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Stereoselective Carbon-Carbon Bond Formation: γ-Alkylation of Lithium Dianion of Chiral Cyclic β-Enamino Ketones.

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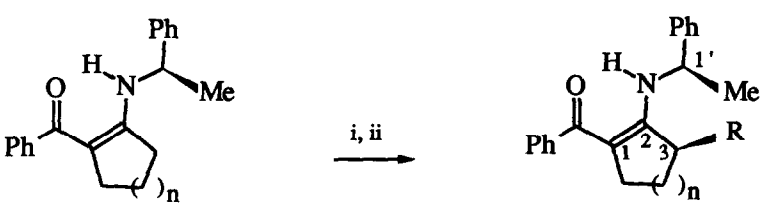
Abstract: The γ-alkylation of the chiral β-enamino ketones (**1**) has been obtained with good yields and d.e. on the *si* face of the lithium dianion intermediate.

The N-substuted imine anion alkylation sequence is one of the best techniques to achieve an efficent and predictable regioselective α-alkylation of ketones with high yields, due to the preference of alkylic electrophiles to attack the carbon atom and to the negligible formation of polyalkylation products.[1] The utilization of optically pure chiral amines to form the imine derivatives offers the opportunity for the stereoselective C-alkylation of the aza-dienolate.[2-6]

We have recently reported on the highly efficient regiospecific alkylation of enamino-ketones.[7] As an extension of our studies we wish now to report an asymmetric synthesis of γ-alkylated enaminones using chiral 1-phenylethylamine as a chiral source. The enaminones **1a,b** were prepared in high yield according to our previously reported procedure through the reaction of methyl benzoate with lithium dianion of N-[(*R*)-1-phenylethyl]-cycloalkaneimines obtained by condensation of cyclopentanone or cyclohexanone with (*R*)-(+)-1-phenylethylamine.[8] The synthesis of **1** by direct condensation of the chiral amine with the corresponding β-diketones must be avoided since it gives a mixture of both the isomeric enaminones.

A Typical procedure follows: lithium dianion was prepared by treatment of enaminone **1** at room temperature with 2.5 eq. of methyl lithium in the presence of 2.5 eq. of HMPA, for 1 hour. The mixture was cooled at - 100 °C and then treated with 1.5 eq. of alkyl halide. Usual work up gave the pure 3-alkyl-1-benzoyl-2-[N-(1-phenylethyl)]-aminocycloalkene **2**.[9]



(**1**) (**2**)

Reagents : i) 2.5 eq. MeLi / HMPA / THF, 20 °C; ii) 1.5 eq R-X, -100 °C.

The absolute configuration of the new γ chiral carbon atom (C-3) was determined on the basis of the ^{1}H-NMR spectroscopic analysis. In all the diastereomers examined a strong n.O.e. between H-1' and H-3 or R-3 was observed (ROESY). These findings support the view that the H-1' hydrogen is located between H-3 and R-3 in the stable conformation as depicted in fig. 1. As a consequence the 1'-phenyl substituent causes a shielding effect on neighbouring groups of about 0.3 ppm, with respect to the corresponding signal of the epimers.[10] The negligible difference in chemical shifts observed in (3*R*) **2ae** for the diastereotopic methyls of isopropyl group (δ= 0.97, 1.03 ppm) and the remarkable one observed in the epimer (3*S*) **2ae** for the corresponding methyl groups (δ= 0.75, 0.95 ppm) confirm this interpretation.

1	n	R-X	2	Yield (%)[a]	d.e.[b]	(confn)	$[\alpha]_D^{20}$	(c)[c]
a	1	Me-I	**aa**	93	27	(3*S*)	- 459.4	(1.1)
a	1	Bn-Cl	**ab**	89	68	(3*R*)	- 275.4	(1.2)
a	1	Et-I	**ac**	87	74	(3*S*)	- 440.1	(0.9)
a	1	Bu-I	**ad**	85	87	(3*S*)	- 420.2	(5.2)
a	1	Pr^i-I	**ae**	75	93	(3*R*)	- 480.1	(2.6)
b	2	Me-I	**ba**	77	34	(3*S*)	- 381.5	(1.7)
b	2	Et-I	**bc**	82	98	(3*S*)	- 434.6	(3.9)
b	2	Bu-I	**bd**	79	98	(3*S*)	- 466.3	(3.6)

[a] Combined yield of both diastereomers. [b] Determined by HPLC-MS analysis of purified but unresolved mixtures. [c] Optical rotations of pure diastereomers were taken in $CHCl_3$.

As shown in the table, the diastereomeric γ-alkylated enaminoketone, was obtained in good to excellent yield and high diastereoisomeric excess. The d.e. increases with the steric hindrance of the entering alkyl group. Better d.e. were obtained in the case of enaminone **1b** with respect to **1a**.

