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Asymmetric Michael Reaction. Deracemization of Enolate by Chiral Crown Ether

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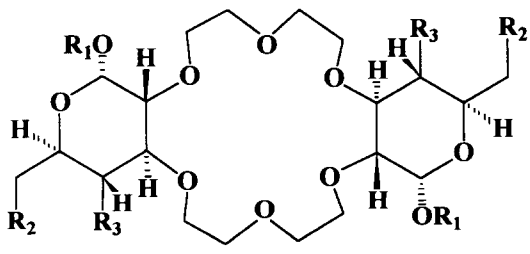
Abstract: *Crown ethers anellated to sugar units have been used to catalyse the enantioselective carbon-carbon bond forming reaction of methyl phenylacetate with methyl acrylate. A novel CH-acid deracemization has also been discovered in this study.*

Aiming at the synthesis and use of crown ethers we have synthesised a number of crown ethers and criptands anellated to sugar units and studied their complex forming abilities[1a-i]. In this communication we describe our findings on an asymmetric carbon-carbon bond forming reaction as well as on a novel catalytic enolate deracemization observed during the Michael addition of methyl phenylacetate to methyl acrylate catalysed by chiral crown-potassium tert.-butylate complex. Although many publications have appeared on the catalytic enantioselective Michael addition[2a-h], there is still a need in collecting further data for a better understanding of the mechanism of the chiral catalysis in these processes. The crown ethers used for the above purposes have a C_2-symmetry axis[2b,c] and have easily been obtained from crown ether **1a** synthesized by us earlier[1a,c,e] (Scheme 1).

Scheme 1. Chiral crown ethers used in this work

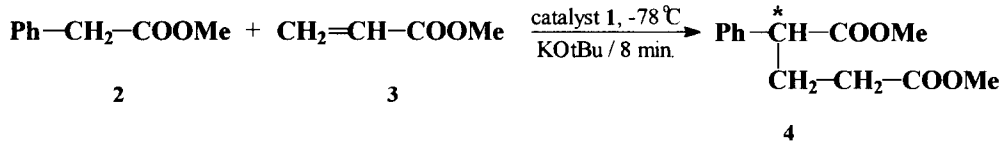


1

	R_1	R_2	R_3
1a[1a]	Me	Ph—CH(O—)(O—)	
1b[1j]	Me	O-hexyl	O-hexyl
1c[1j]	H	OMe	OMe
1d[1e]	Me	OBu	OBu
1e[1c]	Me	OMe	OMe
1f[1a]	Me	OH	OH

Crown ethers **1b** and **1c** are new compounds[1j]. Crown ether **1b** has been made from **1f** with hexylbromide according to the procedure described,[1e] but in this case 0,05 mmol of tetrabuthyl ammonium bromide is used as phase transfer (PT) catalyst. Crown ether **1c** was prepared from **1e** with 2M aqueous HCl at 100 °C for one hour and the solution was subsequently evaporated to dryness. The addition of methyl phenylacetate to methyl acrylate was used as model reaction[2b,c,d,g,h] for testing the catalytic activity of the macrocycles **1a-f**. The reaction conditions[2h] are in Table 1.

Table 1 Michael addition reactions in the presene of chiral macrocycles



Reaction of **2** (1.49 mmol) with **3** (1.14 mmol) in the presence of **1** (0.073 mmol) and KOtBu (0.39 mmol).

Entry	Catalyst	Conditions	Yield of **4** (%)	ee(%) for S-**4**
1	**1a**	toluene	59.5	17.5
2	**1b**	toluene	69.5	46.0
3	**1c**	toluene	67.0	24.0
4	**1d**	CH_2Cl_2	47.0	25.3
5	**1d**	toluene	100.0	80.0
6	**1d**	toluene, 1 min.	82.3	84.4
7	**1d**	toluene, 0.09 mmol for 1d	100.0	79.0
8	**1d**	toluene, 0.032 mmol for 1d	100.0	76.4
9	**1e**	toluene	100.0	76.4
10	-	toluene	43.5	-

The asymmetric induction expressed in terms of the enantiomer excess (ee) was monitored by measuring the optical rotations of the product **4** and comparing to the literature value[2a] and by ^{1}H-NMR using (+)-Eu-(fod)$_3$ as a chiral shift reagent.

Findings: *1.* Good results are obtained only by using crowns fully alkylated at the sugar units (**1b,1d,1e**), *2.* The reaction is very fast even at -78°C as the result of the 1 minute reaction (entry 6) is similar to that of the 8 minute one (entry 5), *3.* The yields and the ee-values are comparable to or better than those described in the literature for similar catalytic reactions[2b,c,d,g,h].

Additional information has been obtained from the experiments carried out with the (±)- and (S)-form of the reaction product **4**. When the toluene solution of the (±)-**4** was treated under the conditions used for the Michael reaction of the optically active **4** was separated with 39.9, 8.0 and 4.0% ee for the (S)-antipode, depending on the quality of the chiral source (entries 2,7 and 5 in Table 2), on the ratio of the crown ether to KOtBu (entries 2 and 3) and on time (entry 4).

Table 2. Deracemization experiments with (±)-**4** (1.49 mmol) by KOtBu (0.39 mmol) and crown ether catalyst **1** (0.073 mmol) at -78°C, 8 min., in toluene

Entry	Catalyst	Notes	ee for S (%)
1	**1b**	-	36.0
2	**1b**	0.146 mmol of **1b**	39.9
3	**1b**	1.00 mmol of KOtBu	28.3
4	**1b**	16 min.	33.1
5	**1d**	-	4.0
6	**1d**	0.37 mmol of **2** also added	0
7	**1c**	-	8.0
8	**1b**	(+)-**4** (ee=75% for S)	33.2
9	**1d**	(+)-**4** (ee=75% for S)	40.5
10	**1b**	20 °C	18.5
11	**1b**	THF	23.2
12	**1e**	-	0

The result of the so-called deracemization seems to be thermodynamically controlled as the ee value of (+)-**4** decreased under the deracemization conditions (entry 8) reaching almost the same value observed when starting from (±)-**4** (entry 1). Entry 6 in Table 2 shows that the deracemization process is to some extent retarded by the presence of methyl phenylacetate **2**. Under the Michael addition circumstances where **2** is present in large excess the value of enantioselectivity in the C-C bond forming step is preserved. However the 'deracemization ability' of the chiral crown-KOtBu complex is still being reflected in the ee values observed in the Michael reaction (compare entry 2 or 12 in Table 2 to entry 2 or 9 in Table 1).

Excellent deracemization procedures have been published recently for CH-acids by Vedejs's[3,4], Hünig's[5-9], Fehr's[10], Krause's[11] and Trost's[12] groups using one equivalent of a chiral proton source for the enantioselective protonation of the enolates under kinetically controlled conditions. In our experiments the chiral environment for the enolate protonation is supplied by the chiral crown ether from the chiral crown ether-potassium ion complex which is present only in catalytic amount in the reaction mixture and the proton source is achiral (tBuOH).

Further work is in progress on this novel deracemizatio to make it n more useful for preparative purposes. We try to improve the ee values in Michael reactions and in other C-C bond forming reactions catalysed by chiral crown ether-potassium base complexes.

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