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

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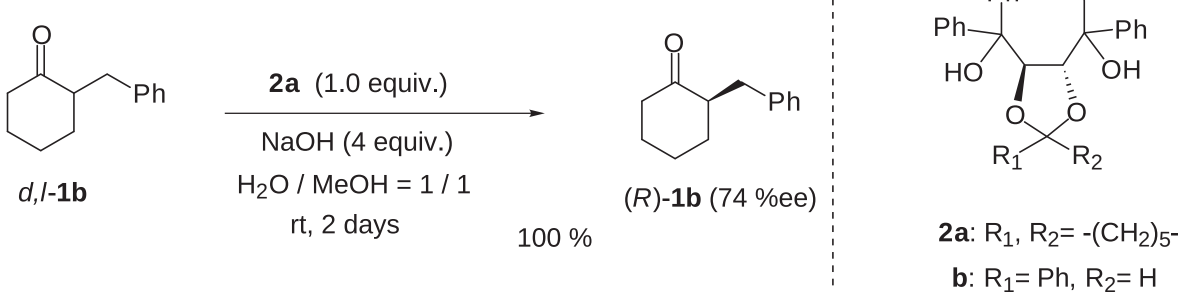
Abstract - Based on host-guest inclusion complexation in the solid state, α-substituted cycloalkanones were deracemized using optically active host compound, TADDOL (**2a**) in alkaline conditions.

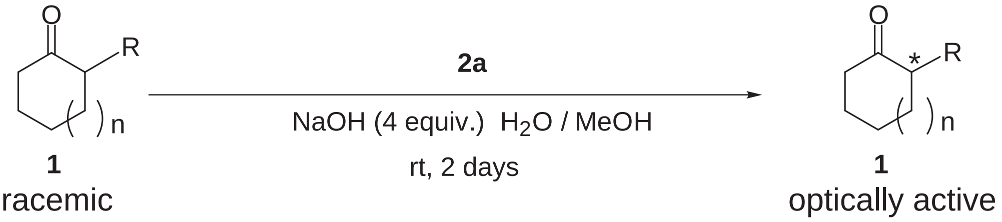
In a previous paper, we described *thermodynamically controlled* deracemization[1] of a few cyclohexanones, such as 2-benzylcyclohexanone (**1b**), using TADDOLs (**2a,b**)[2] in basic suspension media (e. g. Scheme 1). That study showed that deracemization based on inclusion chemistry could provide 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 - H_2O (1 : 1, 25 mL) was stirred at room temperature for 2 days. The resulting mixture was treated with aq. saturated NH_4Cl 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_2O / MeOH	yield (%)	% ee (configuration)
1*	0	-CH_2Ph	(**1a**)	1.0	1 / 1	85	10
2**	1	-CH_2Ph	(**1b**)	1.0	1 / 1	100	74 (*R*)
3	2	-CH_2Ph	(**1c**)	1.0	1 / 1	100	36 (*R*)
4	1	-Ph	(**1d**)	1.0	1 / 1	92	46 (*R*)
5	1	-CH_2CH_2Ph	(**1e**)	1.0	1 / 1	100	54 (*R*)
6	1	-$CH_2C_6H_4Me$-*o*	(**1f**)	1.0	2 / 1	97	66 (*R*)
7	1	-$CH_2C_6H_4Me$-*m*	(**1g**)	1.0	2 / 1	98	86 (*R*)
8	1	-$CH_2C_6H_4Me$-*p*	(**1h**)	1.0	1 / 1	96	82 (*R*)
9**	1	-$CH_2CH{=}CH_2$	(**1i**)	1.0	1 / 1	96	34 (*R*)
10	1	-$CH_2CH{=}CMe_2$	(**1j**)	1.0	4 / 1	97	90 (*R*)
11	1	-$CH_2CH_2CHMe_2$	(**1k**)	1.0	2 / 1	92	46 (*R*)
12**	1	-CH_2CH_2OMe	(**1l**)	2.0	2 / 1	96	94 (*R*)
13	1	-$CH_2CH_2CH_2OMe$	(**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.

ACKNOWLEDGEMENTS

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3. The optical purity of **1** was determined by HPLC and/or GLC analysis using a chiral column. The absolute configuration of **1b-e**, **1i-l** was elucidated by $[\alpha]_D$ and/or CD spectrum. see a) A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.*, 1981, **103**, 3081. b) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, 1972, **20**, 246. c) G. Berti, B. Macchia, and F. Macchia, *J Chem. Soc.(C)*, 1971, 3371.
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