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SIMPLE CHIRAL CROWN ETHERS COMPLEXED WITH POTASSIUM *TERT*-BUTOXIDE AS EFFICIENT CATALYSTS FOR ASYMMETRIC MICHAEL ADDITIONS

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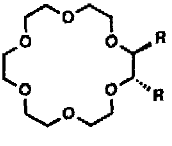
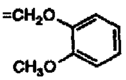
Summary: Simple C_2-symmetric chiral crown ether **1** complexed with KO*t*Bu was found to work as an efficient chiral catalyst in Michael additions to cause high asymmetric induction. The results with various chiral crown ethers as catalysts suggest that diaxial-like conformation of the vicinal methyl groups of **1**•potassium enolate complex is responsible for the chiral induction.

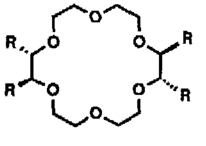
Catalytic asymmetric reactions to form carbon-carbon bonds have been a challenging problem in organic synthesis.[1] Cram's excellent results of asymmetric Michael additions inspired efficacies of chiral crown ethers as chiral catalysts.[2] Although many chiral crown ethers have been synthesized and their abilities of chiral recognition have been investigated,[3] only a few of them have been successfully applied in catalytic asymmetric synthesis.[4] Chiral recognition in complexes at the transition states leading to asymmetric induction is not so well understood as that of the ground states. Therefore, development of readily accessible chiral crown ethers as an efficient chiral catalyst is desirable not only for practical uses, but also for better understanding of chiral recognition in complexes at the transition states. We have found that simple C_2-symmetric chiral crown ethers **1**~**7** complexed with KO*t*Bu catalyze Michael additions to cause high asymmetric induction (Eq. 1), and that vicinal diaxial substituents in complexes appear to be responsible for the chiral induction.

Optically active crown ethers **1**~**9**[5] were prepared from easily accessible optically active diols. The Michael additions of phenylacetate derivatives to methyl acrylate were carried out in toluene at -78°C in the presence of 5 mol% of crown ether•KO*t*Bu complexes, and the results are summarized in Table 1.

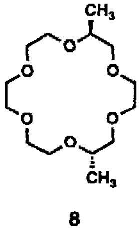


1: R=CH$_3$
2: R=CH$_2$OCH$_3$
3: R=CH$_2$OCH$_2$Ph
4: R=CH$_2$OCHPh$_2$
5: R =CH$_2$O





6: R=CH$_3$
7: R=CH$_2$OCH$_2$Ph



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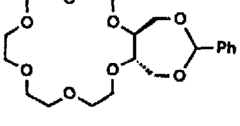

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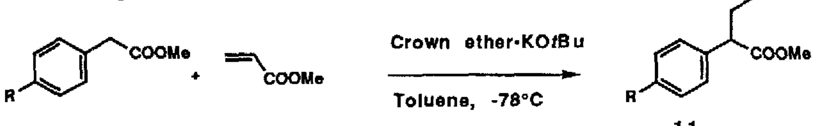

10 **11** (1)

Table 1. Asymmetric Michael Additions Catalyzed by Chiral Crown Ethers (Eq. 1)[a]

entry	crown	R	Time (hr)	yields(%)	ee(%)[b]	config.
1	**1**	H	3	95	79	*S*
2	**1**	OMe	2.5	66	81	-[d]
3[c]	**1**	NO_2	48	73	60[e]	-[d]
4	**1**	Me	2	80	79	-[d]
5	**2**	H	3	97	48	*S*
6	**3**	H	3	98	74	*S*
7	**4**	H	3	99	70	*S*
8	**5**	H	1	72	63	*S*
9	**6**	H	3	89	56	*R*
10	**7**	H	3	91	56	*R*
11	**8**	H	3	79	1	*R*
12	**9**	H	3	96	2	*R*

a) Phenylacetates:acrylate:crown•KO*t*Bu=2:1:0.05. b) Determined by optical rotations and/or by ^{1}H-NMR using (+)-Eu-DPPM as a chiral shift reagent.. c) Carried out at -45°C. d) Not yet determined. e) The value decreased to 38% ee after 4 days, indicating some racemization during this reaction.

The simplest (*S*,*S*)-**1** prepared from (2*S*,3*S*)-butanediol exhibited the highest asymmetric induction in 79% ee for (*S*)-**11** (R=H), and this is the highest value so far reported by using chiral crown ethers as catalysts.[2,4a,c~d] Additional ether coordination sites with increased steric bulkiness in **2**~**5** caused only a little change on the degree of chiral induction. It is noteworthy that (*S*,*S*,*S*,*S*)-**6** and (*S*,*S*,*S*,*S*)-**7** bearing two (2*S*,3*S*)-butanediol units induced the opposite *R* configuration in somewhat lower enantiomeric excesses than **1** and **3**, respectively.

Crystal structures of (*S*,*S*)-**1**•KSCN and (*S*,*S*,*S*,*S*)-**6**•KSCN indicate that potassium cations are located in the center of the crown cavity, and that the vicinal methyl groups are anti to the each other and diaxial-like.[6] Furthermore, both (*S*,*S*)-**8** with two methyl groups at a remote position and (*S*,*S*)-**9** with the substituents fixed by an acetal unit, in which the substituents are supposed to be equatorial in the complexes, showed almost negligible chiral induction. These facts suggest that the vicinal methyl groups in **1** and **6** are diaxial-like in the crown-potassium enolate complexes similarly as in the crystal structures, and that chirality can be efficiently induced in adducts only in such a conformation. Study is now in progress on the mechanism of the asymmetric induction by **1** and the reverse induction by **6**, as well as the extension of the crown ether catalysts to the other asymmetric synthesis.

References and Notes

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5. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds.
6. These crystal structures will be reported elsewhere (we are grateful to Messrs Takatoshi Kawai and Tadashi Sato at Tsukuba Res. Lab., Eisai Co., Ltd. for X-ray crystallography).

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