Catalytic Kinetic Resolution Reaction of (±)-5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione

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We have recently developed an efficient catalytic asymmetric Michael addition of thiols to α,β-unsaturated carbonyl compounds[1] using heterobimetallic asymmetric complexes,[2] in particular, LaNa$_3$tris(binaphthoxide) (LSB) and SmNa$_3$tris(binaphthoxide) complexes.[3] As an extension of this catalytic asymmetric reaction, we became very interested in catalytic kinetic resolutions using Michael addition of thiols as a key step. In this paper, we describe a catalytic kinetic resolution of (±)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione (1), in which interesting additive effects and nonlinear effects are also discussed.

5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione (1)[4] is a versatile intermediate for the synthesis of several natural products such as coriolin.[5] Opically active 1 was initially synthesized by Trost and Curran using an intramolecular asymmtric Wittig reaction, giving 1 in 40% ee.[4] This enantioselectivity was soon greatly improved to 77% ee by the same group.[6] In 1987, Brooks and Woods succeeded in synthesizing 1 in greater than 98% ee by bakers' yeast.[7] To the best of our knowledge, however, there have been no reports concerning an asymmetric synthesis of 1 using a molecular catalyst.

We envisioned that (±)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione (1) would be a suitable Michael acceptor for the catalytic asymmetric Michael addition of thiols, hopefully resulting in the formation of optically active 1 and the Michael adduct 2, with the opposite absolute configuration on the bridgehead carbon atom (Scheme 1). Furthermore, optically active 2 was expected to be transformed into the other enantiomer of 1. Thus, both enantiomers of 1 could be readily obtained using a catalytic amount of a heterobimetallic asymmetric complex. To examine the feasibility of the above-mentioned strategy, a large amount of racemic 1 was synthesized according to the procedure developed by Trost and Curran.[4] On the basis of our precedent,[1] racemic 1 was first treated with 0.5 equiv of 4-*tert*-butyl(thiophenol), in the presence of (R)-

(1) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043−4044.

(2) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256.

(3) For other catalytic asymmetric Michael additions of thiols, see: (a) Suzuki, K.; Ikegawa, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277−3282. (b) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974−12975. (c) Tomioka, K.; Okuda, M.; Nishimura, K.; Manabe, S.; Kanai, M.; Nagaoka, Y.; Koga, K. *Tetrahedron Lett.* **1998**, *39*, 2141−2144.

(4) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699−5700.

(5) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380−7381.

(6) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929−4932.

(7) Brooks, D. W.; Woods, K. W. *J. Org. Chem.* **1987**, *52*, 2036−2039.

Scheme 1. Strategy for Catalytic Kinetic Resolution of (±)-5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione
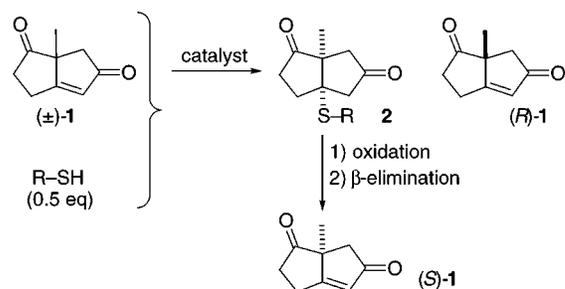
LSB (5 mol %) (toluene/THF 40:1, −40 °C, 0.5 h), giving 2′ as a single stereoisomer (see ^{13}C NMR) (47%) (R_f = 0.70, hexanes−ethyl acetate 1:1 (v/v), silica gel plate) in only 9% ee and (R)-1 (49%) (R_f = 0.31, hexanes−ethyl acetate 1:1 (v/v), silica gel plate) in 8% ee. The enantiomeric excesses of 2′ and (R)-1 were determined by HPLC analysis using a chiral stationary phase column (DAICEL CHIRALCEL OJ, *i*-PrOH/hexane 1:9 for 2′ and 2:98 for (R)-1), and the absolute configuration of (R)-1 was determined by optical rotation.[4] On the other hand, the relative stereochemistry of 2′ was tentatively assigned on the basis of the precedent.[5] Changing the solvent to CH$_2$Cl$_2$ allowed the enantiomeric excesses of both compounds to be improved, although ee's were still modest (37% for 2′ and 36% ee for (R)-1). We then turned our attention to the use of other heterobimetallic asymmetric complexes. It was first observed that treatment of racemic 1 with 0.5 equiv of 4-*tert*-butyl(thiophenol) in the presence of a AlLibis((R)-binaphthoxide) ((R)-ALB) complex (15 mol %) (THF, 0 °C, 2 h) afforded 2′ (48%, 19% ee) and (R)-1 (49%, 20% ee). After several attempts, we were pleased to find that the use of toluene as a solvent, instead of THF, gave rise to 2′ (47%, 63% ee) and (R)-1 (48%, 60% ee) even at room temperature[8] (entry 4, Table 1).

