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A facile and practical method of preparing optically active α-monosubstituted cycloalkanones by thermodynamically controlled deracemization

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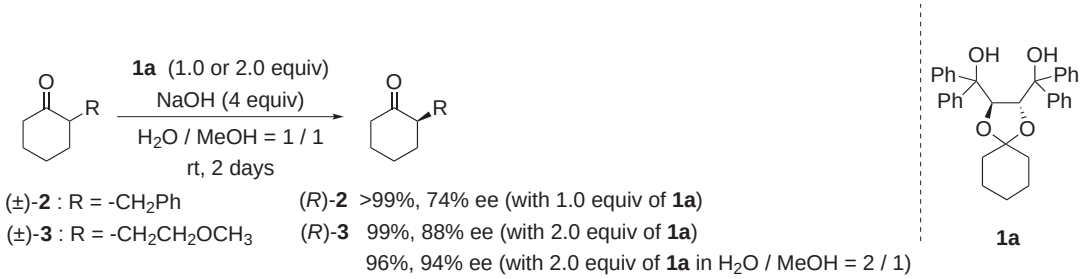
ABSTRACT

Racemic 2-monosubstituted cycloalkanones were converted to *R*-isomers when TADDOLs (e.g., **1a**, **b**) were used as host molecules in alkaline aqueous MeOH. The efficiency of this thermodynamically controlled deracemization was strongly influenced by the mixture ratio of the solvent, H_2O/MeOH. Based on this finding, an improved method of preparing (*R*)-2-monosubstituted cycloalkanones with higher optical purity was developed. For example, (*R*)-2-(4-methylbenzyl)cyclohexanone (**5**) was obtained in 85% yield with 98% ee, when a 1:1 mixture of H_2O/MeOH was used as the solvent in the presence of **1a**.

1. Introduction

Optically active α-monosubstituted ketones are widely used as starting materials in the syntheses of complex molecules, such as natural products and biologically active compounds. Enantioselective protonation[1–3] and alkylation[4] of ketones (enolates) and their derivatives, such as enamines,[5] imines,[6] and hydrazines,[7] are necessary to obtain such optically active ketones. These methods, however, require multistep transformations and carefully controlled conditions. In contrast, inclusion complexation can be easily and successfully used for the optical resolution of ketones bearing a chiral center at the α-position.[8,9] The resolution efficiency (*E*)[10] of this method, however, cannot exceed 100%.

In previous papers, we reported *thermodynamically controlled* deracemization[11,12] of several cycloalkanones using host–guest chemistry in basic suspension media. For example, the use of (2*R*,3*R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (**1a**)[13] (1.0–2.0 equiv) as a host molecule with alkaline aqueous MeOH converted racemic 2-benzylcyclohexanone (**2**) and 2-(2-methoxyethyl)cyclohexanone (**3**) to the *R*-isomer in quantitative yield with 74% ee and 94% ee, respectively (Scheme 1). The *E* values of deracemization for (±)-**2** and **3** were increased up to 148% and 180%, respectively.



Scheme 1. Deracemization of (±)-2-benzyl- and (±)-2-(2-methoxyethyl)cyclohexanone.

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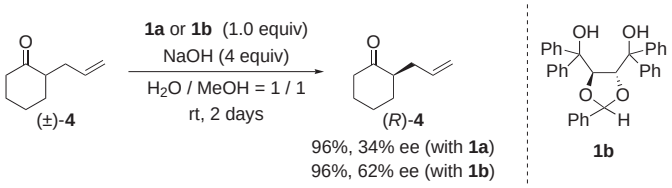
We revealed that this unique phenomenon was accomplished by chiral molecular recognition induced by inclusion complexation. Furthermore, X-ray analytical studies disclosed the nature of this chiral molecular recognition process in solid phase in detail.[14] Thus, deracemization could provide a convenient and excellent method of preparing optically active α-monosubstituted cyclohexanones.

