A Modified Thermodynamically Controlled Deracemization of 2-Allylcyclohexanone and Its Application to Asymmetric Synthesis of (*R*)-(−)-Epilachnene

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The efficiency of thermodynamically controlled deracemization was influenced considerably by the solvent used. Based on this finding, an improved method was developed, by which 2-allylcyclohexanone was converted to the *R*-isomer of 93% ee in 72% yield. As an application of the method, (*R*)-(−)-epilachnene, an antipode of the defensive droplets from the Mexican bean beetle, *Epilachna varivestis*, was synthesized in short steps.

Thermodynamically controlled deracemization which is conceptually summarized in Figure 1[1] was developed as a new method to prepare optically active α-monosubstituted cyclohexanones. The method was substantiated in basic suspension media based on inclusion complexation.[2,3]

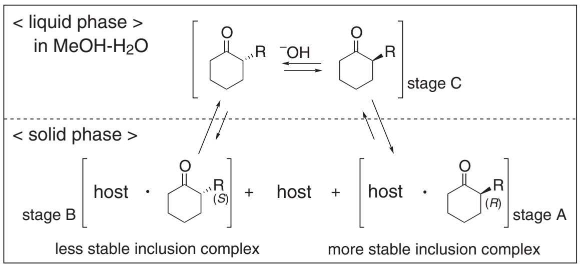
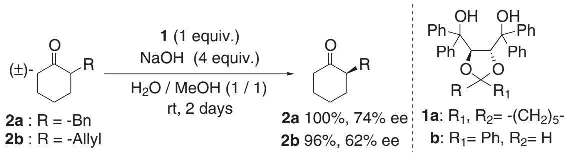


Figure 1. Concept of thermodynamically controlled deracemization.

For example, use of (*R*,*R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (**1a**)[4] (1.0 equiv.) with alkaline in aqueous MeOH converted racemic 2-benzylcyclohexanone (**2a**) to the *R*-isomer of 74% ee in quantitative yield. Further, (*R*)-2-allylcyclohexanone (**2b**) of 62% ee was obtained in 96% yield, when **1b** was used in place of **1a** (Scheme 1). Resolution efficiency (*E*)[5] of the deracemization for **2a** and **2b** reached 148 and 119%, respectively. Thus, the deracemization provided a convenient and excellent method for the preparation of optically active α-substituted cyclohexanones.

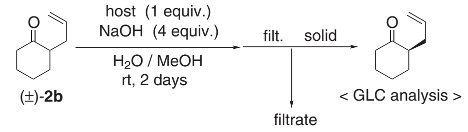


Scheme 1.

However, the ketone recovered was not optically pure enough for use as a starting material for asymmetric syntheses. In preliminary studies, we recognized the importance of the solubility of guest molecules into aqueous MeOH used as the solvent. Actually, the proportion of water in aqueous MeOH influenced the optical purity of the ketones. In this paper, we would like to describe new findings, a new procedure of the deracemization of **2b**, and its application to an asymmetric synthesis of (*R*)-(−)-epilachnene (**3**), which is the antipode of the natural epilachnene isolated as a component of the defensive droplets from glandular hairs of the pupa of the Mexican bean beetle, *Epilachna varivestis*.[6]

In the previous method (Scheme 1), the reaction mixture was treated with a saturated NH_4Cl aq and extracted with ether to recover satisfactorily all of the guest molecules (ketone). As a result, the recovered guest molecules were contaminated with the free guest molecules, which were not included by the host molecules and were a 1:1 mixture of racemic isomers (See Figure 1). When the amount of guest molecules remaining in the liquid phase increases, the optical purity of the recovered ketone lowers to some extent. That is, the enantiomeric excess of the ketone is presumed to lower considerably when the solubility of the ketone into the solvent (into the liquid phase) increases according as the decrease of the proportion of water in aqueous MeOH used as a solvent.

In the present study, therefore, the solid phase was separated from the liquid phase by filtration after the deracemization in order to evaluate exactly the efficiency of the molecular recognition process (Scheme 2). Optical and chemical yields of the guest compound recovered from the solid phase were examined and were plotted against the proportion (in %) of water in aqueous MeOH. First, the results of the combination of **2b** and **1a** are shown in Figure 2a.



Scheme 2.

When the proportion of water was 40%, none of **2b** was obtained from the solid phase because of the high solubility of **2b** into the solvent. In 60% water, 55% ee of **2b** was recovered in about 60–80% yield. Thus, as the proportion of water became higher, **2b** was recovered more effectively. However, optical purity of **2b** decreased gradually down to 40% ee. A more or less similar phenomenon was observed in the combination of **2b**·**1b**. The results are shown in Figure 2.

By comparison between Figures 2a and 2b, it was clear that **1b** was superior to **1a** to recognize **2b**. This fact corresponded to the finding reported in the previous paper,[2] in which **2b** was converted more effectively to the *R*-isomer (62% ee) in the presence of **1b** than **1a** (34% ee) in H_2O–MeOH (50:50). However, as mentioned above, the optical purity was unsatisfactory owing to the procedure by which all of the guest molecules **2b** were recovered.