To further improve this result, we paid attention to the structure of the ALB complex in toluene. It was found that the ^{13}C NMR spectrum of ALB in THF clearly showed 10 peaks corresponding to the binaphthyl moiety, while that of ALB in benzene[9] did not show any significant peaks. These results appeared to indicate that the ALB complex exists as an oligomeric form in toluene. Consequently, we were interested to see the result obtained by the disaggregation of ALB in the reaction mixture. To do this, we decided to add 9 mol % (1.2 equiv of OH moiety to ALB)[10] of (R)-BINOL to ALB (15 mol %) in toluene and then carry out a catalytic kinetic resolution (rt, 6 h). Under these conditions, a better result was obtained (entry 5, Table 1), giving 2′ (46%, 76% ee) and (R)-1 (49%, 73% ee). Furthermore, as shown in entry 6 (Table 1), we observed an interesting result by the addition of an achiral alcohol, such as *tert*-butyl alcohol[11]

(8) The reaction at 0 °C gave 2′ in 62% ee.

(9) Benzene was used instead of toluene for simplifing the ^{13}C NMR spectrum.

(10) The addition of 18 mol % of (R)-BINOL gave similar results.

(11) For the effects of *tert*-butyl alcohol on a heterobimetallic catalysis, see: Funabashi, K.; Saida, Y.; Kanai, M.; Arai. T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557−7558.

Table 1. Catalytic Kinetic Resolution of 5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione

entry	catalyst (mol %)	additive (mol %)	solvent	T (°C)	time (h)	(R)-**1** yield (%)	(R)-**1** ee (%)	**2′** yield (%)	**2′** ee (%)
1	(R)-LSB (5)	none	toluene-THF (40:1)	−40	0.5	49	8	47	9
2	(R)-LSB (5)	none	CH$_2$Cl$_2$	−40	0.5	48	36	47	37
3	(R)-ALB (15)	none	THF	0	2	49	20	48	19
4	(R)-ALB (15)	none	toluene	rt	6	48	60	47	63
5	(R)-ALB (15)	(R)-BINOL (9)	toluene	rt	6	49	73	46	76
6	(R)-ALB (15)	t-BuOH (18)	toluene	rt	6	48	72	47	73
7	(R)-ALB (15)	4-MeOC$_6$H$_4$OH (18)	toluene	rt	6	49	77	48	78
8[a]	(R)-ALB (8)	4-MeOC$_6$H$_4$OH (9.6)	toluene	rt	6	47	79 (91)[b]	48	78

[a] 1.80 g of (±)-**1** (12 mmol) was used. [b] (±)-**1** was separated by selective crystallization.
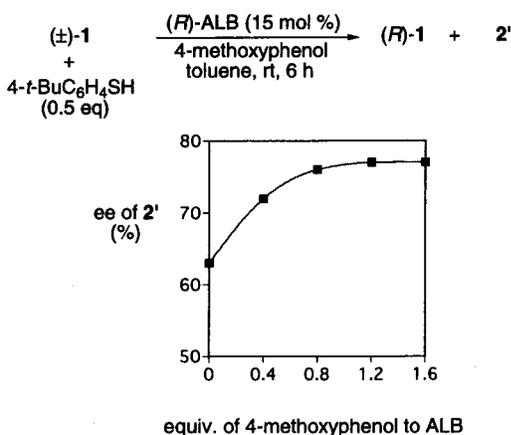
Figure 1. Influence of the amount of 4-methoxyphenol on ee.

(18 mol %), which gave rise to **2′** (47%, 73% ee) and (R)-**1** (48%, 72% ee). After several attempts, the addition of 4-methoxyphenol (18 mol %: 1.2 equiv to ALB) was found to give the best result, providing **2′** (48%, 78% ee) and (R)-**1** (49%, 77% ee) (entry 7, Table 1). As shown in Figure 1, the enantiomeric excess of **2′** was highest with the addition of 1.2 equiv of 4-methoxyphenol, while no improvement was obtained by adding more than 1.2 equiv. In a larger scale experiment (1.8 g of **1**), we were able to decrease the catalyst amount of ALB to 8 mol %, affording **2′** (48%, 78% ee) and (R)-**1** (47%, 79% ee) (entry 8, Table 1). The Michael adduct **2′** was readily converted to (S)-**1** through the sulfoxide (91% yield). Based on the fact that such additive effects were not observed when THF was used as a solvent, the above-mentioned improved result can be attributed to the disaggregation of the oligomeric ALB in toluene. To clarify the role of 4-methoxyphenol, ^{7}Li NMR and ^{27}Al NMR observations were performed. The ^{7}Li NMR spectrum of ALB in toluene showed two signals at $\delta = -0.33$ and -1.07 ppm with similar intensities. After the addition of 4-methoxyphenol (1.6 equiv to ALB), one major peak ($\delta = -0.08$ ppm) was obtained together with a small peak ($\delta = -1.02$ ppm). On the other hand, the ^{27}Al NMR spectrum of ALB in toluene did not give rise to the obvious change after the addition of 4-methoxyphenol. Thus, 4-methoxyphenol appears to coordinate to the lithium atom of ALB, and the resulting monomeric ALB should catalyze the kinetic resolution as shown in Scheme 2.