Although (4*R*,5*R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-2-phenyl-1,3-dioxolane (**1b**)[13] gave better results than **1a** for the deracemization of (±)-2-allylcyclohexanone (**4**), efficiency was maintained at 62% ee (*R*-isomer) with 96% yield (*E* value=119%) (Scheme 2). To obtain **4** with higher enantiomeric excess, we focused on the solubility of **4** in aqueous MeOH as the solvent, and found that the proportion of water in the aqueous MeOH influenced the optical purity of the ketone **4**. Furthermore, the optical purity of **4** increased



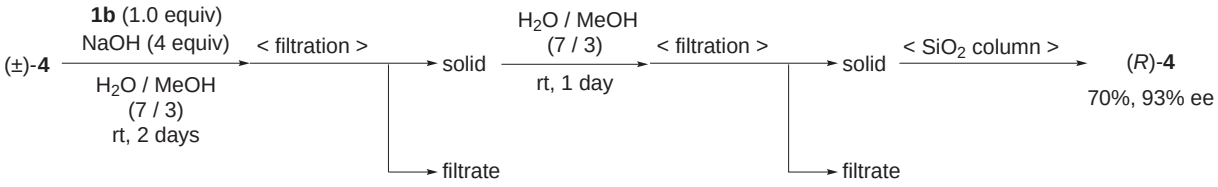
Scheme 2. Deracemization of (±)-2-allylcyclohexanone.

when the recovery of **4** was sacrificed to some extent by filtration. Eventually, (*R*)-**4** was afforded in 70% yield with 93% ee when a 7:3 mixture of H_2O/MeOH was used as the solvent (Scheme 3).[15]

The solvent dependence of the deracemization of (±)-**2** using **1a** is shown in Fig. 1a. When the proportion of water was 10%, **2** was not recovered from the solid phase because of the high solubility of **2** in the solvent. In 20% water, (*R*)-**2** was obtained in about 50% yield with 90% ee. Although most of guest molecule **2** was recovered from the solid phase in more than 50% of water, the optical purity of **2** decreased gradually to 66% ee, suggesting that some of guest molecule **2** simply adhered to the surface of solid phase (host **1a**) due to the low solubility of oily **2** in the water-enriched solvent.

A somewhat similar phenomenon was observed with the combination of **1a** and cycloalkanones **3**–**9** (Fig. 1b–h). Cycloalkanones **2**, **3**, **5**, and **7** were recognized by host **1a** with good to excellent efficiency. In the case of **3**, 2 equiv of host **1a** was required for deracemization with high efficiency, because a 1:2 inclusion complex must be formed.[11,16] In contrast, the chiral recognition efficiency of **4**, **6**, and **8** by **1a** was only moderate. The introduction of some methyl groups on the side chain (**4** versus **7**) and on the aromatic ring (**2** versus **5**) influenced the molecular recognition process. Efficiency was dramatically decreased by the absence of a π-electron system on the side chain (**7** vs **8**), especially, **9** was not included by **1a** (**4** vs **9**). The ring size of cycloalkanones (**2** vs **6**) also affected the affinity between the host and guest molecules. Exchanging host molecule **1a** for **1b** led to more effective inclusion of (*R*)-**4** into the solid phase (Fig. 2 versus Fig. 1c). Thus, deracemization was influenced by the functionality, π-electron, and architecture of the α-alkyl side chain, and the ring size of the cycloalkanones.[17]

Based on these findings shown in Figs. 1 and 2, an improved procedure for deracemization was developed. Deracemization of

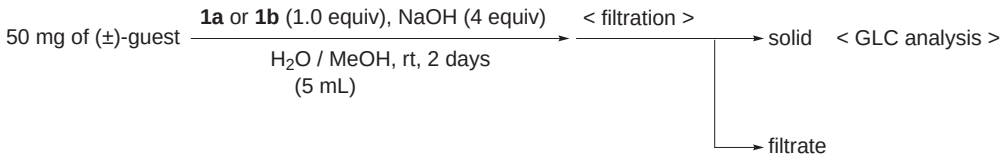


Scheme 3. Deracemization of (±)-2-allylcyclohexanone.

Here we describe in detail that deracemization of various α-monosubstituted cycloalkanones is solvent-dependent, as in the case of **4** with **1b**. Moreover, we present a newly developed procedure that provides a facile and practical method for preparing optically active α-monosubstituted cycloalkanones.

2. Results and discussion

In the present study, the solid phase was separated from the liquid phase by filtration after deracemization to precisely evaluate the efficiency of the molecular recognition process (Scheme 4). (±)-**2** using **1a** was focused on as an example. In the original method (Scheme 1), 50% aqueous MeOH was used as a solvent and the reaction mixture was treated with a saturated NH_4Cl aqueous solution and extracted with ether to satisfactorily recover the entire **2**. However, the enantiomer excess of recovered **2** was only 74% ee. When the same ratio of H_2O/MeOH (orange line in Fig. 1a) was used, **2** was recovered in 95% yield with 80% ee. So, it was presumed that the recovered **2** in original method was contaminated by adhesion of solute molecule **2**, which was not included by the host **1a**, resulting in a 1:1 mixture of racemic isomers. This was why the optical purity of the recovered **2** remained at 74% ee of the *R*-isomer,



Scheme 4. Method for deracemization.

