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Chirality transfer during alkylation of chiral amides

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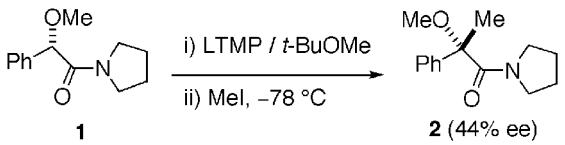
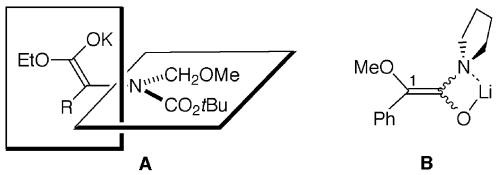
Chiral amides derived from *O*-methyl mandelic acid and achiral amines underwent enantioselective α-methylation on treatment with LTMP followed by addition of methyl iodide; chirality transfer from an undeprotonated chiral amide into an achiral enolate in a mixed aggregate is supposed to be responsible for the asymmetric induction.

Asymmetric synthesis has been extremely developed during the last few decades and it is a mature area of science.[1] Development of a conceptually novel method for asymmetric induction, however, is still of great importance. Seebach and Wasmuth have reported a pioneering work for enantioselective α-alkylation of an aspartic acid derivative, and proposed a mechanism involving a mixed aggregate of enolates.[2] We have reported a novel method for enantioselective α-alkylation of α-amino acid derivatives which proceeds *via* chiral nonracemic enolates (**A**) with dynamic axial chirality.[3–5] In the course of further study on asymmetric synthesis *via* enolate intermediates, we found an unprecedented asymmetric induction in alkylation of chiral amides derived from (*S*)-*O*-methyl mandelic acid and achiral amines (Scheme 1). We describe here the preliminary results and a possible mechanism for the asymmetric induction.



1 **2** (44% ee)

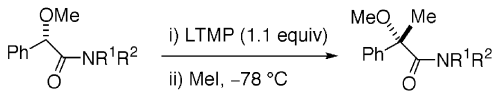
Scheme 1



Amide **1** was readily prepared by condensation of (*S*)-*O*-methyl mandelic acid and pyrrolidine in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide in 82% yield. Treatment of **1** with 1.1 equivalents of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in *tert*-butyl methyl ether[6] at −78 °C followed by addition of methyl iodide gave *nonracemic* product **2** (44% ee) in 34% yield with 54% recovery of **1**. It was surprising for us that asymmetric induction appears to occur *via* enolate intermediate **B** that does not possess any elements of chirality.[7]

To investigate the structural requirements of substrates to cause asymmetric induction, several amides were prepared from (*S*)-*O*-methyl mandelic acid and achiral amines, and their α-methylation was examined (Table 1). Piperidine amide **3** underwent α-methylation in 41% ee by the same treatment as that for **1** (entry 1). *N*,*N*-Dimethylamide **5**, *N*,*N*-diethylamide **7**, and *N*,*N*-dibutylamide **11** gave α-methylated products in 44, 37 and 56% ee, respectively, by the similar treatment (entries 2, 3, and 5). *N*,*N*-Dibenzylamide **9** showed exceptionally low enantioselectivity (9% ee) on α-methylation (entry 4). The enantioselectivity of α-methylation was found to be highly solvent-dependent.[6] While use of THF as a solvent resulted in the formation of racemic α-methylated product **12** (entry 7), use

Table 1 Asymmetric methylation of amides derived from *O*-methyl mandelic acid and achiral amines[a]



Entry	Substrate	R^1	R^2	Solvent	Product	Yield[b] (%)	Ee[c] (%)	Abs. confg.
1	**3**	$-(CH_2)_5-$		*t*-BuOMe	**4**	28 (82)	41	*S*
2	**5**	Me	Me	*t*-BuOMe	**6**	27 (68)	44	*S*
3	**7**	Et	Et	*t*-BuOMe	**8**	31 (74)	37	[d]
4	**9**	CH_2Ph	CH_2Ph	*t*-BuOMe	**10**	22 (50)	9	[d]
5	**11**	*n*-Bu	*n*-Bu	*t*-BuOMe	**12**	25 (71)	56	*S*
6[e]	**11**	*n*-Bu	*n*-Bu	*t*-BuOMe	**12**	25 (44)	49	*S*
7	**11**	*n*-Bu	*n*-Bu	THF	**12**	72 (95)	~0	—
8	**11**	*n*-Bu	*n*-Bu	CPME[f]	**12**	30 (90)	64	*S*
9[g]	**11**	*n*-Bu	*n*-Bu	CPME[f]	**12**	49 (79)	33	*S*
10	**13**	*n*-Bu	Me	CPME[f]	**14**	20 (34)	62	*S*
11	**13**	*n*-Bu	Me	THF	**14**	20 (35)	~0	—
12[h]	**15**	*t*-Bu	H	*t*-BuOMe	**16**	17 (39)	14	[d]

[a] *Typical procedure*: *n*-BuLi (1.49 M in hexane, 0.37 mL, 0.55 mmol) was added to a solution of TMP (101 μL, 0.60 mmol) in 3.5 mL of dry *t*-butyl methyl ether at 0 °C, and the mixture was stirred for 10 min. After cooling to −78 °C, a solution of a substrate (0.5 mmol) in 1.5 mL of *tert*-butyl methyl ether was added dropwise. After stirring for 10 min, methyl iodide (0.31 mL, 5.0 mmol) was added and the resulting mixture was stirred at −78 °C for 20 h. [b] Numbers in parentheses indicate yields based on the recovered substrate. [c] Determined by HPLC analysis with chiral stationary phases: **2**: Chiralpak AD, 2% *i*-PrOH–hexane; **4**: Chiralcel OD, 1% *i*-PrOH–hexane; **6**: Chiralpak AD, 1% *i*-PrOH–hexane; **8**: Chiralpak AD, 1% *i*-PrOH–hexane; **10**: Chiralpak AD, 5% *i*-PrOH–hexane; **12**: Chiralcel OJ-R, 70% MeOH–H_2O; **14**: Chiralcel OJ-R, 70% MeOH–H_2O; **16**: Chiralpak AD, 2% *i*-PrOH–hexane. [d] Not determined. [e] 2.2 Mol equivalents of LTMP were used. [f] Cyclopentyl methyl ether. [g] Run in the presence of TMEDA (5.0 equiv.). [h] 2.2 Mol equivalents of LTMP were used.

