditions for five-membered cyclization (NaHMDS in THF at –78 ˚C, Table 1, entry 8) to give **9b** as the only detectable product in 86% yield via the β-elimination of hydrogen iodide (Table 2, entry 2). The use of KHMDS gave dihydrobenzopyran **8b** via six-membered cyclization in 40% yield as a racemate together with **9b** in 24% yield (entry 3). Racemic **8c** (R^1=*i*-Pr) was also obtained by treatment of **7c** with KHMDS in 17% yield, along with the concomitant formation of **9c** in 54% yield (entry 4). The formation of racemic products in the six-membered cyclization under the conditions for the highly enantioselective five-membered cyclization indicates that the six-membered cyclization proceeds slower than the corresponding five-membered cyclization (Table 2, entries 3 and 4 *vs.* Table 1, entries 2, 6, and 8) (A similar tendency was observed for the relative rates of the five- *vs.* six-membered cyclization of axially chiral enolates with a chiral C-N axis. See reference 1d). We then examined substrate **7d**, and anticipated that the introduction of an additional substituent at C(3) would increase the rate of six-membered cyclization by a buttressing effect.[12] The reaction of **7d** possessing two methyl substituents at C(6) and C(3) with NaHMDS gave **8d** in 15% yield and 52% ee and **9d** in 16% yield (entry 5). Although the use of KHMDS as a base gave racemic **8d** in 35% yield, the use of LDA gave **8d** via six-membered cyclization in 77% yield and 43% ee (entry 7). The substituents at C(6) and C(3) were further examined. Treatment of **7e** bearing an isopropyl group at C(6) and a methyl group at C(3) with LDA gave **8e** in 74% ee and 88% yield without formation of the product from β-elimination (entry 8). With the use of a bulky base, TMS(*t*-Bu)NLi,[13] **8e** was obtained from **7e** in 85% ee and 66% yield (entry9). Treatment of **7f** possessing a methyl group at C(6) and an isopropyl group at C(3) with TMS(*t*-Bu)NLi gave **8f** in 66% ee (entry 10). The best result was obtained in the

Table 2. Asymmetric Six-Membered Cyclization of Aryl Alkyl Ether[a]



7 **8** **9**

entry	substrate: R^1, R^2	base	product **8** (% yield)	% ee of **8**[b,c]	product **9** (% yield)
1	**7a** : H, H	NaHMDS	**8a** (27)	0	**9a** (39)
2	**7b** : Me, H	NaHMDS	**8b** (~0)	–	**9b** (86)
3	**7b** : Me, H	KHMDS	**8b** (40)	0	**9b** (24)
4	**7c** : *i*-Pr, H	KHMDS	**8c** (17)	0	**9c** (54)
5	**7d** : Me, Me	NaHMDS	**8d** (15)	52	**9d** (16)
6	**7d** : Me, Me	KHMDS	**8d** (35)	0	**9d** (27)
7	**7d** : Me, Me	LDA	**8d** (77)	43	**9d** (~0)
8	**7e** : *i*-Pr, Me	LDA	**8e** (88)	74	**9e** (~0)
9	**7e** : *i*-Pr, Me	TMS(*t*-Bu)NLi	**8e** (66)	85	**9e** (~0)
10	**7f** : Me, *i*-Pr	TMS(*t*-Bu)NLi	**8f** (44)	66	**9f** (~0)
11	**7g** : *t*-Bu, Me	TMS(*t*-Bu)NLi	**8g** (89)	91	**9g** (~0)

[a] Reactions were run at a substrate concentration of 0.1 M. [b] Ee's were determined by HPLC analysis with a chiral stationary phase; see Supporting Information. [c] The absolute configuration of **8e** was determined to be *R* by the PGME method. See Supporting Information. The absolute configurations of **8d**, **8f**, and **8g** were not determined.

asymmetric cyclization of substrate **7g** possessing a *tert*-butyl group at C(6) and a methyl group at C(3) (entry 11). Treatment of **7g** with TMS(*t*-Bu)NLi in THF at –78 ˚C gave **8g** in 91% ee and 89% yield without formation of the product from β-elimination. These results indicate that both a bulky substituent at C(6) and an additional substituent at C(3) are indispensible for highly enantioselective six-membered cyclization. The absolute configuration of **8e** was determined to be *R* by the PGME method[14] (see Supporting Information). This indicates that the six-membered cyclization of **7e** proceeds with inversion of configuration.

In conclusion, we have developed a novel method for asymmetric synthesis via short-lived axially chiral enolates based on the restricted rotation of the C-O bond. This method provides a unique entry to chiral cyclic ethers with a tetrasubstituted chiral center. These compounds were prepared via asymmetric C-C bond formation by the present method, while they have usually been constructed via asymmetric C-O bond formation.[15] Readily available and abundant L-ethyl lactate is used not only as a functionalized carbon resource but also as a chiral source for the construction of chiral benzofuran and chroman derivatives with tetrasubstituted carbon, which frequently appear in biologically active products.[16,17]

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic data for all new compounds. Variable-temperature NMR of **6**. This material is available free of charge via Internet at http://pubs.acs.org.

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(8) The racemization barrier of the chiral sodium enolate derived from **2c** could be quite different from the rotational barrier of **6** because of the aggregation of the sodium enolate. However, we previously observed that the racemization barrier of a chiral potassium enolate with a C-N axis generated from an amino acid derivative, which was determined experimentally by periodic quenching of the enolate, was found to be comparable with the rotational barrier of the C-N axis of the the corresponding silyl ketene acetal, which was determined by VNMR measurement. See reference 1a.

(9) Chiral enolate structure **C(2c)** based on the restricted rotation of the C(1')-O bond was shown tentatively. While that based on the restricted rotation of the C(1)-O bond cannot to be excluded, we prefer the former because asymmetric cyclization of **2** either with a smaller (Me) or a larger (Me_3Si) substituent at C(6) than CH_2Br at C(2) gave the product with the same absolute configuration (Table 1).

(10) A conformational search for **2c** was performed by a molecular modeling search (MCMM 50,000 steps) with an OPLS 2005 force field using MacroModel (V. 9.0). Conformer **2c-II** was suggested to be 5.8 kcal/mol less stable than the most stable conformer **2c-I**. For details, see Supporting Information.

(11) The importance of the chelation may be suggested by the decrease in the enantioselectivity of the asymmetric cyclization of **2b** in the presence of 15-crown-5. Treatment of **2b** under the conditions identical to those in entry 6 of Table 1, except for the addition of 15-crown-5 (3.0 equivalents), gave **3b** in 30% ee and 72% yield. The similar chelating effect affecting stereochemistry of enolate alkylation was reported. See: Willimas, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, 110, 5927-5929.

(12) The electrophilic center (C(2)-CH_2-$\underline{C}H_2$-I) of the chiral enolates generated from **7d-g** may be in close proximity to the nucleophilic enolate moiety due to the buttressing effect of the substituent at C(3), which facilitates intramolecular alkylation before complete racemization of the chiral enolate takes place. For the detailed discussion, see Supporting Information (Scheme SI-1). The rate acceleration by the buttressing effect of the ortho substituent in carbene C-H insertion has been reported. See: Tomioka, H.; Kimoto, K.; Murata, H.; Izawa, Y. *J. C. S. Perkin I*, **1991**, 471-477.

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