Optical and chemical yields of the guest compound (cycloalkanone) recovered from the solid phase were determined by gas–liquid chromatography (GLC) and plotted against the proportion (in %) of water in aqueous MeOH.

even though 90% ee of (*R*)-**2** was included in the solid phase (green line in Fig. 1a).

Therefore, a new procedure was developed with the following considerations: (1) To ensure high optical purity, recovery of **2** is

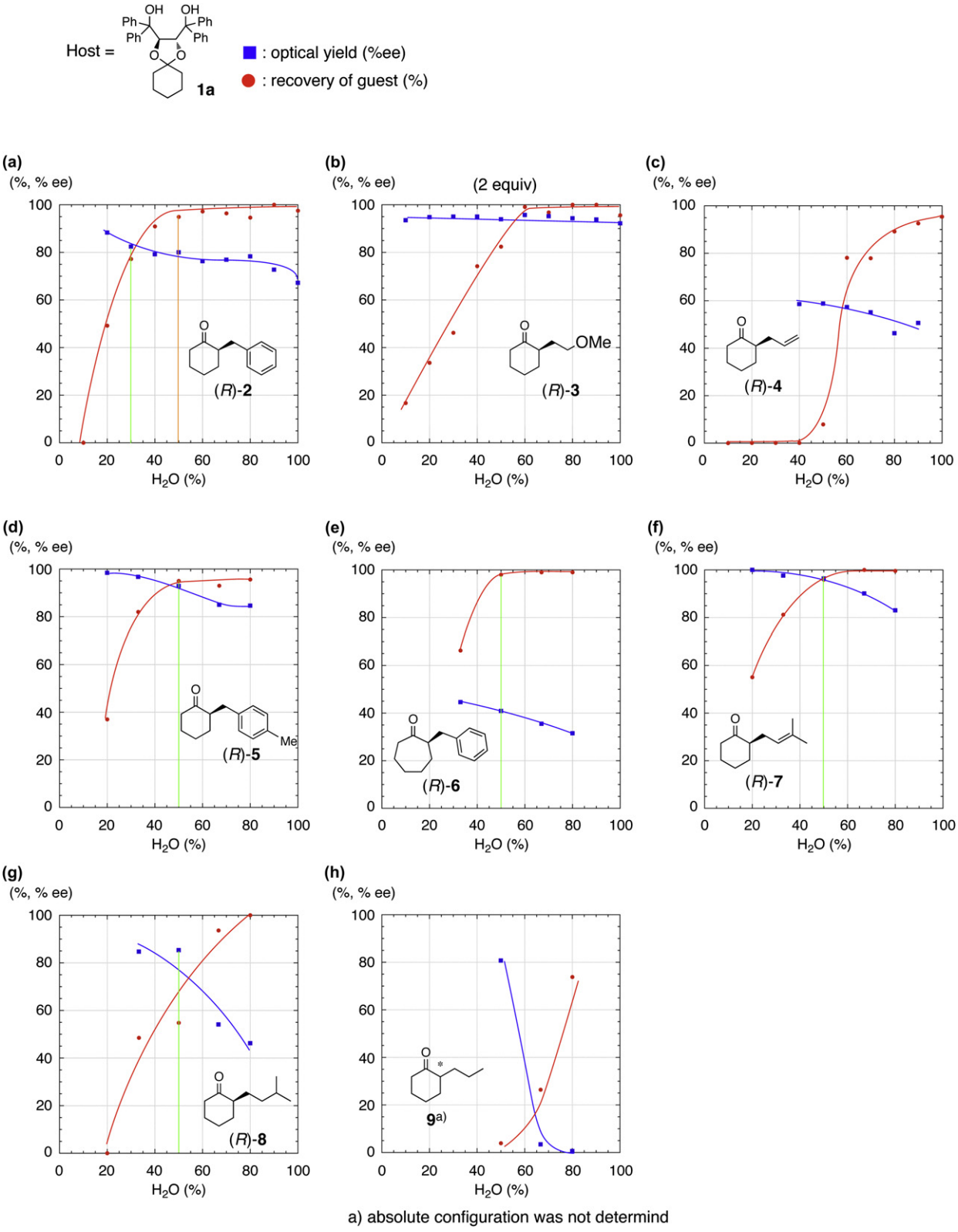


Fig. 1. Solvent dependence of chemical and optical yields of **2**–**9** recovered from the solid phase using **1a**.

