Asymmetric Alkylation of a Chiral α-Amino Alkenenitrile

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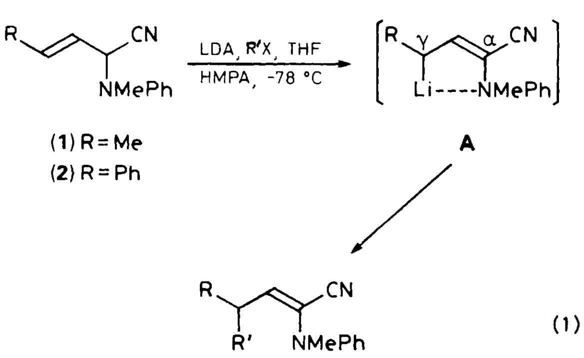
Alkylation of the unsymmetric allylic anion generated from 2-(L-ephedrino)-4-phenylbut-3-enenitrile occurred exclusively at C-4 to give predominantly products having the 4*R*-configuration; the stereoselectivity increased remarkably when the reaction was conducted in a mixture of hexamethylphosphoramide and lithium iodide.

Regiochemical control in reactions of heteroatom-substituted allylic anions is a long-standing problem.[1] On study of unsaturated α-aminonitriles, we found that the alkylation of asymmetric allyl-lithiums generated from aminonitriles (**1**) and (**2**) occurred exclusively at the γ-positions to give predominantly products having the 2*Z*-configuration (equation 1).[2] The regio- and stereo-selectivity may be explained by a transition state **A**, in which the bulky *N*-methylanilino group exerts a steric effect to disfavour α-alkylations but its co-ordination with lithium induces the formation of 2*Z*-products.[3] Based on this assumption, we studied further the asymmetric alkylation of a chiral aminonitrile (**3**). By substitution of *N*-methylaniline with L-(−)-ephedrine (1*R*, 2*S*), a bicyclic transition state **B** having lithium chelating with both amino and alkoxy groups may facilitate the entry of alkylating agents to the *exo*-face (Scheme 1).

Compound (**3**) (C-2 epimers, 1:1) was prepared by condensation of equimolar amounts of cinnamaldehyde, potassium cyanide, and L-(−)-ephedrine hydrochloride.[2] Transformation of (**3**) into a single isomer of conjugated alkenenitrile (**4a**) (2*Z*-configuration) was achieved by removal of H-2 with a strong base, lithium di-isopropylamide (LDA, 1.5 equiv.), followed by protonation at C-4 with aqueous NH_4Cl at −78 °C. On the other hand, treatment of (**3**) with LDA at 0 °C for 20 min afforded exclusively the 2*E*-isomer (**4b**). The configurations of (**4**) were readily determined from their NMR spectra,[4] *i.e.* the resonances of H-3 and C-3 in the 2*Z*-isomer (**4a**) appearing at lower fields δ 6.12 and 139.7, with those of the 2*E*-isomer (**4b**) occurring at δ 5.00 and 115.4. The isomerisation experiments inferred that the allyl-lithium of (**3**) might exist as the proposed 2*Z*-form **B** at low temperature but that the 2*E*-isomer would be thermodynamically favoured.

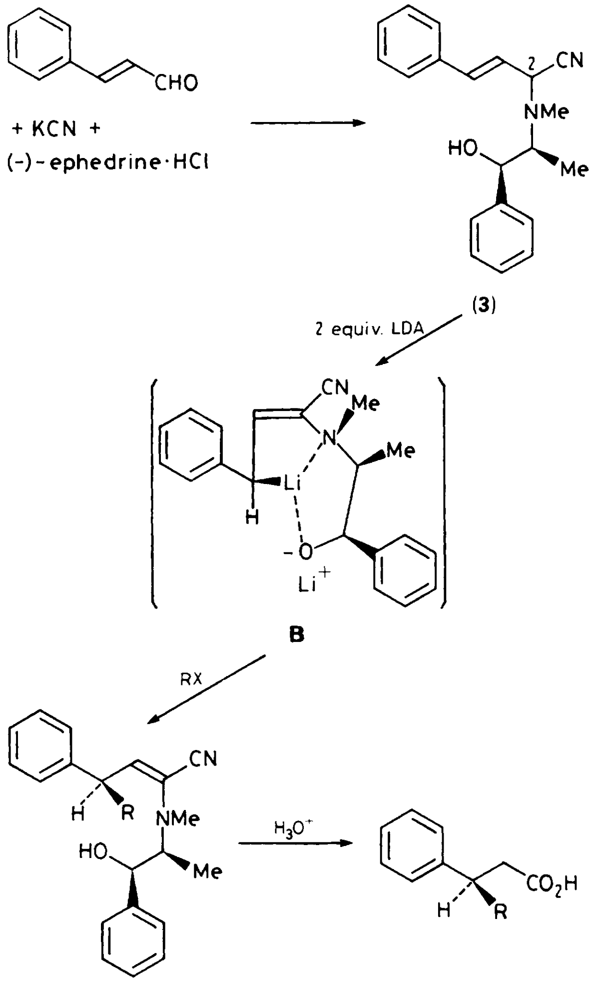
Alkylation of (**3**) with several halides under various conditions gave mainly γ-substitution products (Table 1). No formation of *O*-alkylating compounds was observed. The isomers of alkylating products (**5**)—(**10**) were separated by chromatographic methods and their structures were fully characterised (IR, MS, elemental analyses, ^{1}H and ^{13}C NMR). Subsequent hydrolysis of the individual products with oxalic acid in refluxing aqueous tetrahydrofuran (THF) gave rise to the corresponding carboxylic acids (**11**)—(**16**) (Scheme 1), whose chirality was assigned by comparison of the optical rotation with the known value.[5]