Scheme 2. Proposed Catalytic Cycle of the Kinetic Resolution Using Michael Addition of Thiols
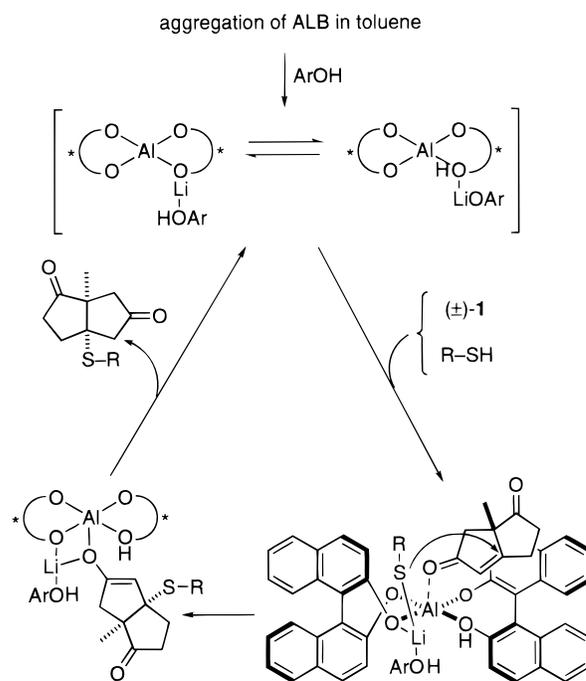

It was also found that interesting nonlinear effects (asymmetric amplification)[12] were observed in the absence and presence of 4-methoxyphenol, as shown in Figure 2. These phenomena suggest that the oligomeric complex, formed from (R)-ALB and (S)-ALB, shows lower reactivity than ALB itself and also suggest that the oligomeric complex is not readily disaggregated even in the presence of 4-methoxyphenol.[13]

We finally attempted to increase the optical purity of (R)-**1** (79% ee) by the separation of racemic **1** as a crystalline solid [hexanes−ethyl acetate 2:1 (v/v), −30 °C], affording (R)-**1** in 91% ee and 85% yield.

In conclusion, we have developed a catalytic kinetic resolution of (±)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione (**1**) by the Michael addition of 4-*tert*-butyl (thiophenol) promoted by ALB and 4-methoxyphenol. Moreover, we

(12) For a recent review, see: Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2922−2959.
(13) The ALB complex consisting of a (R)-BINOL and a (S)-BINOL cannot be formed due to steric hindrance.
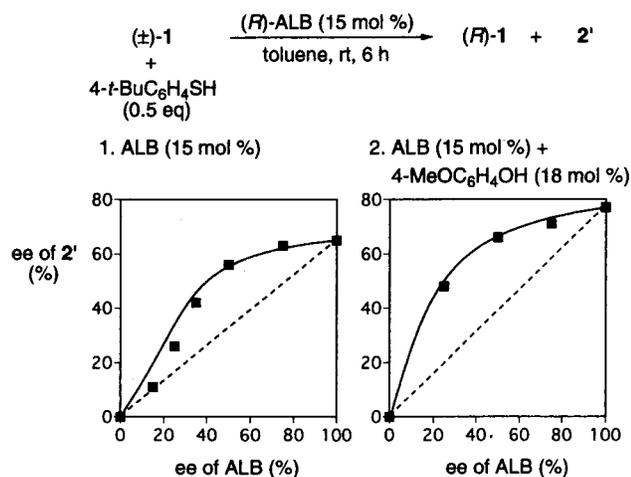
Figure 2. Nonlinear effects in catalytic kinetic resolution.

have found interesting additive effects and asymmetric amplification in the ALB-catalyzed reaction. Although the ee's of both enantiomers are not excellent (91% ee), the method described herein offers a simple method to obtain both enantiomers of **1**, which are synthetically very versatile intermediates.

