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ASYMMETRIC SYNTHESIS WITH NEW CHIRAL AUXILIARIES DERIVED FROM ISOSORBIDE

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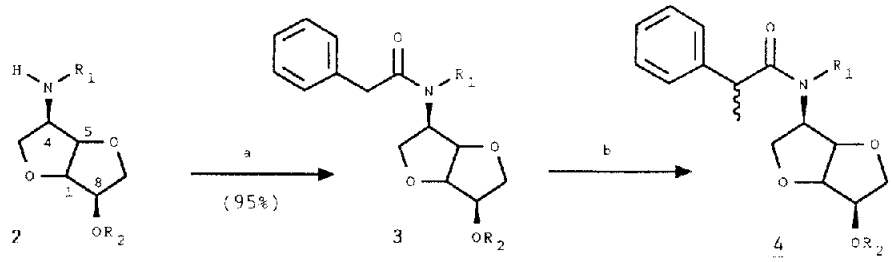
Abstract: *Chiral aminoethers derived from carbohydrates have been used for asymmetric alkylation of phenylacetic amides giving diastereoisomeric excess up to 83%.*

During the last few years, asymmetric synthesis using carbohydrate derivatives as chiral auxiliaries has grown in interest.[1] In this field, we previously described[2] the synthesis of aminoethers and aminoalcohols derived from isosorbide[3] **1** ([1R,4S,5R,8R]-2,6-dioxabicyclo[3.3.0]octan-4,8-diol also called 1-4,3-6-dianhydro-sorbitol), a starch derivative.

We wish to report in the present paper that these new chiral amines can be used to induce the asymmetric alkylation of phenylacetic acid.

The N-acylation (scheme 1) of the amino-compounds **2** to the corresponding phenylacetic amides was carried out by a conventional method (phenylacetic anhydride-pyridine-80°C) in good yield.

scheme 1



(a) $(PhCH_2CO)_2O$, pyridine, 80°C. (b) LDA, HMPA, r.t., then CH_3I, -78°C.

The resulting amides 3 were lithiated[4] by LDA in THF-HMPA at 20°C and then treated with methyl iodide at -78°C. The influence of the R_1 and R_2 moieties on the asymmetric induction was carefully studied as shown in table 1.

table 1. Asymmetric alkylation

				alkylated amides 4			
entry	amides 3	R_1	R_2		yield	de[a]	config.
1	3a	$PhCH_2$	CH_3	4a	75	25	R
2	3b		CH_3	4b	84	64	R
3	3c	iPr	CH_3	4c	78	61	R
4	3d		CH_3	4d	81	34	S
5	3e		H	4d	74	10	R
6	3f		$PhCH_2$	4f	82	65	R
7	3g		CH_2tBu	4g	85	64	R

(a) all diastereoisomeric excesses were determined by gas chromatography.

Good chemical yields as well as low to good diastereoselectivities were observed. The R_1 moiety performs an enantiofacial discrimination and the best results were obtained with R_1= cyclohexyl (entries 2, 6 and 7). The R_2 moiety seems to have little influence on the diastereoselectivity but the free hydroxy function must be avoided (entry 5).

In order to improve the stereoselectivity of the alkylation, various reaction parameters were systematically screened with phenylacetic amide 3b (solvent, cosolvent, base, counterion, temperature and dilution).

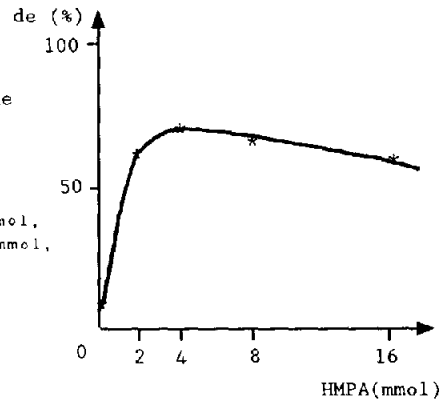


Figure 1. Influence[a] of the quantity of cosolvent on the diastereoselectivity.

(a) conditions: base, 2.4mmol, HMPA, 0 to 16mmol, CH_3I, 8mmol, THF, 10mL, -78°C.

table 2. Influence[a] of base and solvent on diastereoselectivity

base	solvent	de(yield)
LDA	Et_2O	30(93)
LDA	DME	46(88)
LDA	THF	64(97)
LICA	THF	64(97)
LHMDS	THF	59(98)
NaHMDS	THF	64(98)

(a)conditions: base, 2.4mmol, HMPA, 4mmol, 3b, 2mmol, CH_3I, 8mmol, THF, 10mL, -78°C.

table 3. Effect[a] of the dilution and temperature on diastereoselectivity

temperature	dilution	de(yield)
-78°C	0.2	72(97)
-78°C	0.1	72(98)
0°C	0.1	20(84)
-100°C	0.1	83(83)

(a)conditions: LDA, 2.4mmol, HMPA, 8mmol, 3b, 2mmol, CH_3I, 8mmol, THF, 10mL, -78°C.

Unlike the results of Evans[5], Katsuki[6]or Oppolzer[7], the presence of a cosolvent played an important role as shown in figure 1. Without HMPA in THF at -78°C, a very low de was observed whereas a fourfold excess of the same cosolvent improves this value to more than 70%.(The cosolvent amount has little influence in the range of 2 to 16 equivalents). Similar results were observed using DMPU instead of HMPA. THF affords a better chemical yield and diastereoselectivity than DME and diethylether (table 2). The influence of these two parameters can be explained by the presence of numerous chelating sites in 3b leading to different structures of the corresponding amide enolate. Thus, ion-pair dissociation by HMPA, DMPU as well as THF reduces the number of the possible transition states during the alkylation step.

Base and counterion seem to have no effect on the diastereoselectivity (table 2) nor does the dilution (table 3). As expected, the lower the alkylation temperature the better the diastereoselectivity : thus a 83% de could be reached at -100°C (table 3).

In conclusion, similar diastereoisomeric excesses with an easily accessible and unexpensive chiral auxiliary have been obtained in comparison with the results reported for the alkylation of phenylacetic acids using Evans' auxiliaries.[8] Studies are being currently performed to improve the efficiency of our isosorbide derived auxiliary by structural modifications.

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4. typical experiment: amide 3 (2mmol) dissolved in THF (6mL) was added to a solution of LDA (2.4mmol) in THF (10mL) at 20°C and the mixture was stirred for 1/2h. HMPA (8mmol) was added and the mixture was cooled to -78°C. A precooled solution of methyl iodide (8mmol) in THF (4mL) was slowly added and the yellow solution was stirred for 5h at -78°C. The solution was hydrolysed with 1N HCl and then warmed to room temperature. Extraction (CH_2Cl_2), drying and concentration afforded an oil.
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