Deracemization of Acyclic α-Hydroxy Ketone Derivatives by Dynamic Resolution Using an Optically Active Host Compound

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Abstract: The dynamic resolution of racemic acyclic α-hydroxy ketone derivatives is accomplished using an optically active host compound, TADDOL, under basic conditions to give the corresponding optically active ketones.

Key words: acyclic ketones, deracemization, enantiomeric resolution, host–guest systems, optically active compounds

Optically active acyclic α-hydroxy ketones are very important in organic synthesis, and many asymmetric syntheses of such compounds have been developed. For example, the asymmetric protonation of the corresponding enolate as the precursor is one of the useful methods for the synthesis of chiral ketones.[1,2] We have also reported on the asymmetric protonations via the enzymatic hydrolysis of enol esters[3] and the conventional enantioface-differentiating protonation of enolates using chiral proton sources.[4] These procedures, however, could not be used for acyclic compounds, except in rare cases, because the regioselective preparation of the enolates from the corresponding ketones is difficult.

Enzyme-mediated deracemization has been developed as an attractive procedure for preparing optically active compounds.[5–8] This protocol allows the conversion of a racemic mixture into the optically active form of the same material. Although the most common process is the enzymatic deracemization of *sec*-alcohols and amines, microbial deracemization of α-substituted carboxylic acids has also been reported.[7,8] On the other hand, there have been relatively few reports on the non-enzymatic deracemization process.[9–11] As a unique example, the host–guest inclusion complexation technique, which is usually used for the thermodynamic resolution of racemates, was used for the deracemization of α-substituted cyclic ketones under basic conditions by Tsunoda et al.[11] We then noticed that this method can be potentially useful for the most straightforward preparation of optically active acyclic ketones, although the stereocontrol of the acyclic compounds should be more difficult than that of the cyclic one. We now report a new version of the reaction for the preparation of optically active acyclic α-hydroxy ketone derivatives via deracemization of the corresponding racemic mixture using the inclusion complexation methodology.

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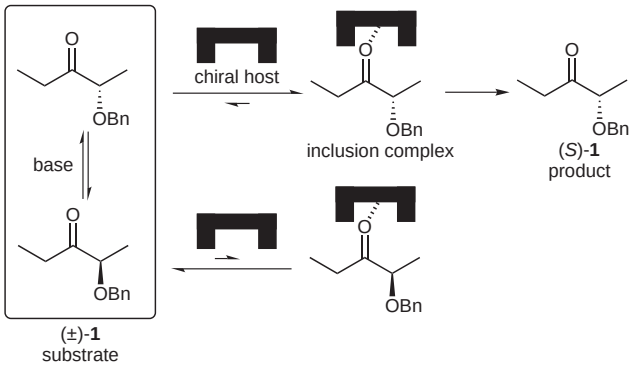
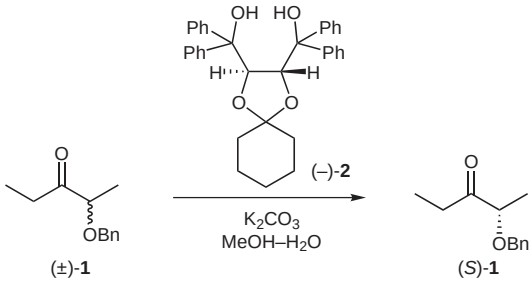
A racemic 2-benzyloxy-3-pentanone [(±)-**1**] was selected as the representative starting material.[12] In the deracemization process, it is essential that the substrates easily racemize under basic conditions and, in the meantime, the enantioselective inclusion complexation with the host compound proceeds (Scheme 1). First, we tested the racemization of the optically active (*S*)-**1** using several bases, i.e., LiOH, NaOH, and K_2CO_3. After several trials, we found that the racemization of (*S*)-**1** easily occurred using any of these bases. For example, the treatment of (*S*)-**1** (95% ee) with K_2CO_3 in a 1:1 mixed solvent of MeOH–H_2O for 24 hours at room temperature gave almost only the racemate **1** (5% ee). We then chose K_2CO_3, which had the weakest basicity, as the standard base.



Scheme 1

In our previous study, we developed a facile method to prepare various kinds of optically active acyclic ketones bearing an α-alkoxy group by thermodynamic resolution with a chiral host, the (–)-TADDOL derivative bearing the cyclohexyl ring, (4*R*,5*R*)-(–)-2,2-pentamethylene-α,α,α′,α′-tetraphenyl-1,3-dioxolan-4,5-dimethanol [(–)-**2**], derived from ethyl L-tartrate.[13] Second, we applied this reaction to the deracemization of (±)-**1** by coupling with the racemization process described above (Scheme 2). The experimental procedure is quite simple, and the typical one is as follows (entry 1, Table 1). A suspension of (±)-**1** (100 mg, 0.52 mmol), (–)-**2** (1 equiv) and K_2CO_3 (4 equiv) in MeOH–H_2O [5 mL:5 mL; substrate concentration (sub. concn) = 52 mM] was stirred for three days at room temperature (20–25 °C). After the reaction was quenched with a saturated aqueous solution of NH_4Cl, the products were extracted with EtOAc (3×), washed with brine, and dried over Na_2SO_4. After evaporation in vacuo,