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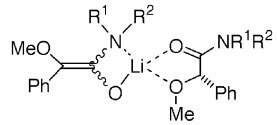
of cyclopentyl methyl ether[8] (CPME) led to the highest asymmetric induction (64% ee, entry 8). Secondary amide **15** also underwent enantioselective α-methylation, albeit with low selectivity (14% ee, entry 12). Thus, any amides derived from (*S*)-*O*-methyl mandelic acid and achiral amines could undergo enantioselective α-methylation when treated with LTMP in *tert*-butyl methyl ether or CPME at −78 °C. *N*,*N*-Dibutylamide **11** and *N*-butyl-*N*-methylamide **13** showed the maximum asymmetric induction among the amides (entries 8 and 10).

Chemical yields of the α-methylation were always low due to the unavoidable recovery (24–67%) of starting materials. Treatment of **11** with 1.1 equivalents of LTMP in *tert*-butyl methyl ether for 10 min followed by addition of CD_3OD gave quantitative recovery of the substrate of 63% ee containing 35% deuterium. This suggests incomplete formation of the enolate under these conditions, provided that internal proton return[9] is not significant. Because loss of the enantiomeric purity (37%) of recovered **11** almost corresponds to the degree of enolate formation (~35% based on the deuterium contents), ee of recovered **11** may be a measure of the enolate formation. In entries 5, 8 and 9 of Table 1, ee's of the recovered **11** were 86, 89 and 90%, respectively, which indicates insufficient enolate formation with 1.1 equivalents of LTMP. Use of 2.2 equivalents of LTMP resulted in the improvement of enolate formation, which is indicated by the ee (29%) of recovered **11**, however, it did not improve the yield of α-methylation (entry 6).[10]

The absolute configuration of **2** was determined to be *S* by comparison of the optical rotation between **2** obtained by the present reaction and (*S*)-**2** independently prepared from (*S*)-*O*-methyl atrolactic acid[11] and pyrrolidine. The absolute configuration of **4**, **6**, **12**, and **14** was also determined to be *S* by a similar manner. Thus, the stereochemical course of the α-methylation was retention in each case.

In order to investigate the mechanism of the present asymmetric induction, a crossover experiment between **3** and **11** was done. Treatment of a 1 : 1 mixture of *rac*-**3** and **11** (> 99% ee) with LTMP (1.1 equivalents of the total amount of **3** and **11**) in *tert*-butyl methyl ether at −78 °C followed by addition of methyl iodide afforded *optically active* **4** (34% ee, 26% yield with 67% recovery) and **12** (49% ee, 25% yield with 59% recovery). Intermolecular chirality transfer was observed during their alkylation. These results strongly indicate that chirality transfer in a mixed aggregate consisting of an achiral enolate with a chiral undeprotonated starting material (**C**) is responsible for the asymmetric induction. Lower enantioselectivity observed in α-methylation in THF (Table 1, entries 7 and 11, ref. 6) or by addition of TMEDA (entries 8 *vs*. 9) is consistent with the proposed mechanism because formation of the mixed aggregate is unfavorable under these conditions. An enantiomerically enriched product yielded during the reaction (such as **12**) was considered as another possible chiral ligand in the mixed aggregate. However, this seems unlikely because the enantioselectivity of alkylation of **11** did not depend on its conversion. Treatment of **11** with 1.1 equivalents of LTMP in CPME at −78 °C for 10 min followed by methyl iodide only for 30 min gave **12** of 67% ee in 7% yield (*cf*. **12** of 64% ee in 25% yield obtained by 20 h-treatment with methyl iodide, entry 8) and recovered starting material of 68% ee in 72% yield.



C

In conclusion, unprecedented asymmetric induction was found in α-methylation of chiral amides derived from optically active *O*-methyl mandelic acid and achiral cyclic, secondary, and primary amines. Chirality transfer by a mixed aggregate mechanism was assumed to be the origin of the asymmetric induction. Further investigation on the generality of the present asymmetric induction is currently underway.

We thank Zeon Corporation (Tokyo, Japan) for a generous gift of CPME.

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5 For asymmetric synthesis based on axial chirality of non-biaryl atropisomers, see: J. Clayden, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 949.

6 Solvent effects on α-methylation of **1** are significant: use of THF or Et_2O led to the production of **2** in 5% ee or 37% ee, respectively.

7 A planar-chiral structure of enolate **B** is possible based on the restricted rotation of the C(1)–OMe bond. However, the barrier of the bond rotation is assumed to be too small to retain chirality even at −78 °C. For an example of the barrier of the related bond rotation, see: M. Nonella, C. Boullais, C. Mioskowski, E. Nabedryk and J. Breton, *J. Phys. Chem. B*, 1999, **103**, 6363.

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10 Several attempts at improving the yield of α-methylation were unsuccessful: *e.g.* prolonged enolate-formation (30–120 min), higher temperature (−60 °C) for enolate formation and/or methylation.

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