New Entry to Chiral Base Catalyst. Asymmetric Michael Addition of α-Substituted β-Keto Esters to Methyl Vinyl Ketone Catalyzed by Podand-type Alkali Metal 2'-Substituted 1,1'-Binaphthalen-2-oxides

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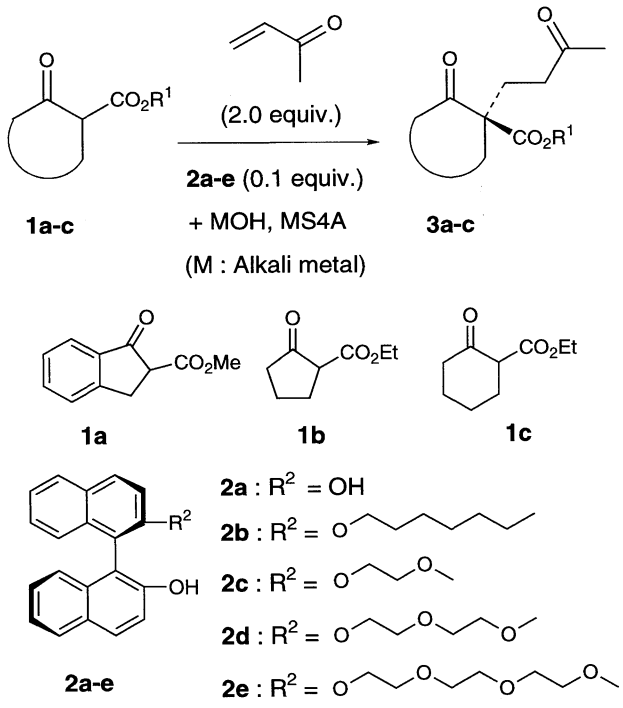
Asymmetric Michael reactions of α-substituted β-keto esters with methyl vinyl ketone catalyzed by 10 mol% of sodium 2'-[2-(2-methoxyethoxy)ethoxy]-1,1'-binaphthalen-2-oxide gave the optically active adducts quantitatively in up to 64% enantiomeric excess.

There has been much attention in the fields of catalytic asymmetric Michael reactions because of the importance of the products as optically active intermediates for many functional compounds.[1] In the asymmetric Michael addition of prochiral α-substituted β-keto esters to achiral α,β-unsaturated carbonyl compounds, many types of the chiral catalysts such as chiral crown ether-achiral alkali metal alkoxide complexes,[2] chiral tertiary amines like alkaloids,[3,4] chiral transition metal complexes,[5] chiral lanthanide complexes,[6] and chiral alkali metal alcoholates[7] have been used. We expected that chiral alkali metal phenoxides would deprotonate the acidic enol proton (pKa~8) of prochiral β-dicarbonyl compounds. In that case, the regenerated chiral phenol would coordinate to the alkali metal enolate to construct a chiral environment for the asymmetric Michael addition of prochiral enolates. However, to the best of our knowledge, only the alkali metal-lanthanum heterobimetallic complex of 1,1'-bi-2-naphthol has been reported as the chiral base catalyst including an alkali metal phenoxide structure,[8] despite the easy availability of chiral phenols as natural and artificial compounds. Herein, we report that alkali metal 2'-substituted 1,1'-binaphthalen-2-oxides can catalyze the asymmetric Michael reaction of α-substituted β-keto esters **1a-c** with methyl vinyl ketone (MVK).

As expected, both the sodium phenoxide and 2-naphthoxide can catalyze the Michael reaction of **1a** with MVK to yield the Michael adduct **3a** in high yields (Table 1, runs 1 and 2). Therefore, the asymmetric Michael reactions were examined as follows.

The enantiopure base catalysts were prepared by adding an equimolar amount of methanolic alkali metal hydroxide to (*R*)-1,1'-bi-2-naphthol **2a** or its known[9] derivatives **2b-e**. After evaporation of the volatiles, to the residue were added the solvent and molecular sieves 4A. The asymmetric Michael reaction was carried out as follows (Scheme 1). The α-substituted β-keto ester **1** was added to the catalyst (0.1 equiv.) mixture at room temperature and then treated with MVK (2 equiv.) at the reaction temperature. After most of the keto ester had been consumed, the reaction was worked up in the usual way. The enantiomeric excesses (e.e.s) of the products **3a-c** were determined by HPLC (**3a**) or GLC (**3b** and **3c**) using chiral stationary phases. The absolute configuration of the



Scheme 1.

