

THERMODYNAMICALLY CONTROLLED DERACEMIZATION OF 2-ALKYLCYCLOALKANONES UTILIZING HOST-GUEST INCLUSION COMPLEXATION

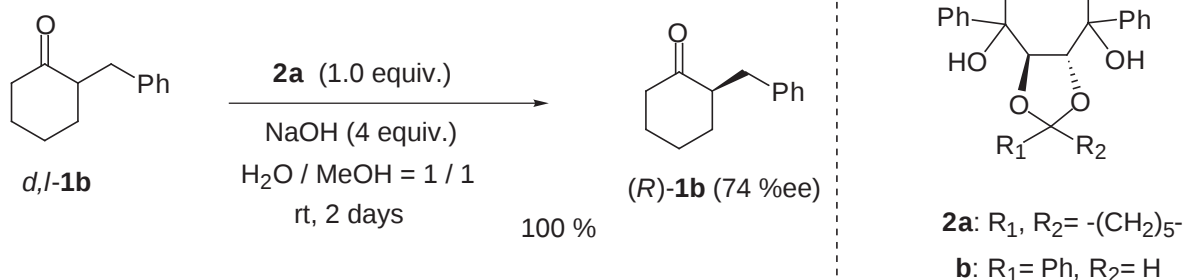
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Abstract - Based on host-guest inclusion complexation in the solid state, α -substituted cycloalkanones were deracemized using optically active host compound, TADDOL (**2a**) in alkaline conditions.

In a previous paper, we described *thermodynamically controlled* deracemization¹ of a few cyclohexanones, such as 2-benzylcyclohexanone (**1b**), using TADDOLs (**2a,b**)² in basic suspension media (e. g. Scheme 1). That study showed that deracemization based on inclusion chemistry could provide a convenient and excellent method for the preparation of optically active α -substituted cyclohexanones. In order to further test the applicability of this methodology and explore the principle of the molecular recognition process, we have extended the reaction to several α -substituted cycloalkanones. Herein the results of our investigation are described.

Scheme 1



In a typical experiment, the mixture of cyclic ketone (**1**) (250 mg), host compound (**2a**), and sodium hydroxide (4 equiv.) in MeOH - H₂O (1 : 1, 25 mL) was stirred at room temperature for 2 days. The resulting mixture was treated with aq. saturated NH₄Cl and extracted with ether. After evaporation of the solvent *in vacuo*, the ketone (**1**) and the host (**2a**) were easily isolated by silica gel column chromatography.³

Table 1 Deracemization of cycloalkanones

entry	n	R		equiv. of 2a	H ₂ O / MeOH	yield (%)	% ee (configuration)
1*	0	-CH ₂ Ph	(1a)	1.0	1 / 1	85	10
2**	1	-CH ₂ Ph	(1b)	1.0	1 / 1	100	74 (<i>R</i>)
3	2	-CH ₂ Ph	(1c)	1.0	1 / 1	100	36 (<i>R</i>)
4	1	-Ph	(1d)	1.0	1 / 1	92	46 (<i>R</i>)
5	1	-CH ₂ CH ₂ Ph	(1e)	1.0	1 / 1	100	54 (<i>R</i>)
6	1	-CH ₂ C ₆ H ₄ Me- <i>o</i>	(1f)	1.0	2 / 1	97	66 (<i>R</i>)
7	1	-CH ₂ C ₆ H ₄ Me- <i>m</i>	(1g)	1.0	2 / 1	98	86 (<i>R</i>)
8	1	-CH ₂ C ₆ H ₄ Me- <i>p</i>	(1h)	1.0	1 / 1	96	82 (<i>R</i>)
9**	1	-CH ₂ CH=CH ₂	(1i)	1.0	1 / 1	96	34 (<i>R</i>)
10	1	-CH ₂ CH=CMe ₂	(1j)	1.0	4 / 1	97	90 (<i>R</i>)
11	1	-CH ₂ CH ₂ CHMe ₂	(1k)	1.0	2 / 1	92	46 (<i>R</i>)
12**	1	-CH ₂ CH ₂ OMe	(1l)	2.0	2 / 1	96	94 (<i>R</i>)
13	1	-CH ₂ CH ₂ CH ₂ OMe	(1m)	2.0	1 / 1	100	16

*) The reaction was carried out for 2 weeks. **) See ref. 1.

Table 1 shows that the *R*-isomer of cyclic ketones was obtained predominantly, and 2-benzylcyclohexanone (**1b**) was deracemized more effectively than 2-benzylcyclopentanone (**1a**) and -cycloheptanone (**1c**) (entry 2 vs 1 and 3). In the case of 2-(ω-arylalkyl)cyclohexanones, the optical purity was dramatically changed by the difference of i) the length of the side chain (entry 2 vs 4 and 5) and ii) the position of the

methyl groups on the aromatic ring (entry 2 vs 6~8). The introduction of methyl group on the side chain influences also the molecular recognition process in the case of 2-allylic cyclohexanone. Thus, 2-prenylcyclohexanone (**1j**) was included into a cavity constituted by the aggregation of a host molecule (**2a**) more effectively than 2-allylcyclohexanone (**1i**) (entry 9 vs 10). On the contrary, the ee(%) was decreased dramatically by the lack of a π -electron system on the side chain (entry 10 vs 11). The presence of a lone pair electron of a oxygen atom also induced excellent host-guest complexation (entry 12). However, one carbon elongation complicated the non-covalent binding interactions between the guest and host molecules again (entry 12 vs 13).

Thus, the deracemization was influenced by chain length, shape, functionality, π -electron and the architecture of the α -alkyl side chain on the cycloalkanone and the ring size. Since X-Ray analytical studies of a host-guest complex are not available, the principle of the molecular recognition process is still unclear. However, thermodynamically controlled deracemization based on inclusion chemistry can provide a convenient method for the preparation of optically active α -substituted cyclohexanones.

Further studies to disclose the principle of the molecular recognition process and the applicability of the present method are now in progress.

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