Based on the fact shown in Figure 2b, an improved procedure for deracemization was developed according to the following con-

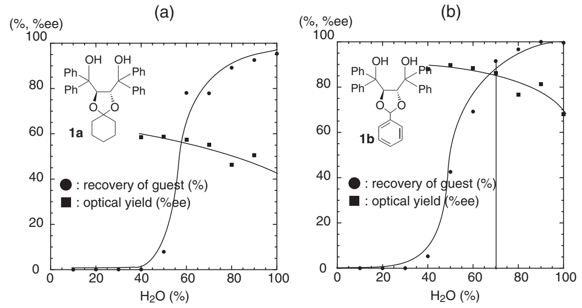
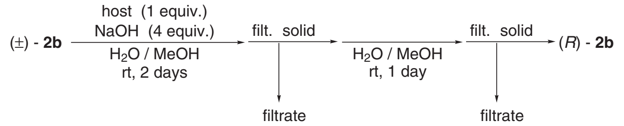


Figure 2. Solvent dependence of chemical and optical yields of **2b** recovered from the solid phase. (a): **2b**·**1a** (b): **2b**·**1b**.

siderations: 1) In order to ensure high optical purity, the recovery of guest molecules is sacrificed to some extent by filtration. 2) In order to increase the optical purity further, the solid phase obtained by the filtration, a mixture of the host and the optically enriched guest molecules, is suspended again into fresh solvent without a base. That is, the mixture is subjected to optical resolution by inclusion recomplexation. 3) It is important that the choice of the H_2O–MeOH ratio influences considerably the efficiency of the new procedure.

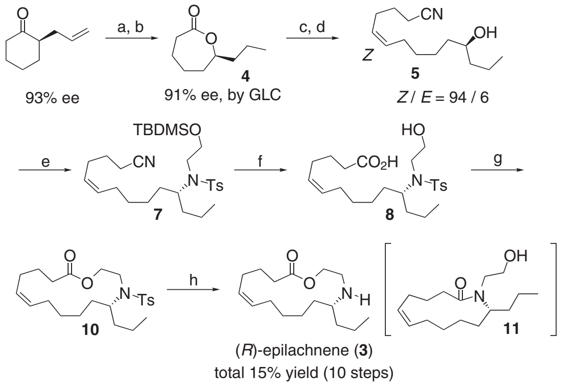
Actually, a 7:3 mixture of H_2O–MeOH (shown as a vertical line in Figure 2b) was chosen as a solvent for improved deracemization of **2b** with **1b**. The suspension of **2b** (50 mg, 0.36 mmol), host compound **1b** (186 mg, 0.36 mmol), and sodium hydroxide (1.4 mmol) in H_2O–MeOH (5 mL) was stirred at room temperature for 2 days. The mixture was filtered and the residue was washed with H_2O–MeOH (7:3, 1 mL 3 times). The resulting residue, the solid phase, was suspended again into a fresh mixture of H_2O–MeOH (7:3, 5 mL) at ambient temperature for 1 day. After filtration followed by washing with H_2O–MeOH (7:3, 1 mL 3 times), the residue was dissolved in ether and subjected to gas chromatography (GC) to afford 93% ee of (*R*)-**2b** in 70% yield (Scheme 3).[7] Thus, the value of *E* increased to 130%.



Scheme 3.

A 2-g-scale reaction of racemic **2b** was successfully achieved in a 67:33 mixture of H_2O–MeOH (200 mL) to give 93% ee of (*R*)-**2b** in 72% yield. When a 70:30 mixture was used, the optical yield of (*R*)-**2b** decreased down to 80% ee. This finding proved that solvent composition has a significant impact upon the efficiency of the deracemization.

In order to demonstrate the usefulness of the improved deracemization, **3** was synthesized using (*R*)-**2b** (93% ee) as the starting material (Scheme 4). First, (*R*)-**2b** was converted to lactone **4** by hydrogenation — Baeyer–Villiger oxidation sequence. DIBAL reduction of **4** followed by Wittig reaction gave hydroxy nitrile **5**, which was subjected to Mitsunobu-type reaction with *N*-[2-(*t*-butyldimethylsilyloxy)ethyl]tosylamide (**6**) in the presence of cyanomethylenetrimethylphosphorane (CMMP)[8] to yield sulfonamide **7** with Walden inversion at the carbinol stereocenter of **5**. Hydrolysis of the nitrile **7** provided seco-acid **8**, which was successfully cyclized by the reaction of 2-chloro-1-methylpyridinium iodide (**9**)[9] under high dilution conditions to afford lactone **10** in 60% yield along with 6% of a dimer and 30% of recovered seco-acid **8**. Although deprotection of the tosyl group of **10** with sodium naphtalenide at −40 °C in DME took place smoothly, the product of the reaction was unfortunately, undesired lactam **11** generated by intramolecular acyl migration. So, *trans*-lactonization[10] of **11** was carried out by treatment with *p*-toluenesulfonic acid to yield **3** as a pale yellow oil, $[\alpha]^{20}_{D}$ −44.0 (*c* 0.47, MeOH), whose physical properties compared well with those in the literature $[\alpha]^{25}_{D}$ +50.8 (*c* 1.36, MeOH)].[11c]



Scheme 4.[a]

[a] Reagent and Conditions: (a) H_2, Pd/C, $NaHCO_3$, ether; (b) *m*-CPBA, NaH_2PO_4, CH_2Cl_2, rt, quant. (2 steps); (c) DIBAL, CH_2Cl_2; (d) $Ph_3P^+(CH_2)_4CN\ Br^-$, sodium dimsylate, DMSO, rt, 30 min, 70% (2 steps); (e) **6** (1.5 equiv.), CMMP (1.5 equiv.), tol., rt, 24 h, 91%; (f) KOH, EtOH, 95 °C, 18 h, quant.; (g) **9**, NEt_3, MeCN, reflux, 30 min, 60%; (h) i) Na, $C_{10}H_8$, DME, −40 °C, 0.5 h, ii) *p*-TsOH, tol., 80 °C, 4 h, 56%.

Thus, since the solubility of the guest molecule into a media has a significant impact upon the efficiency of the deracemization, we are continuing further investigation to obtain highly optically active α-substituted cycloalkanones and to reveal the detailed nature of the molecular recognition process affected by the media.

References and Notes

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