(**1**) R = Me
(**2**) R = Ph

(1)

Alkylation of (**3**) was greatly promoted by the use of a co-solvent hexamethylphosphoramide (HMPA), and even higher yields of the (2*Z*,4*R*)-isomers were obtained by conducting the reaction in the presence of LiI. The combina-



(**4a**) R = H
(**5a**) R = Me
(**6a**) R = Et
(**7a**) R = Pr^i
(**8a**) R = Bu^n
(**9a**) R = $PhCH_2$
(**10a**) R = $CH_2{=}CHCH_2$

(**11a**) R = Me
(**12a**) R = Et
(**13a**) R = Pr^i
(**14a**) R = Bu^n
(**15a**) R = $PhCH_2$
(**16a**) R = $CH_2{=}CHCH_2$

a; (2*Z*, 4*R*)
b; (2*E*, 4*R*)
c; (2*Z*, 4*S*)
d; (2*E*, 4*S*)

Scheme 1

Table 1. Alkylation of the allyl-lithium generated from compound (**3**) (2 equiv. LDA, THF, 2 equiv. halide).

Entry	Halide	HMPA (equiv.)	LiI (equiv.)	Reaction conditions T/°C (time)	Products (% yield), **a**:**b**:**c**:**d**	(**a** + **b**) − (**c** + **d**)
1	MeI	0	0	−78→25 (over 3 h)	(**5**) (55), 38:40:2:20	56
2	EtI	0	0	−78→25 (over 3 h)	(**6**) (28), 0:50:0:50	0
3	EtI	3	0	−78 (50 min)	(**6**) (70), 52:36:0:12	76
4	EtI	3	1	−78 (25 min)	(**6**) (68), 65:27:0:8	84
5	Pr^{i}I	3	0	−78 (30 min)	(**7**) (52), 56:22:0:22	56
6	Bu^{n}I	3	1	−78 (45 min)	(**8**) (84), 61:27:0:12	76
7	PhCH$_2$Br	0	0	−78→25 (over 3 h)	(**9**) (77), 56:22:0:22	56
8	PhCH$_2$Br	3	0	−78 (25 min)	(**9**) (76), 80:11:0:9	82
9	PhCH$_2$Br	3	1	−78 (10 min)	(**9**) (78), 85:15:0:0	100
10	CH$_2$=CHCH$_2$Br	3	1	−78 (10 min)	(**10**) (69), 74:18:0:8	84
11	CH$_2$=CHCH$_2$I	3	0	−78 (10 min)	(**10**) (87), 52:27:8:13	58

[a] Isolated yields are reported. Series **a**, **b**, **c**, and **d** represent compounds having configurations (2*Z*,4*R*), (2*E*,4*R*), (2*Z*,4*S*), and (2*E*,4*S*), respectively. Thus, (**a** + **b**) − (**c** + **d**) indicates the difference between 4*R*- and 4*S*-products.

tion of allyl bromide and LiI appeared to be better for the alkylation than using simply allyl iodide (entries 10 and 11). The real transition state of the alkylation is unclear so far. Based on the experimental data, the reactivity and stereoselectivity may be reflected by aggregate states of the reacting species. A dipolar solvent HMPA and a salt LiI tend to eliminate the degree of aggregation; thus the highly stereoselective alkylation is realised.[6]

Aminonitrile (**3**) serves as a chiral homoenolate equivalent for asymmetric electrophilic reactions. For example, alkylation of (**3**) with benzyl bromide (entry 9) gave 85% of (**9a**) (2*Z*,4*R*) and 15% of (**9b**) (2*E*,4*R*), which yielded (*R*)-3,4-diphenylbutanoic acid (100% enantiomeric excess) on subsequent hydrolysis. This method is useful in the preparation of optically active β,β-disubstituted carboxylic acids, which are alternatively synthesised by nucleophilic addition to chiral α,β-unsaturated carboxylic acid derivatives.[7]

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