sacrificed to some extent by filtration. (2) To eliminate adhesion (vide supra) and further enhance the optical purity of **2**, the solid phase, which is a mixture of **1a** and **2** obtained by filtration, is again suspended again in fresh solvent without a base. That is, the mixture is subjected to optical resolution by inclusion recomplexation to remove unfavorable enantiomers (*S*-isomer) of **2** into the solvent. (3) The H_2O/MeOH ratio appreciably influences the efficiency of this new procedure. When the proportion of MeOH is too high, recovery of **2** decreases. On the other hand, the enantiomeric excess of **2** decreases when the solvent contains a higher proportion of water.

A 3:7 mixture of H_2O/MeOH (green line in Fig. 1a) was selected as the solvent for improved deracemization of (±)-**2** with **1a**. For example, the host molecule **1a** (5.38 g, 10.6 mmol) was added to

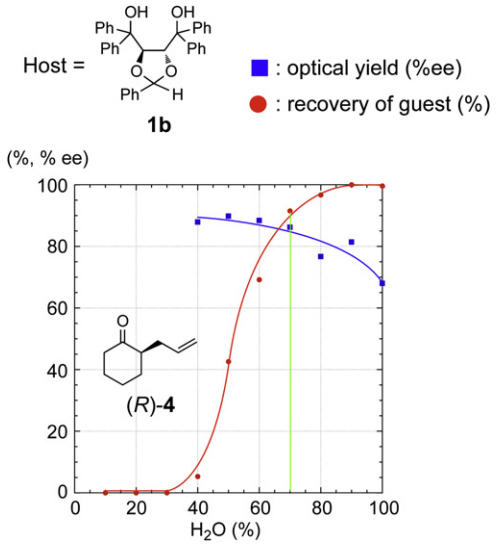


Fig. 2. Solvent dependence of chemical and optical yields of **4** recovered from the solid phase using **1b**.

a solution of (±)-**2** (2.02 g, 10.7 mmol) in H_2O (17.5 mL) and MeOH (140 mL), then a 1 M sodium hydroxide aqueous solution (42.5 mL, 42.5 mmol) was added to the suspension (finally, the ratio of H_2O/MeOH was 3:7). The mixture was stirred at room temperature for 2 days, and the resulting mixture was filtered and the residue was washed with H_2O/MeOH (3:7, 5 mL×3). The resulting residue, the solid phase, was then suspended again in a fresh mixture of H_2O/MeOH (3:7, 200 mL) without a base at ambient temperature for 1 day. After filtration followed by washing with H_2O/MeOH (3:7, 5 mL×3), the residue was separated by column chromatography to afford (*R*)-**2** with 93% ee in 72% yield (Scheme 5).

3. Conclusions

We found that the efficiency of thermodynamically controlled deracemization was appreciably influenced by the ratio of H_2O/MeOH used as a solvent, which led to the development of an improved method to prepare (*R*)-2-monosubstituted cycloalkanones with higher optical purity. Further studies to disclose the principle of the molecular recognition process and the applicability of the present method are in progress.

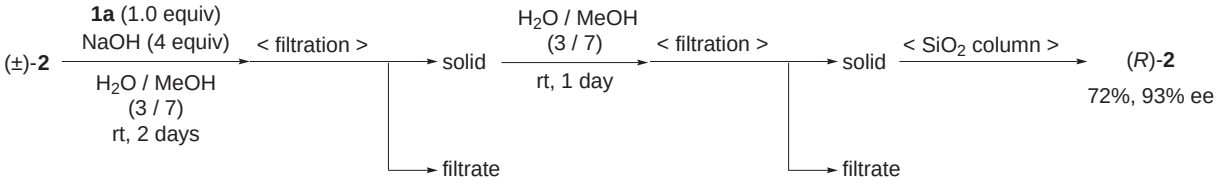
4. Experimental section

4.1. General

Melting points were determined on a Yanaco MP-3 apparatus and were uncorrected. Infrared (IR) spectra were recorded from either neat liquid films or solids in KBr pellets on a JASCO Model FT/IR-410 spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian Gemini 200 (200 MHz), Varian Unity 200 (200 MHz), Varian Mercury 300 (300 MHz), or Varian 400 MR (400 MHz) spectrometer in $CDCl_3$. Chemical shifts were reported in parts per million (δ) relative to internal Me_4Si (0.00 ppm), and coupling constants are given in hertz. The abbreviations s=singlet, d=doublet, t=triplet, m=multiplet, br=broad were used. ^{13}C NMR spectra were obtained on a Varian 400 MR (100 MHz) and chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ 76.9 ppm). Mass spectra, including high-resolution mass spectra, were recorded on a JEOL AX-500 spectrometer.

