

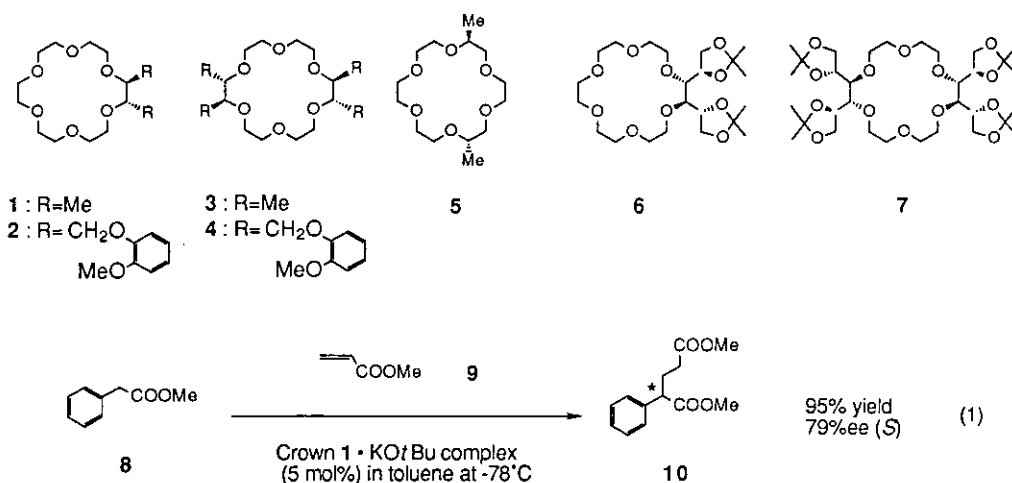
ASYMMETRIC MICHAEL ADDITION REACTION OF METHYL
PHENYLTHIOACETATE TO 2-CYCLOPENTENONE CATALYZED
BY CHIRAL CROWN - KOtBu COMPLEXES¹

Shin Aoki, Shigeki Sasaki,² and Kenji Koga*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku,
Tokyo 113, Japan

Abstract Asymmetric Michael addition reaction of methyl phenylthioacetate (12) to 2-cyclopentenone (11) using chiral crown ether - KOtBu complexes as catalysts is reported. Crown (7) has been found to give 14 of 71%ee (enantiomeric excess).

The design of efficient catalysts for asymmetric induction has been a recent focus in synthetic organic chemistry. Crown ethers have been used as asymmetric catalysts by several groups.³⁻⁵ We have previously reported the simple chiral crown (*S,S*)-1 • KOtBu complex which efficiently catalyzes 1,4-addition of methyl phenylacetates (8) to methyl acrylate (9) to give (*S*)-10 (95% yield, 79%ee, Eq. 1).⁶



In 1988 Yamamoto *et al.* have developed Michael addition reactions of active methylene compounds stabilized by phenylthio group to cycloalkenones catalyzed by $\text{KOtBu} \cdot$ chiral crown complexes, and succeeded in enantiofacial discrimination of the Michael acceptor.⁷

We report here the results of 1,4-addition reaction of methyl phenylthioacetate (**12**) to 2-cyclopentenone (**11**) catalyzed by several chiral crowns complexed with KOtBu (Eq. 2).

The Michael reaction of **12** to **11** was carried out in the presence of 10 mol% of crown $\cdot\text{KOtBu}$ complexes and the results are summarized in Table 1. The product (**13**) was converted to δ -keto ester (**14**) in good yields with methods described by Gutierrez's and Yamamoto's groups; desulfurization with $(n\text{Bu})_3\text{SnH}$ in the presence of AIBN.^{7,8}

The highest enantioselectivity was obtained in toluene, a less polar solvent. We have expected that chiral crown (*S,S*)-**1** and (*S,S,S,S*)-**3** would give **14** with relatively high optical yields, because methyl groups of **1** and **3** are in axial position in the complexes to affect the enantioselectivity.⁶ But both gave the 1,4-adduct of rather low optical purity. (*S,S*)-**5**, in which two methyl groups are supposed to be equatorial in the complex, indicated no enantiofacial discrimination (entry 5).

We therefore prepared **2**, **4**, **6** and **7** bearing bulky substituents. Among them, **2** and **7** were found to induce relatively high enantioselectivity with 68%ee (*R*) and 71%ee (*S*), respectively (entries 2 and 7). It also should be mentioned that crowns having same chiral units exhibit the same sense of asymmetric induction (**1** and **3** for (*R*)-**14**, **2** and **4** for (*R*)-**14**, **6** and **7** for (*S*)-**14**).¹³

Mechanistic studies are now in progress.