Experimental Section

General Methods. In general, reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Toluene was distilled from sodium.

Catalytic Kinetic Resolution Reaction of (±)-5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione (1). A solution of (*R*)-ALB (0.96 mmol) in THF (9.6 mL)[14] was concentrated under reduced pressure for 30 min at room temperature. To the residual (*R*)-ALB was added a solution of 4-methoxyphenol (143 mg, 1.2 mmol) in toluene (13 mL) at 0 °C, and the mixture was stirred for 30 min at 0 °C. To this mixture (0 °C) was successively added a solution of (±)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione (**1**) (1.80 g, 12 mmol) in toluene (12 mL) and then 4-*tert*-butyl-(thiophenol) (1.00 mL, 6.0 mmol). After being stirred for 6 h at room temperature, the reaction mixture was quenched with 1 N HCl (20 mL), and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated. The residue was purified by flash column chromatography (SiO$_2$, ethyl acetate−hexane 1:5 then 1:1) to give the Michael adduct **2′** (1.81 g, 48%) as a colorless oil

(14) Shimizu, S.; Ohori, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 7547−7551.

and (*R*)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione ((*R*)-**1**) (840 mg, 47%) as a colorless oil.

The spectral data of (*R*)-**1** were identical to those previously reported.[7] The enantiomeric excess of (*R*)-**1** was determined by chiral stationary-phase HPLC analysis (DAICEL CHIRALCEL OJ, *i*-PrOH−hexane 2:98; flow rate, 1.1 mL/min; retention time, 46.8 min (minor), 50.7 min (major)). The absolute configuration of (*R*)-**1** was determined by the optical rotation: [α]$^{20}_D$ −104° (*c* 0.80, CHCl$_3$) (79% ee).

Compound **2′**: IR (neat) 1746 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.32 (s, 9H), 1.34 (s, 3H), 2.05−2.09 (m, 1H), 2.25−2.31 (m, 2H), 2.35−2.46 (m, 2H), 2.62−2.75 (m, 3H) 7.37−7.43 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 17.2, 31.2, 31.3, 34.5, 34.7, 46.4, 50.3, 57.4, 60.7, 126.4, 126.7, 136.4, 152.9, 212.7, 217.8; MS *m/z* 316 (M$^+$); [α]$^{20}_D$ +66.3° (*c* 0.66, CHCl$_3$) (78% ee). Anal. Calcd for C$_{19}$H$_{24}$O$_2$S: C, 72.11; H, 7.64. Found: C, 71.79; H, 7.51. The enantiomeric excess of **2′** was determined by chiral stationary-phase HPLC analysis (DAICEL CHIRALCEL OJ, *i*-PrOH-hexane 1:9; flow rate, 1.0 mL/min; retention time, 12.4 min (major), 21.1 min (minor)). The absolute configuration of **2′** was determined by the optical rotation after its conversion into (*S*)-**1**.

Conversion of 2′ to (*S*)-5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione ((*S*)-1). To a solution of **2′** (1.4 g, 4.4 mmol) in CH$_2$Cl$_2$ (10 mL) was added *m*-chloroperbenzoic acid (5.3 mmol) at 0 °C. After being stirred for 0.5 h at the same temperature, the reaction mixture was quenched with saturated aqueous Na$_2$S$_2$O$_3$. The resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were vigorously stirred with saturated aqueous NaHCO$_3$ (150 mL). Then the organic layer was washed with brine, dried (Na$_2$SO$_4$), and concentrated. The residue was purified by flash column chromatography (SiO$_2$, ethyl acetate−hexane 1:1) to give (*S*)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione ((*S*)-**1**) (601 mg, 91%) as a colorless oil: [α]$^{20}_D$ +102° (*c* 0.82, CHCl$_3$) (77% ee). The spectral data of (*S*)-**1** were identical to those previously reported.[7]

Increase in the Optical Purity of (*R*)-5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione ((*R*)-1) by Selective Crystallization of (±)-5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione ((±)-1). (*R*)-5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione ((*R*)-**1**) (79% ee) (420 mg, 2.8 mmol) was dissolved in hexanes−ethyl acetate (2:1, v/v) (4 mL). To this solution was added a seed of (±)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione ((±)-**1**) (0.5 mg) at 0 °C, and then the mixture was kept at −30 °C for 40 h. (±)-**1** was obtained as a crystalline solid. The supernatant solution was separated by decantation and then concentrated to give (*R*)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione ((*R*)-**1**) (357 mg, 85%) as a colorless oil in 91% ee.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of the Michael adduct **2′**. This material is available free of charge via the Internet at http://pubs.acs.org.