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

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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. 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).
In 1988 Yamamoto et al. have developed Michael addition reactions of active methylene compounds stabilized by phenylthio group to cycloalkenones catalyzed by KOrBu • 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 phenylthioacetae (12) to 2-cyclopentenone (11) catalyzed by several chiral crowns complexed with KOrBu (Eq. 2).

The Michael reaction of 12 to 11 was carried out in the presence of 10 mol% of crown-KOrBu 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 (nBu)3SnH 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 (SS,SS,SS)-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.

![Diagram](image_url)

**Table 1. Asymmetric Michael Additions Catalyzed by Chiral Crown Ethers (Eq. 2)**

<table>
<thead>
<tr>
<th>entry</th>
<th>crown</th>
<th>conditions</th>
<th>yield of 13 (%)</th>
<th>ee(%) of 14</th>
<th>config. of 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>6,98 a)</td>
<td>30</td>
<td>21</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6,9 2 day</td>
<td>46</td>
<td>68</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>6,98 b)</td>
<td>97</td>
<td>26</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>10</td>
<td>82</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>6,9 10</td>
<td>62</td>
<td>36</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>-78°C 1 day</td>
<td>86</td>
<td>71</td>
<td>S</td>
</tr>
</tbody>
</table>

a) Ester : enone : crown-KOrBu = 2 : 1 : 0.1. For procedure, see ref.11.
b) Determined by optical rotations according to ref.12. Maximum rotations were calculated to be [α]D -121.0° (CHCl3) for (S) - 14.
ACKNOWLEDGEMENT
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REFERENCES AND NOTES
1. This paper is dedicated to Dr. Masatomo Hamana, Professor Emeritus of Kyushu University, on the occasion of his 75th birthday.
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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), KOtBu (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 (8.3 mg, 0.05 mmol) 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).
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.

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