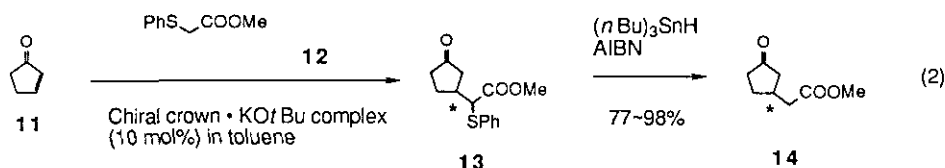


Table 1. Asymmetric Michael Additions Catalyzed by Chiral Crown Ethers (Eq. 2)^{a)}

entry	crown	conditions	yield of 13 (%)	ee(%) of 14	confg. ^{b)} of 14
1	1 ^{6,9a)}	-78°C 1 h + 0°C 10 min	30	21	<i>R</i>
2	2 ⁶⁾	-78°C 2 day	46	68	<i>R</i>
3	3 ^{6,9b)}	-78°C 1 h	97	15	<i>R</i>
4	4	-78°C 1 h + 0°C 10 min	82	26	<i>R</i>
5	5 ⁶⁾	-78°C 1 h + 0°C 10 min	48	1	<i>S</i>
6	6	-78°C 1 day	62	36	<i>S</i>
7	7 ¹⁰⁾	-78°C 1 h + 0°C 10 min	86	71	<i>S</i>

a) Ester : enone : crown $\cdot\text{KOtBu}$ = 2 : 1 : 0.1. For procedure, see ref. 11.

b) Determined by optical rotations according to ref. 12. Maximum rotations were calculated to be $[\alpha]_D -121.0^\circ$ (CHCl_3) for (*S*)-**14**.

ACKNOWLEDGEMENT

Partial financial support from the Ministry of Education, Science, and Culture, Japan is gratefully acknowledged (Grant-in-aid for Encouragement of Young Scientists, No. 03857308).

REFERENCES AND NOTES

1. This paper is dedicated to Dr. Masatomo Hamana, Professor Emeritus of Kyushu University, on the occasion of his 75th birthday.
2. Present address : Faculty of Pharmaceutical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812, Japan.
3. D. J. Cram and G. D. Y. Sogah, *J. Chem. Soc., Chem. Commun.*, 1981, 625 ; D. J. Cram and D. Y. Sogah, *J. Am. Chem. Soc.*, 1985, 107, 8301.
4. M. Alonso-López, M. Martín-Lomas, and S. Penadés, *Tetrahedron Lett.*, 1986, 27, 3551 ; M. Alonso-López, J. Jimenez-Barbero, M. Martín-Lomas, and S. Penadés, *Tetrahedron*, 1988, 44, 1535.
5. E. V. Dehmloew and C. Sauerbier, *Liebigs Ann. Chem.*, 1989, 181.
6. S. Aoki, S. Sasaki, and K. Koga, *Tetrahedron Lett.*, 1989, 30, 7229.
7. M. Takasu, H. Wakabayashi, K. Furuta, and H. Yamamoto, *Tetrahedron Lett.*, 1988, 29, 6943.
8. C. G. Gutierrez and L. R. Summerhays, *J. Org. Chem.*, 1984, 49, 5206.
9. a) S. T. Jolley, J. S. Bradshaw, and R. M. Izatt, *J. Heterocycl. Chem.*, 1982, 19, 3.
b) R. B. Dyer, D. H. Metcalf, R. G. Ghirardelli, R. A. Palmer, and E. M. Holt, *J. Am. Chem. Soc.*, 1986, 108, 3621.
10. W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J. Chem. Soc., Chem. Commun.*, 1975, 835.
11. A typical experiment (entry 7) : A solution of **11** (264 mg, 3.2 mmol) in toluene (11 ml) was added to a solution of **12** (1.17 g, 6.4 mmol), KO^tBu (38.0 mg, 0.34 mmol) and **7** (213.8 mg, 0.32 mmol) in toluene (21 ml) at -78°C. After stirring for 1 h at -78°C and 10 min at 0°C, the reaction mixture was quenched with aq. NH₄Cl and extracted with ethyl acetate. The organic layer was dried over MgSO₄ and concentrated to give a crude product. Purification by column chromatography (SiO₂, ether - hexane) gave **13** (734 mg, 86% yield) as a pale yellow oil (1:1 mixture of two diastereomers). A solution of **13** (238.7 mg, 0.93 mmol), (nBu)₃SnH (0.49 ml, 1.8 mmol), and AIBN (8.3mg, 0.05mmol) in benzene (3 ml) was heated under reflux for 1 h and cooled down. The resulting solution was directly subjected to column chromatography (SiO₂, ether-benzene). After bulb-to-bulb distillation, **14** (113 mg, 80% yield) was obtained as a colorless liquid of [α]_D -86° (c 2.2, CHCl₃).
12. a) R. K. Hill and A. G. Edwards, *Tetrahedron*, 1965, 21, 1501.
b) H. Kuritani, Y. Takaoka, and K. Shingu, *J. Org. Chem.*, 1979, 44, 452.
13. a) Satisfactory analytical and spectroscopic data were obtained for all new compounds.
b) Crown ethers (1~7) were prepared by the conventional methods. Details will be published in due course.

Received, 1st November, 1991