

EFFECT OF CROWN ETHER COMPLEXATION ON ASYMMETRIC
INTRAMOLECULAR NUCLEOPHILIC ATTACK

Toshio Wakabayashi* and Yoshinori Kato

Teijin Institute for Biomedical Research

4-3-2 Asahigaoka, Hino, Tokyo 191, Japan

(Received in Japan 16 February 1977; received in UK for publication 2 March 1977)

Although it is well known that crown ether enhances reactivity of a nucleophile in a non-polar solvent,¹ there is no precedent for a reversal of diastereoselectivity of a nucleophilic attack in a presence of crown ether. We recently developed a novel asymmetric intramolecular Michael addition of chiral amidate ion on the double bond of α,β -unsaturated esters.^{2,3,4}

In order to investigate crown ether complexation effect on a stereochemical course of an intramolecular reaction, we chose an asymmetric intramolecular cyclization⁴ of methyl (R)-6- α -methylbenzylaminocarbonylhex-2-enoate (1) with catalytic amount of potassium t-butoxide (KOBu^t) because of the following reasons; (1) The diastereoselectivity of the intramolecular nucleophilic attack of the amidate ion produced by KOBu^t would depend upon medium; (2) The separation of potassium ion from the amidate ion would be achieved by crown ether complexation⁵; (3) The absolute configurations of the cyclization products 2 and 3 have respectively been determined as (S) and (R) at C-6.⁴

Asymmetric cyclization of 1 with catalytic amount of KOBu^t (0.1 equiv. mole) in a non-polar solvent with or without a cation complexing agent, 18-crown-6,

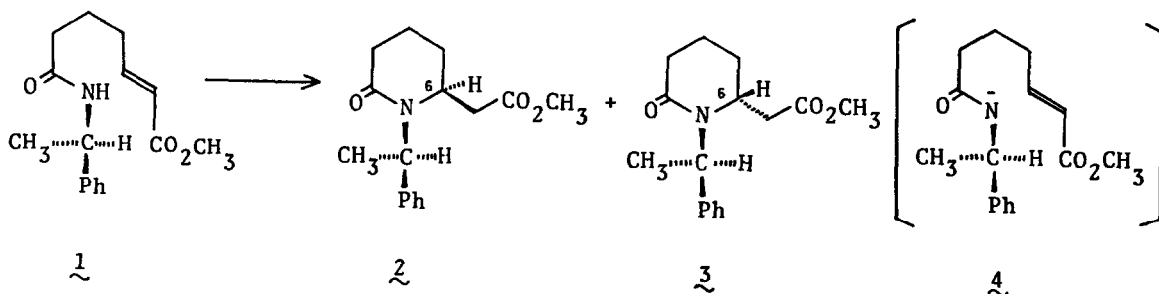


Table. Medium and Temperature Effects in Asymmetric Cyclization of Methyl (R)-6- α -Methylbenzylaminocarbonylhex-2-enoate (1) with KOBu^t (0.1 equiv.)

Entry		Temp(°C)	Time(min)	Yield	Diastereomer Excess(%)
1	Chlorobenzene	26	45	69	S (5.5)
2	Chlorobenzene	-40	310	60	S (24.0)
3	Chlorobenzene 18-crown-6 (0.1 equiv.)	26	20	63	R (12.8)
4	Chlorobenzene 18-crown-6 (0.1 equiv.)	-40	150	57	R (23.7)

gave a mixture of the diastereomeric esters 2 and 3, the ratio of which was determined by the relative intensities of nmr signals for methyl protons of the methoxy group.⁴ The results obtained are summarized in Table. In chlorobenzene, a non-polar solvent, at -40°C, the ratio of 2:3 was 62:38 (entry 2). 18-crown-6 (0.1 equiv.) was added to chlorobenzene at -40°C to remove the potassium ion from the anionic site of the chiral amidate ion intermediate 4 resulting in the preferential formation of 3 and the enhanced reactivity⁶ of 4 (entry 4). This is the first demonstration of crown ether causing the reversed diastereoselectivity of the nucleophilic attack in the asymmetric reaction.⁷

Further study is necessary to clarify the mechanism of the diastereoselectivity in this asymmetric intramolecular reaction, especially the mechanism of the change of the diastereoselectivity in the presence of crown ether. Nevertheless, it is especially noteworthy that a change of medium alone causes profound influence on the stereoselectivity.

Acknowledgement. We thank Drs. T. Noguchi and S. Ishimoto for their support.

References and Notes

- (1) R. A. Bartsch, Acc. Chem. Res., **8**, 239 (1975).
- (2) T. Wakabayashi, Y. Kato, and K. Watanabe, Chemistry Letters, 1283 (1976).
- (3) T. Wakabayashi and M. Saito, Tetrahedron Letters, 93 (1977).
- (4) T. Wakabayashi, K. Watanabe, Y. Kato, and M. Saito, Chemistry Letters, 223 (1977).
- (5) C. J. Pederson and H. K. Frensdorff, Angew. Chem. Int. Ed. Engl., **11**, 16 (1972).
- (6) Tlc monitoring of the reaction mixture with or without 18-crown-6 at -40°C revealed that the presence of 18-crown-6 showed about 3 times rate acceleration.
- (7) Tsuchihashi, et al. recently reported the first efficient alteration of the stereochemical course by changing solvents in an asymmetric intramolecular reaction; G. Tsuchihashi, I. Mitamura, and K. Ogura, Tetrahedron Lett., 855 (1976).