the residue was purified by flash column chromatography on silica gel to afford **1**. The chiral host (–)-**2** was also quantitatively recovered. As a result, compound **1** was certainly recovered as the optically active form in a 97% isolated yield [(*S*)-**1**, 49% ee].[14–17] The absolute configuration agrees with our previous results which show the preferential synthesis of the inclusion complex between (–)-**2** and (*S*)-**1**.[13] The temperature significantly affected the enantioselectivity, and the reactions at the lower (entry 2) and higher temperatures decreased the ee of **1** (entry 3). Using a higher amount of the host compound (–)-**2** improved the ee, and the ee of the resulting (*S*)-**1** for the reaction with two equivalents of (–)-**2** (entry 4) was up to 61%. Unfortunately, using four equivalents of (–)-**2** (entry 5) did not remarkably affect the enantioselectivity. On the other hand, the racemizations using not only H_2O (entry 6), but also MeOH (entry 7) as the independent solvent did not proceed at all,[18] and the highly enantioselective reaction proceeded only in the mixed solvent of MeOH and H_2O. Interestingly, changing the amount of the solvent dramatically improved the ee. While the reaction in MeOH–H_2O (10 mL:10 mL; lower sub. concn, 26 mM) gave (*S*)-**1** with only a 6% ee (entry 8), using smaller amount of solvent produced better results (entry 9–12). To our surprise, the deracemization using only 1.26 mL (sub. concn 416 mM; entry 11) and 0.62 mL (sub. concn 832 mM; entry 12) of the mixed solvent proceeded with an excellent enantioselectivity, and the ee of the resulting (*S*)-**1** were up to 96% ee; $[\alpha]_D^{15}$ –44.6 (*c* 1.01, $CHCl_3$).[19] These results indicate that the solvent and the substrate concentration are very important factors in the deracemization to construct the inclusion complex stabilized by a sophisticated interaction with van der Waals contacts and hydrogen bondings.



Scheme 2

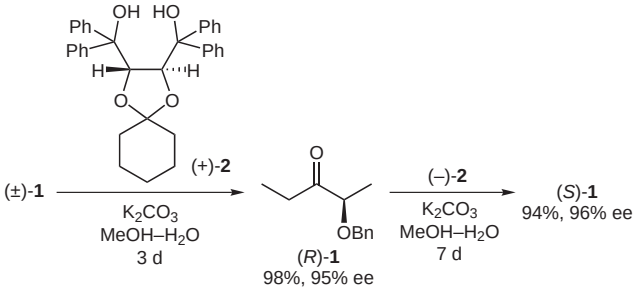
If the enantioselective dynamic resolution by the inclusion complexation of (*S*)-**1** with (–)-**2** thermodynamically proceeded, the treatment of (±)-**1** with the (+)-antipode **2** derived from ethyl D-tartrate should give the *R*-enantiomer of **1**. We then examined the reaction of (±)-**1** with (+)-**2** (Scheme 3). As expected, the deracemization of **1** occurred in the sterically opposite mode to afford (*R*)-**1** with a 95% ee in 98% yield; $[\alpha]_D^{21}$ +41.9 (*c* 1.21, $CHCl_3$). Furthermore, the sequential experiment of the resulting (*R*)-**1** with (–)-**2** for seven days produced the *S*-enantiomer of **1** with a 96% ee in 94% yield. The reaction needed a longer reaction time due to the need for the racemization step from (*R*)-**1**.

We next applied the reaction to various acyclic α-hydroxy ketone derivatives (Scheme 4). These results are summarized in Table 2. Although the optimum conditions for the substrate concentration and the type of base depended on the substrates, in all cases, the deracemizations proceeded to afford the corresponding optically active ketones.[20] In particular, excellent enantioselectivities were observed in the cases of (±)-**3** (R^1 = Pr, entry 1) and (±)-**7** (R^1 = Ph, entry 5) to give (*S*)-**3** and (*S*)-**7** in a 95% ee and 98% ee,

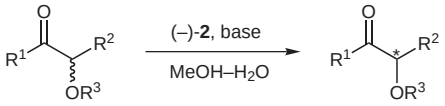
Table 1 Deracemization of (±)-**1** with (–)-**2**[a]

Entry	MeOH (mL)	H_2O (mL)	Sub. concn (mM)	(–)-**2** (equiv)	Temp (°C)	Yield (%)	ee (%)
1	5	5	52	1	r.t.	97	49
2	5	5	52	1	4	94	34
3	5	5	52	1	40	94	ca. 0
4	5	5	52	2	r.t.	98	61
5	5	5	52	4	r.t.	95	62
6	0	10	52	2	r.t.	100	6
7	10	0	52	2	r.t.	96	ca. 0
8	10	10	26	2	r.t.	92	6
9	2.5	2.5	104	2	r.t.	99	82
10	1.25	1.25	208	2	r.t.	93	93
11	0.63	0.63	416	2	r.t.	95	96
12	0.31	0.31	832	2	r.t.	100	96

[a] Unless otherwise specified, the reaction was performed using (±)-**1** (100 mg, 0.52 mmol), (–)-**2**, and K_2CO_3 (4 equiv) for 3 d.



