Pergamon

Tetrahedron Letters, Vol. 38, No. 44, pp. 7759-7760, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10071-5

Deracemization of 2-Alkylcyclohexanones Utilizing Host-Guest Molecular Association with Optically Active Host Compounds in Basic Suspension Media

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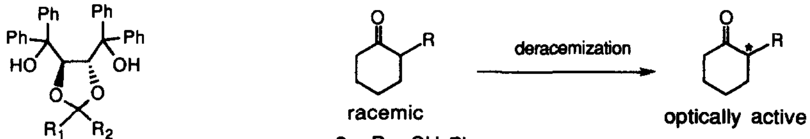
***Abstract*:** Based on host-guest inclusion complexation in the solid state, α-substituted cyclohexanones **2a~c** were deracemized using optically active host compounds in alkaline conditions to optically active **2** in excellent chemical yield with high enantiomeric excess. © 1997 Elsevier Science Ltd.

Host-guest inclusion complexation utilizing optically active host compounds, such as 1,3-dioxolanes **1a**, **1b**, derived from tartaric acid, has now provided an effective method for optical resolution of a wide variety of racemic guest modifications.[1] However, there are only a few successful studies for the optical resolution of α-substituted cyclohexanones.[2,3] Because of our interest in host-guest inclusion complexation in the solid state, we recently attempted the optical resolution of 2-benzylcyclohexanone (**2a**) using **1a** and found that (*R*)-**2a** of 64% ee was obtained in 37% yield from a 1 : 1 inclusion complex of **1a** and **2a**.[6] Encouraged by this finding, we carried out *thermodynamically controlled* deracemization[7,8] of **2a~c** with **1** in basic suspension media (Scheme 1), because this method permits the possibility of 100% conversion of starting racemic **2** to corresponding optically active **2**. Herein we describe a novel method for the preparation of optically active **2** in excellent chemical yield with high enantiomeric excess.



1a: $R_1 = R_2 = -(CH_2)_5-$
b: $R_1 = Ph$, $R_2 = H$

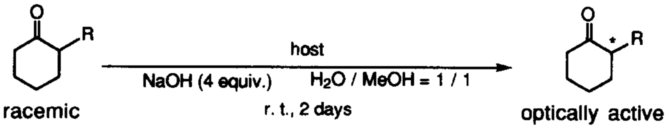
2a: $R = CH_2Ph$
b: $R = CH_2CH{=}CH_2$
c: $R = CH_2CH_2OMe$

(Scheme 1)

In a typical experiment, the suspension of **2** (250 mg), host compound **1**, and sodium hydroxide (4 equiv) in MeOH - H_2O (1 : 1, 25 m*L*) was stirred at room temperature for 2 days. The mixture was treated with a saturated NH_4Cl aq. and extracted with ether. After evaporation of the solvent *in vacuo*, the ketone **2** and the host **1** were easily isolated by silica gel column chromatography.[9]

The Table clearly shows that 1) the *R*-isomer of **2a** was enriched by **1a** (entries 1~3), and 2) these results correspond with the optical resolution in which the same isomer was included predominantly by **1a**. 3) The use of one equivalent of **1a** afforded (*R*)-**2a** with the highest optical purity (entries 1~3). 4) **1b**

Table. Deracemization of cyclohexanones



entry	R	host (equiv.)	recovery of host (%)	recovery of guest (%)	ratio of guest (*R* : *S*)
1	$PhCH_2$-	**1a** (0.5)	100	90	74 : 26
2	(**2a**)	(1)	99	100	87 : 13
3		(2)	97	98	85 : 15
4		**1b** (1)	100	99	38 : 62
5		(2)	99	99	36 : 64
6	$CH_2{=}CHCH_2$-	**1a** (1)	99	96	67 : 33
7	(**2b**)	(2)	99	98	66 : 34
8		**1b** (1)	100	96	81 : 19
9		(2)	100	98	87 : 13
10	$MeOCH_2CH_2$-	**1a** (1)	100	93	75 : 25
11	(**2c**)	(2)	100 (99)[a]	99 (96)[a]	94 : 6 (97 : 3)[a]
12		**1b** (1)	100	89	50 : 50
13		(2)	100	91	50 : 50

a: Deracemization was carried out in MeOH-H_2O (2 :1) .

slightly favored (*S*)-**2a** (entries 4, 5). On the other hand, 5) *rac*-**2b** was converted to (*R*)-**2b** of 74% ee in the presence of two equivalents of **1b** (entry 9), and 6) **2c** was deracemized to the *R* isomer of 94% ee with two equivalents of **1a** (entry 11). 7) **1a** could not be successfully applied to the deracemization of **2b** (entries 6, 7), and 8) **1b** could not recognize the chirality of **2c** at all (entries 12, 13).

Thus, the present study discloses that deracemization based on inclusion chemistry can provide a convenient and excellent method for the preparation of optically active α-substituted cyclohexanones.

REFERENCES AND NOTES

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(*Received in Japan* 23 *July* 1997; *accepted* 4 *September* 1997)