Asymmetric Synthesis using Chiral Bases: Enantioselective α-Alkylation of Carboxylic Acids

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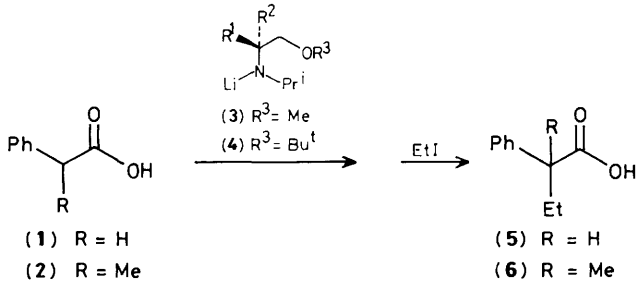
Enantioselective alkylation of carboxylic acids (**1**) and (**2**) at the α-position can be performed using the chiral lithium isopropylamides (**3**) or (**4**), which function as both a strong base and a chiral auxiliary.

Recently, the use of chiral bases which function as both a strong base and a chiral auxiliary has attracted considerable attention in asymmetric synthesis.[1] However, only a few reports[1b,1c] have been concerned with enantioselective carbon–carbon bond formation. We now report our results on the enantioselective α-alkylation of carboxylic acids (**1**) and (**2**) using the chiral lithium isopropylamides (**3**) or (**4**), shown in Scheme 1.

The chiral amines (**7**) and (**8**) necessary for the formation of the chiral lithium amides (**3**) and (**4**) were easily prepared from readily available α-amino acids (**9**), shown in Scheme 2. L-Valine (**9a**) was first converted into its *N*-isopropyl derivative (**10a**), according to the method developed by Ohfune and co-workers.[2] Reduction of (**10a**) with lithium aluminium hydride gave the amino alcohol (**11a**). *O*-Methylation and *O*-t-butylation of (**11a**) afforded the chiral amines (**7a**) and (**8a**), respectively. D-α-Phenylglycine was analogously converted into the chiral amines (**7b**) and (**8b**).†

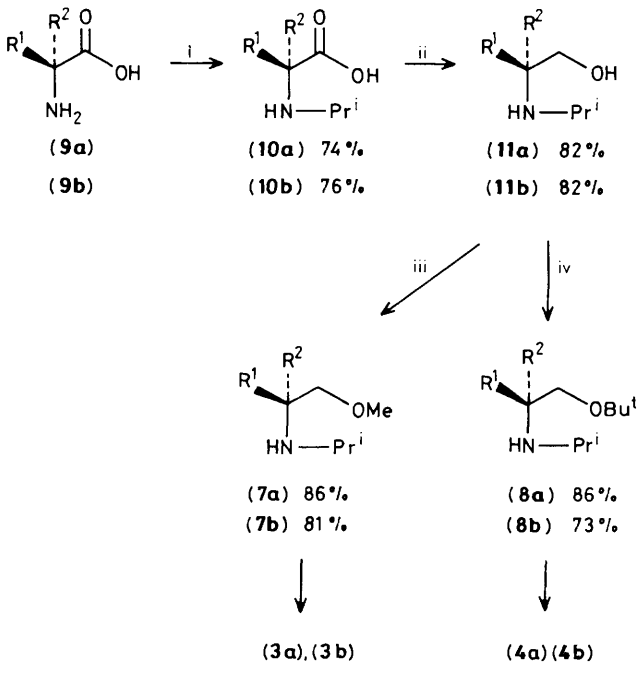


a; $R^1 = Pr^i$, $R^2 = H$
b; $R^1 = H$, $R^2 = Ph$

Scheme 1

† (**7a**), b.p. 74—77.5 °C/40 mmHg, $[\alpha]_D^{23}$ −6.8° (*c* 1, EtOH). (**8a**), b.p. 73—75 °C/10 mmHg, $[\alpha]_D^{22}$ −10.3° (*c* 1, EtOH). (**7b**), b.p. 74—75 °C/3 mmHg, $[\alpha]_D^{24}$ −69.7° (*c* 1, EtOH). (**8b**), b.p. 85—95 °C/1 mmHg, $[\alpha]_D^{25}$ −53.2° (*c* 1, EtOH).

The chiral lithium isopropylamides (**3**) and (**4**) were smoothly produced from (**7**) and (**8**), respectively, in tetrahydrofuran (THF) by treatment with equimolar amounts of n-butyl-lithium. Addition of the carboxylic acid (**1**) or (**2**) (1.0 equiv.) to the solution of the chiral amide (**3**) or (**4**) (2.4 equiv.) immediately generated the dilithium salt, which was treated with ethyl iodide (1.5 equiv.) for a few hours to give



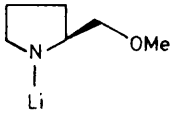
a; $R^1 = Pr^i$, $R^2 = H$
b; $R^1 = H$, $R^2 = Ph$

Scheme 2. i, $MeCOMe$, $NaBH_3CN$, MeOH; ii, $LiAlH_4$, tetrahydrofuran (THF); iii, NaH–MeI, THF; iv, $Me_2C{=}CH_2$, H_2SO_4, CH_2Cl_2.

Table 1. Enantioselective α-alkylation of carboxylic acids.