Optional rotations were measured on a JASCO DIP-1000 polarimeter using a 10-cm microcell. Capillary gas chromatographic analyses were performed on a Shimadzu GC-14A gas chromatograph equipped with 30 m×0.25 mm fused-silica α-DEX120 SUPELCO columns. Helium was used as the carrier gas and peak area integrations for the flame ionization detector response were uncorrected. Analytical HPLC was performed on a JASCO system consisting of a pump (PU-980) and a photodiode array detector (UV-970, set at 254 nm) and equipped with a Daicel CHIRALCEL OJ or AD column. Peak areas were measured by electronic integration on a Shimadzu C-R7Aplus chromatopac.

In general, reagent grade solvents were used. *N*,*N*-Dimethylformamide (DMF) was distilled from CaH_2 under reduced pressure. Dichloromethane and triethylamine were distilled from CaH_2 under argon atmosphere. Analytical thin layer chromatography (TLC) was performed on precoated silica-gel 60 F-254 plates (0.2-mm layers) on glass with fluorescent indicator, supplied by E. Merck. For column chromatography, a Fuji Silysia BW-127ZH (100–270 mesh) or BW-300 (200–400 mesh) was used.



Scheme 5. Deracemization of (±)-**2** using new method.

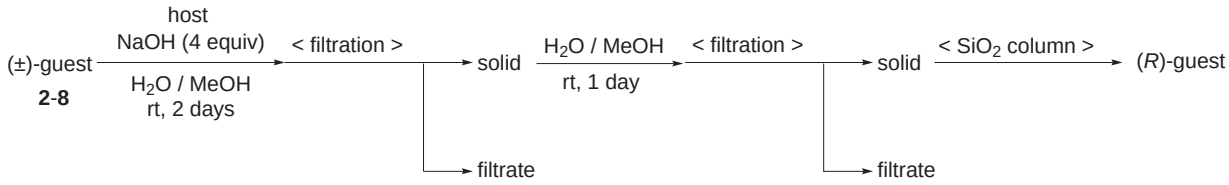
Deracemization of (±)-**3**–**8** was performed similarly using the new procedure. These results along with those of our previous studies are summarized in Table 1. In the case of **5**, a 1:1 mixture of H_2O/MeOH (see Fig. 1d, green line) was necessary for the reaction to afford (*R*)-**5** with 98% ee in 85% yield (entry 2). In contrast, **6** was not adequately recognized by **1a** (see Fig. 1e), so the deracemization efficiency remained at only 50% ee (*R*-isomer) in 78% yield, even using the new procedure (entry 3).

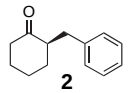
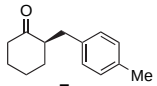
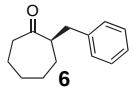
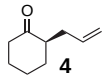
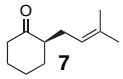
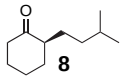
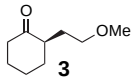
Compound (*R*)-**7** fitted more effectively than (*R*)-**4** into the chiral cavity constituted by aggregation of the optically active host molecule **1a** (Fig. 1f vs 1c). Then, (*R*)-**7** was obtained with 96% ee in 96% yield (entry 5). Applying the new procedure to **8**, a hydrogenated compound of **7**, gave only a moderate yield (46%), but provided excellent optical purity (96% ee). Host molecule **1b** was significantly superior to **1a** for the deracemization of (±)-**4** in a 7:3 mixture of H_2O/MeOH to provide the *R*-isomer with 93% ee in 70% yield (Fig. 1c versus 2, entry 4). Because **3** was recognized effectively by two equimolar amounts of **1a**, the new procedure was not necessary for deracemization in this case.

4.2. Solvent dependence of deracemization (Scheme 4)

In a 5-mL flask, distilled water and 1 M sodium hydroxide aqueous (4 equiv) were added to a mixture of ketone (50 mg) and host **1a** or **1b** in methanol. The resulting mixture was stirred vigorously at ambient temperature for 2 days and then filtered. The obtained white solid was dissolved in ether and dried over $MgSO_4$.