Scheme 3



3: R^1 = Pr, R^2 = Me, R^3 = Bn
4: R^1 = Bu, R^2 = Me, R^3 = Bn
5: R^1 = but-3-en-1-yl, R^2 = Me, R^3 = Bn
6: R^1 = Me, R^2 = Me, R^3 = Bn
7: R^1 = Ph, R^2 = Me, R^3 = Bn
8: R^1 = Et, R^2 = Et, R^3 = Bn
9: R^1 = Et, R^2 = Me, R^3 = BOM
10: R^1 = Et, R^2 = Me, R^3 = MPM
11: R^1 = Et, R^2 = Me, R^3 = Pr

Scheme 4

respectively. On the other hand, we obtained (*R*)-**6** (entry 4) and (*R*)-**10** (entry 8) with the absolute configurations opposite for those of the other substrates. These results are not inconsistent with our previous report because the chiral host (–)-**2** preferentially captured the *R*-enantiomers for only **6** and **10**.[13] It is noteworthy that an aromatic function of the substrates is not necessary for the deracemization. The reaction for compound (±)-**11** bearing a propyloxy group (R^3 = Pr, entry 9) also proceeded to afford the corresponding optically active (*S*)-**11**, although the isolated yield was low for the high volatility.

In summary, a simple and efficient approach to optically active acyclic α-hydroxy ketone derivatives by deracemization based on dynamic resolution with a chiral host compound has been developed. This method is applicable for various compounds, and is expected to be a potentially useful tool for organic synthesis.

Acknowledgment

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Table 2 Deracemization of Several Racemic Substrates with (–)-**2**[a]

Entry	Substrate	Sub. concn (mM)[b]	Base	Product	Yield (%)	ee (%)
1	(±)-**3**	416	K_2CO_3	(*S*)-**3**	99	95
2	(±)-**4**	208	K_2CO_3	(*S*)-**4**	95	63
3	(±)-**5**	104	K_2CO_3	(*S*)-**5**	94	61
4	(±)-**6**	416	K_2CO_3	(*R*)-**6**	96	52
5	(±)-**7**	104	LiOH	(*S*)-**7**	86	98
6	(±)-**8**	104	LiOH	(*S*)-**8**	95	71
7	(±)-**9**	416	NaOH	(*S*)-**9**	81	35
8	(±)-**10**	208	NaOH	(*R*)-**10**	100	72
9	(±)-**11**	416	LiOH	(*S*)-**11**	44	63

[a] Unless otherwise specified, the reaction was performed using the racemic substrate (ca. 100 mg, 0.52 mmol), (–)-**2**, and base (4 equiv) in MeOH–H_2O (1:1) for 3 d at r.t.
[b] The substrate concentration was adjusted by changing the volume of the solvent.

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(12) The substrate (±)-**1** was easily prepared from (±)-lactic acid in four steps. The details of this synthesis have been reported in ref. 13.

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(14) The absolute configuration of **1** was confirmed by comparing the obtained optical rotation value with the reported value: Lit.[21] $[\alpha]_D^{24}$ –45.9 (*c* 1.16, $CHCl_3$), *S*-form.

(15) The ee of **1** was determined by HPLC analysis with CHIRALCEL OJ (Daicel Chemical Industries, Ltd.); eluent, hexane–2-PrOH = 180:1; flow rate, 0.5 mL min^{-1}; t_R = 40 (*R*) and 50 (*S*) min.

(16) The deracemization did not occur for the reactions using the other TADDOL derivatives bearing a cyclopentane ring and a dimethyl group [(–)-2,2-tetramethylene- and 2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolan-4,5-dimethanol, respectively], (+)-1,1′-bi-2-naphthol, and (–)-hydrobenzoin as chiral host compounds under the same conditions.

(17) Although the ee of (*S*)-**1** increased according to the extension of the reaction time (42% ee for one day), the reaction for over three days gave almost the same result as that of the three-day reaction. We then decided that the racemizations in all cases were carried out for three days.

(18) The reaction using EtOH, *i*-PrOH, *t*-BuOH, and cyclohexane as an alternative mix solvent with H_2O gave only the racemate **1**.

(19) A white solid was obtained by filtration when a sat. NH_4Cl aq and EtOAc were not added to the reaction mixture. ESI-TOFMS analysis of the collected solid showed the peak of [**1** + **2** + Na]$^+$ ion (*m/z* = 721.3 for $C_{46}H_{50}O_6Na$) in the same manner as the case of the optical resolution.[13] The peak would mean the construction of the 1:1 inclusion complex (**1** and **2**) in the reaction mixture.

(20) The ee of the products can be improved by a sequential optical resolution using (–)-**2** without a base.[13]

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