Run	Carboxylic acid	Chiral base	Lithiation temp./°C	Alkylation Temp./°C	Alkylation Time/h	% Isolated yield[a]	% E.e.[b]	Config.[c]
1	(1)	(3a)	−10	−70	4.5	39(64)	0	—
2	(1)	(3a)	−45	−70	4.5	51(77)	0	—
3	(1)	(3a)	−70	−70	4	82	8	(*S*)
4	(1)	(3a)	−70	−70	4.5[d]	22	12	(*S*)
5	(1)	(3a)	−20	−95	2.5	11(42)	2	(*S*)
6	(1)	(3a)	−95	−95	2	18(42)	24	(*S*)
7	(1)	(3b)	−70	−70	2.5	74	4	(*R*)
8	(1)	(4a)	−70	−70	4.5	70	12	(*S*)
9	(1)	(4a)	−70	−70	2[e]	79	0	—
10	(1)	(4a)	−70	−70	3	75	20	(*S*)
11	(1)	(4b)	−70	−70	2.5	79	4	(*R*)
12	(2)	(3a)	−15	−70	4	54(70)	0	—
13	(2)	(3a)	−70	−70	4.5	38(86)	20	(*S*)
14	(2)	(3b)	−70	−70	3	57	6	(*R*)
15	(2)	(4a)	−70	−70	6	No reaction		
16	(2)	(4a)	−10	−10	2	41(85)	2	(*S*)
17	(2)	(4b)	−70	−70	3.5	No reaction		

[a] Yields in parentheses are based on consumed starting acid. [b] The e.e. of the products (**5**) and (**6**) in each reaction was determined by g.c. measurement (Sumiphase OA-500) of the t-butylamide of (**5**) and by h.p.l.c. measurement (Sumipax OA-1000) of the 3,5-dinitroanilide of (**6**). [c] See refs. 3 and 4. [d] Ethyl bromide was used in place of ethyl iodide. [e] Hexamethylphosphoric triamide (2 equiv.) was added.



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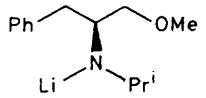
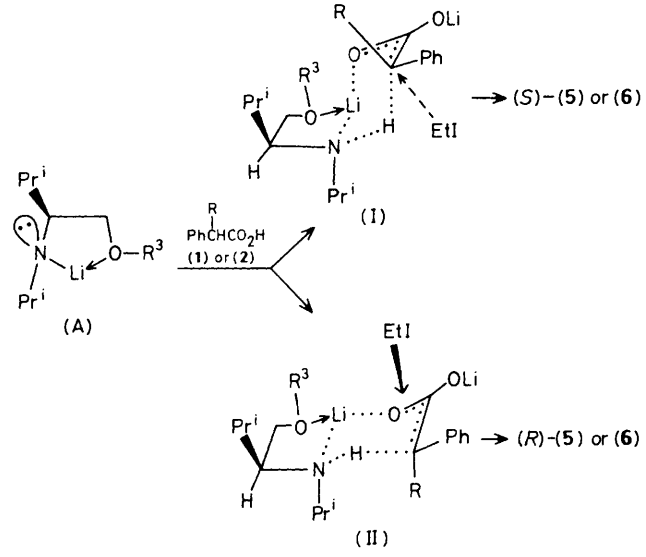


(13)

the α-alkylated carboxylic acid (**5**) or (**6**). The enantiomeric excess (e.e.) values for (**5**) and (**6**) were determined, after derivatization, by g.c. or h.p.l.c. using a chiral stationary phase column. The results are summarized in Table 1.

Several noteworthy features are apparent from Table 1. Alkylation using the chiral bases (**3a**) and (**4a**) derived from L-valine (**9a**) afforded the carboxylic acids (**5**) or (**6**) with the (*S*)-configuration‡ in excess. The (*R*)-isomer‡ of (**5**) or (**6**) was obtained in excess using (**3b**) and (**4b**) derived from D-α-phenylglycine. Higher asymmetric induction was observed on lowering the lithiation (deprotonation) temperature even when the alkylation temperature was unchanged. This clearly demonstrates that the asymmetric efficiency is largely dependent on enantioselective deprotonation. The reaction was carried out in 0.1 M solution, and the concentration of the reaction mixture did not affect significantly either chemical yields or asymmetric efficiency. Replacing ethyl iodide with ethyl bromide gave a lower chemical yield. Tetrahydrofuran seems to be a better solvent than diethyl ether or toluene since no reaction occurred in these solvents when (**4a**) was used in the alkylation of (**1**); addition of hexamethylphosphoric triamide to this reaction, however, lowered the asymmetric induction. Incidentally, the use of the chiral bases (**12**) and (**13**) derived from L-proline and L-phenylalanine, respectively, showed a much lower asymmetric efficiency (less than 4% e.e.) than (**3**) or (**4**).

‡ The absolute configuration of the major isomer in each reaction was determined by comparison of specific rotation with the reported one and by chromatographic behaviour. For (**5**), see ref. 3; (**4**), see ref. 4.



Scheme 3. R^3 = Me or Bu^t.

The above results lead to the probable mechanism (shown for the L-valine derivatives) in Scheme 3. The chiral bases (**3a**) and (**4a**) adopt the chelated structure (A) as proposed by Koga and co-workers.[1g] Interaction of (A) with the carboxylic acid (**1**) or (**2**) results in the formation of the transition states (I) and (II). The *C*-isopropyl group of (I) blocks the top face while the *N*-isopropyl group of (II) blocks the bottom side, allowing ethyl iodide to attack preferentially the bottom side and the top face, respectively. On the basis of the absolute stereochemistry of the major isomer obtained in this manner, structure (I) is designated as the major transition state.

Thus a certain degree of asymmetric induction has been observed in the chiral base mediated α-alkylation of carb-

oxylic acids, this method offering the following advantages: (i) it is a simple operation; (ii) chiral compounds can be obtained in a single step; and (iii) chiral bases are easily recovered and re-used. Hence this reaction provides a new method for enantioselective carbon–carbon bond formation.

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