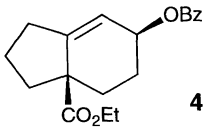
adduct (-)-**3b** was determined to be (*R*) by the CD exiton chirality method after converting it into the allylic benzoate **4** by the conventional method.[10]

Table 1 shows the results of the Michael reactions. The reactions of **1a** catalyzed by the podand-type sodium phenoxides (runs 5-7) gave the optically active Michael adduct (*S*)-(-)-**3a**[4] in quantitative yields, the phenoxide of **2d** giving the highest e.e. (28% e.e., run 6). On the other hand, the reactions catalyzed by the phenoxides having no oligoether group afforded almost racemic **3a** (runs 3 and 4). Furthermore, the enantioselectivity significantly depended on the alkali metal cation of the phenoxide (runs 6, 10-13); the sodium phenoxide resulted in the highest e.e. (run 6), whereas the lithium phenoxide showed no chiral induction (run 10). The reaction temperature and the solvent also influenced on the selectivity (runs 6, 8, 9 and 14); the reaction catalyzed by the sodium phenoxide of **2d** in dichloromethane at - 78 °C gave the highest e.e. (57% e.e., run 14). The Michael reactions of other β-keto esters **1b** and **1c** also yielded the optically active adducts (*R*)-(-)-**3b** and (*R*)-(+)-**3c**[4] in 64% e.e. and 51% e.e., respectively (runs 15 and 16). It should be noted that the

Table 1. Asymmetric Michael addition of α-substituted β-keto esters **1a-c** to MVK catalyzed by alkali metal phenoxides[a]

Run	Subst. **1**	ArOH(M)	Temp °C	Time h	Yield[b] %	E.e.[c] %	Abs. Confign.[d]
1	**1a**	2-NapOH(Na)	20	8	87	-	-
2	**1a**	PhOH(Na)	20	8	84	-	-
3	**1a**	**2a**(Na)	20	3	91	3	R
4	**1a**	**2b**(Na)	20	10	89	0	-
5	**1a**	**2c**(Na)	20	6	97	22	S
6	**1a**	**2d**(Na)	20	2	98	28	S
7	**1a**	**2e**(Na)	20	3	97	15	S
8	**1a**	**2d**(Na)	20	1	94[e]	20	S
9	**1a**	**2d**(Na)	20	3	95[f]	14	S
10	**1a**	**2d**(Li)	20	1	95	0	-
11	**1a**	**2d**(K)	20	1	98	23	S
12	**1a**	**2d**(Rb)	20	1	99	17	S
13	**1a**	**2d**(Cs)	20	1	99	7	S
14	**1a**	**2d**(Na)	-78	144	81[g]	57	S
15	**1b**	**2d**(Na)	-78	120	93	64[h]	R[i,j]
16	**1c**	**2d**(Na)	-78	168	97[k]	51[h]	R[j]

[a]Unless otherwise noted, reactions were performed using 10 mol% of **2** and equimolar amount of alkali metal hydroxide (MOH) in dichloromethane in the presence of molecular sieves 4A powder (15 mg/ml of solvent). [Substrate] = 0.1 mol dm^{-3}. [b]Isolated yield. [c]Determined by HPLC analysis using a Daicel Chiralcel OB column [4.6 mm (i.d.) x 25 cm, eluent: 15% ethanol in hexane, flow rate: 0.5 ml min^{-1}]. [d]Determined by comparison of the specific rotation with the reported data.[4] [e]Solvent: toluene. [f]Solvent: ether. [g][Substrate] = 0.2 mol dm^{-3}. The chemical yield based on the consumed **1a** was 99%. [h]Determined by GLC analysis using an ASTEC Chiraldex G-TA column [0.25 mm (i.d.) x 20 m, column temperature: 120 °C (**3b**), 150 °C (**3c**), carrier gas: He]. [i]Determined by the CD exiton chirality method after converting **3b** into its allylic benzoate **4**.[10] [j]Change in *R* and *S* nomenclature is due to the change of the priority order of the substituents. [k][Substrate] = 0.2 mol dm^{-3}.



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negligible nucleophilicity of the alkali metal phenoxides enables the high yields of the products and the quantitative recovery of the catalysts despite the excess MVK used.

In conclusion, we have found for the first time that the sodium phenoxide of the readily available chiral phenolic podand **2d** can catalyze the asymmetric Michael addition of α-substituted β-keto esters **1a-c** to MVK to give the optically active adducts **3a-c** quantitatively. The Michael reactions of prochiral α-substituted β-keto esters have been used to obtain important synthetic intermediates having a quaternary asymmetric carbon center,[11] suggesting the high potential of chiral alkali metal phenoxides as the chiral base catalysts.

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