Table 1
Deracemization of α-substituted cycloalkanones



Entry	Guest	Host (equiv)	<Previous work>	<Present work>
			% Yield (% ee)/(ratio of H_2O/MeOH)	% Yield (% ee)/(ratio of H_2O/MeOH)
1	 **2**	**1a** (1)	100 (74:*R*)/(1/1)	71 (93:*R*)/(3/7)
2	 **5**	**1a** (1)	96 (82:*R*)(1/1)	85 (98:*R*)/(1/1)
3	 **6**	**1a** (1)	100 (36:*R*)/(1/1)	78 (50:*R*)/(1/1)
4	 **4**	**1b** (1)	96 (62:*R*)/(1/1)	70 (93:*R*)/(7/3)
5	 **7**	**1a** (1)	97 (90:*R*)/(2/1)	96 (96:*R*)/(1/1)
6	 **8**	**1a** (1)	92 (46:*R*)/(2/1)	48 (96:*R*)/(1/1)
7	 **3**	**1a** (2)	96 (94:*R*)/(2/1)	—[a]

[a] No experimental results.

This solution was used for analyses. The optical purity of ketone was determined by GLC using a chiral column (SUPELCO, α-DEX120). To determine the yield of recovered ketone, a straight-chain hydrocarbon (dodecane or hexadecane) was added as an internal standard. The optical and chemical yields of the guest compound recovered from the solid phase were plotted against the proportion (in %) of water in aqueous MeOH (Figs. 1 and 2).

4.3. General method for improved deracemization (Table 1)

Distilled water and 1 M sodium hydroxide aqueous (4 equiv) were added to a suspension of ketone and host **1a** or **1b** in methanol. By considering Fig. 1 or 2, the ratio of water/methanol at the level of the green line was determined. The suspension was stirred at ambient temperature for 2 days. The mixture was filtered and the residue was washed with the same ratio of a mixture of H_2O/MeOH (2 mL×3). The resulting residue, the solid phase, was suspended again into a fresh mixture of H_2O/MeOH at ambient temperature for 1 day. After filtration followed by washing with H_2O/MeOH (2 mL×3), the residue was dissolved in ether and subjected to GLC to afford an enantiomeric excess of ketone. Purification of the residue by silica gel column chromatography (hexane/ether) yield gave the ketone as a colorless oil.

4.4. Typical experiment of improved deracemization (Table 1, entry 2)

The host molecule **1a** (627.2 mg, 1.24 mmol) was added to the solution of **5** (250.1 mg, 1.24 mmol) in distilled H_2O (11.3 mL) and MeOH (12.5 mL), then a 4 M sodium hydroxide aqueous solution (1.24 mL, 4.96 mmol) was added to the suspension (finally, the ratio of H_2O/MeOH was 1:1, green line in Fig. 1d). The resulting mixture was stirred at room temperature for 2 days. The mixture was filtered and the residue was washed with the same ratio of a mixture of H_2O/MeOH (1:1, 2 mL×3). The resulting residue, the solid phase, was suspended again into a fresh mixture of H_2O/MeOH (1:1, 25 mL) at ambient temperature for 1 day. After filtration followed by washing with H_2O/MeOH (1:1, 2 mL×3), the residue was dissolved in ether and subjected to GLC analysis to be 98% ee of (*R*)-**5**. Purification of the residue by silica gel column chromatography (hexane/ether) yielded (*R*)-**5** (212.9 mg, 85%) as a colorless oil.

*4.4.1. (R)-2-Benzylcyclohexanone: (R)-**2**[18].* Chiral GLC analysis, t_R=32.7 (*R*), 33.3 (*S*) min (SUPERCO, α-DEX120, 150 °C).

$[\alpha]_D^{25}$ +28.6 (*c* 1.17, MeOH) (61% ee). CD_{CHCl3} [θ]=+1720, $\Delta\varepsilon$=+0.52 (78% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (dddd, *J*=3.7, 12.1, 12.1, 13.3 Hz, 1H), 1.52–1.63 (m, 1H), 1.63–1.74 (m, 1H), 1.83

(dddd, J=1.6, 3.7, 7.2, 11.1 Hz, 1H), 1.98–2.10 (m, 2H), 2.33 (dddd, J=1.3, 6.0, 12.7, 13.7 Hz, 1H), 2.41 (dd, J=8.8, 13.9 Hz, 1H), 2.40–2.47 (m, 1H), 2.50–2.59 (m, 1H), 3.23 (dd, J=4.9, 13.9 Hz, 1H), 7.13–7.21 (m, 3H), 7.24–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 28.2, 33.6, 35.6, 42.4, 52.7, 126.1, 128.5, 129.3, 140.5, 212.8; IR (ATR) 1704.8 (C=O) cm^{-1}; MS (EI) m/z: 188 (M^+, base peak), 159, 145, 97, 91; HRMS (EI) m/z: (M^+) calcd for $C_{13}H_{16}O$, 188.1201; found, 188.1195.

*4.4.2. (R)-2-(2-Methoxyethyl)cyclohexanone: (R)-**3**[18].* Chiral GLC analysis, t_R=24.6 (*R*), 25.3 (*S*) min (SUPERCO, α-DEX120, 100 °C).

$[\alpha]_D^{25}$ +1.1 (*c* 8.68, $CHCl_3$) (68% ee). CD_{CHCl3} $[\theta]$=+1880, $\Delta\varepsilon$=+0.57 (94% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45–1.33 (m, 2H), 1.75–1.60 (m, 2H), 1.90–1.81 (m, 1H), 2.10–2.02 (m, 1H), 2.18–2.10 (m, 2H), 2.36–2.27 (m, 1H), 2.44–2.36 (m, 1H), 2.53–2.45 (m, 1H), 3.31 (s, 3H), 3.39 (ddd, J=5.9, 6.9, 9.4 Hz, 1H), 3.43 (ddd, J=5.9, 6.5, 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 28.0, 29.3, 34.2, 42.1, 47.1, 58.4, 213.0; IR (ATR) 1706.7 (C=O) cm^{-1}; MS (EI) m/z: 156 (M^+), 98 (base peak); HRMS (EI) m/z: (M^+) calcd for $C_9H_{16}O_2$, 156.1150; found, 156.1152.

*4.4.3. (R)-2-Allylcyclohexanone: (R)-**4**[18].* (±)-Allylcyclohexanone was purchased from Aldrich and used without further purification.

Chiral GLC analysis, t_R=24.6 (*R*), 25.2 (*S*) min (SUPERCO, α-DEX120, 90 °C).

$[\alpha]_D^{25}$ +8.7 (*c* 1.08, MeOH) (68% ee). CD_{CHCl3} $[\theta]$=+1970, $\Delta\varepsilon$=+0.60 (78% ee).

*4.4.4. (R)-2-(4-Methylbenzyl)cyclohexanone: (R)-**5**.* Chiral HPLC analysis, t_R=28.0 (*R*), 37.3 (*S*) min (DAICEL CHIRALCEL AD, hexane/isopropanol=999/1, flow rate 0.5 mL/min, UV254).

$[\alpha]_D^{24}$ +36.0 (*c* 1.00, $CHCl_3$) (78% ee). CD_{CHCl3} $[\theta]$=+2058, $\Delta\varepsilon$=+0.624 (78% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (dddd, J=3.5, 11.9, 11.9, 13.3 Hz, 1H), 1.51–1.63 (m, 1H), 1.61–1.74 (m, 1H), 1.82 (dddd, J=1.6, 3.8, 7.5, 11.2 Hz, 1H), 1.98–2.09 (m, 2H), 2.27–2.36 (m, 1H), 2.31 (s, 3H), 2.37 (dd, J=9.0, 14.1 Hz, 1H), 2.39–2.47 (m, 1H), 2.48–2.56 (m, 1H), 3.19 (dd, J=4.7, 13.9 Hz, 1H), 7.04 (d, J=8.0 Hz, 2H), 7.08 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.9, 27.9, 33.2, 34.9, 42.0, 52.4, 128.8, 128.9, 135.3, 137.1, 212.6; IR (ATR) 1706.7 (C=O) cm^{-1}; MS (EI) m/z: 202 (M^+), 173, 159, 105 (base peak), 97; HRMS (EI) m/z: (M^+) calcd for $C_{14}H_{18}O$, 202.1358; found, 202.1362.

*4.4.5. (R)-2-Benzylcycloheptanone: (R)-**6**[19].* Chiral HPLC analysis, t_R=12.0 (*R*), 16.7 (*S*) min (DAICEL CHIRALCEL OJ, hexane/isopropanol=9/1, flow rate 0.5 mL/min, UV254).

$[\alpha]_D^{21}$ +19.2 (*c* 1.00, $CHCl_3$) (27% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26–1.40 (m, 3H), 1.56–1.68 (m, 1H), 1.72–1.90 (m, 4H), 2.42–2.48 (m, 2H), 2.56 (dd, J=8.4, 13.7 Hz, 1H), 2.77–2.86 (m, 1H), 3.08 (dd, J=5.9, 13.7 Hz, 1H), 7.13–7.21 (m, 3H), 7.24–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 28.5, 29.2, 30.2, 37.8, 43.1, 53.5, 125.9, 128.2, 129.0, 139.9, 215.5; IR (ATR) 1697.0 (C=O) cm^{-1}; MS (EI) m/z: 202 (M^+, base peak), 159, 145, 91; HRMS (EI) m/z: (M^+) calcd for $C_{14}H_{18}O$, 202.1358; found, 202.1357.

*4.4.6. (R)-2-Prenylcyclohexanone: (R)-**7**.* Chiral GLC analysis, t_R=18.8 (*R*), 19.2 (*S*) min (SUPERCO, α-DEX120, 120 °C).

$[\alpha]_D^{22}$ +22.7 (*c* 1.01, $CHCl_3$) (99% ee). CD_{CHCl3} $[\theta]$=+2100, $\Delta\varepsilon$=+0.636 (99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (dddd, J=3.9, 11.9, 11.9, 13.1 Hz, 1H), 1.58–1.74 (m, 2H), 1.60 (d, J=0.4 Hz, 3H), 1.69 (d, J=1.0 Hz, 3H), 1.81–1.89 (m, 1H), 1.96 (ddd, J=7.4, 8.0, 14.7 Hz, 1H), 2.00–2.08 (m, 1H), 2.08–2.16 (m, 1H), 2.24–2.34 (m, 2H), 2.36–2.46 (m, 2H), 5.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 24.9, 25.7, 27.7, 27.9, 32.3, 41.9, 51.0, 121.9, 132.9, 213.1; IR (ATR) 1708.6 (C=O) cm^{-1}; MS (EI) m/z: 166 (M^+), 111, 98 (base peak); HRMS (EI) m/z: (M^+) calcd for $C_{11}H_{18}O$, 166.1358; found, 166.1355.

*4.4.7. (R)-2-Isopentylcyclohexanone: (R)-**8**.* Chiral GLC analysis, t_R=40.3 (*R*), 41.4 (*S*) min (SUPERCO, α-DEX120, 110 °C).

$[\alpha]_D^{20}$ +14.8 (*c* 0.997, $CHCl_3$) (46% ee). CD_{CHCl3} $[\theta]$=+1323, $\Delta\varepsilon$=+0.401 (46% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.871 (d, J=6.6 Hz, 3H), 0.883 (d, J=6.6 Hz, 3H), 1.10–1.24 (m, 3H), 1.39 (dddd, J=3.6, 11.2, 11.2, 13.2 Hz, 1H), 1.52 (m, 1H), 1.58–1.64 (m, 1H), 1.64–1.72 (m, 1H), 1.72–1.80 (m, 1H), 1.80–1.89 (m, 1H), 1.98–2.06 (m, 1H), 2.07–2.15 (m, 1H), 2.18–2.26 (m, 1H), 2.26–2.33 (m, 1H), 2.39 (dddd, J=1.4, 4.3, 4.3, 13.3, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 17.5, 19.7, 22.1, 22.9, 23.1, 28.7, 31.3, 36.8, 45.9, 208.6; IR (ATR) 1708.6 (C=O) cm^{-1}; MS (EI) m/z: 168 (M^+), 145, 126, 111, 98 (base peak); HRMS (EI) m/z: (M^+) calcd for $C_{11}H_{20}O$, 168.1514; found, 168.1517.

*4.4.8. 2-Propylcyclohexanone: **9**.* Chiral GLC analysis, t_R=17.3, 17.6 min (SUPERCO, α-DEX120, 90 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.899 (t, J=7.2 Hz, 3H), 1.13–1.24 (m, 1H), 1.24–1.35 (m, 2H), 1.34–1.44 (m, 1H), 1.59–1.81 (m, 3H), 1.81–1.89 (m, 1H), 1.96–2.06 (m, 1H), 2.06–2.14 (m, 1H), 2.23–2.33 (m, 2H), 2.39 (dddd, J=1.4, 4.3, 4.4, 13.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.2, 24.7, 27.9, 31.4, 33.7, 41.8, 50.4, 213.6; IR (ATR) 1706.7 (C=O) cm^{-1}; MS (EI) m/z: 140 (M^+), 111, 98 (base peak); HRMS (EI) m/z: (M^+) calcd for $C_9H_{16}O$, 140.1201; found, 140.1203.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.09.085.

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