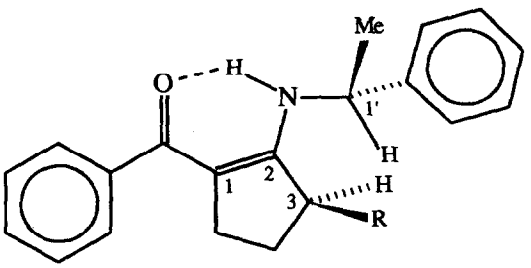


fig. 1

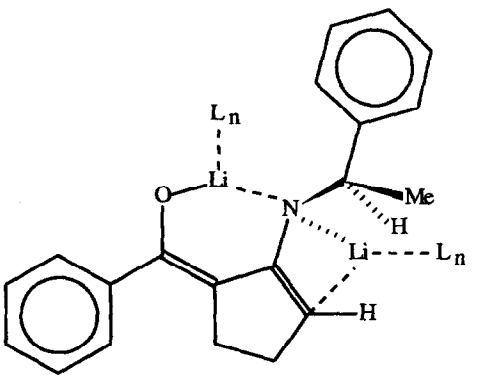


fig. 2

A possible explanation of the asymmetric induction can be proposed on the basis of comparison with analogous systems.[11,12] The lithium ions are probably intramolecularly chelated providing the conformational rigidity necessary for high asymmetric induction. The configuration of the chiral substituent at the N atom determines the structure of the lithium enaminone dianion complex (see fig. 2). While the first Li ion is in the molecular plane between O and N, constraining the aza-dienolate system in the *syn* configuration, the second chelated Li ion (L = HMPA) resides in the less hindered side (*re* face in the case of the (*R*)-amine). Thus the approach of the alkyl halide would take place preferentially from the *si* face. In fact the use of a deficiency or an excess of HMPA causes a dramatic decrease in stereoselectivity. Different ligand agents tested (TMEDA, DMPU) gave less satisfactory results.

The operational simplicity of the present method and the use of 1-phenylethylamine as a chiral source (non expensive and commercially available in either pure enantiomeric form) are additional advantages in a process which provides access to a variety of alkylated products in quite high stereoisomeric purity wherein the absolute configuration can be predicted with a great deal of confidence. Further development of this methodology and the application a range of enaminones and electrophiles are in progress.

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9. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted with diethyl ether. The organic layer was dried, evaporated under reduced pressure and the residue obtained was submitted to HPLC-MS analysis for the determination of the yield of conversion and the diastereomeric excess. Column chromatographic separation of crude material (n-hexane/ethyl acetate, 90:10) furnished the pure diastereomers.
10. **(2*R*,3*R*)-1-benzoyl-3-isopropyl-2-[N-(1-phenylethyl)]-aminocyclopentene** (2*R*,3*R*)-**2ae.** $[\alpha]_D^{20}$ = - 480.1 (c 2.6, $CHCL_3$). IR (film) 3200 (broad), 1585, 1520, 1310, 745, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (d, *J* 6.7, Me-CH-Me), 1.03 (d, *J* 6.9, Me-CH-Me), 1.50-1.65 (m, H-4), 1.59 (d, *J* 6.7, Ph-CH-Me), 1.68-1.77(m, H-4), 2.17 (quint.d, *J* 6.7, 3.6, Me-CH-Me), 2.45-2.54 (ddd, *J* 13.6, 9.3, 1.1, H-5), 2.58 (dd, *J* 8.5, 3.6, H-3), 2.79 (ddd, *J* 13.4, 9.8, 7.8, H-5), 4.74 (dq, *J* 9.0, 6.9, Ph-CH-Me), 7.20-7.45 (m, 8H), 7.64-7.67 (m, 2H), 11.02(broad d, *J* 9.0, NH). ^{13}C-NMR ($CDCl_3$) δ: 16.76 (q), 21.70(q), 23.54(t), 24.59(q), 30.42(d), 31.05(t), 48.81(d), 53.79(d), 105.09(s), 125.21(d),

126.87(d), 127.02(d), 127.50(d), 128.55(d), 129.17(d), 142.06(s), 144.45(s), 171.42(s), 189.28(s). MS, m/z (%): 333 (M^+, 36), 290 (26), 228 (36), 186 (20), 105 (100).

(2*R*,3*S*)-1-benzoyl-3-isopropyl-2-[N-(1-phenylethyl)]-aminocyclopentene (2*R*,3*S*)-**2ae.** $[\alpha]_D^{20}$ = - 417.4 (c 2.9, $CHCL_3$). IR (film) 3200 (broad), 1585, 1520, 1450, 1310, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (d, *J* 6.7, Me-CH-Me), 0.95 (d, *J* 7.0, Me-CH-Me), 1.61 (d, *J* 6.7, Ph-CH-Me), 1.80-1.89 (m, 3H), 2.52-2.61 (m, H-5), 2.78-2.90 (m, H-5), 2.94-3.00 (m, H-3), 4.76 (dq, *J* 10.4, 6.7, Ph-CH-Me), 7.20-7.40 (m, 8H), 7.64-7.67 (m, 2H), 11.30(broad d, *J* 10.4, NH). ^{13}C-NMR ($CDCl_3$) δ: 16.22 (q), 21.70(q), 23.53(t), 25.79(q), 30.14(d), 31.38(t), 48.91(d), 54.19(d), 104.70(s), 125.23(d), 127.03(d), 127.16(d), 127.64(d), 128.56(d), 129.28(d), 142.16(s), 143.62(s), 171.21(s), 189.08(s). MS, m/z (%): 333 (M^+, 34), 290 (25), 228 (31), 186 (20), 105 (100).

(2*R*,3*S*)-1-benzoyl-3-methyl-2-[N-(1-phenylethyl)]-aminocyclopentene (2*R*,3*S*)-**2aa** M.p. 94-95 °C (Hexane). $[\alpha]_D^{20}$ = -459.4 (c 1.1, $CHCL_3$). IR (nujol) 3300 (broad), 1590, 1515, 1315, 1265, 750, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (d, *C* 7.0, Me-3), 1.48 (dd, *J* 7.0, 12.2, 1H), 1.61 (d, *J* 6.72, Ph-CH-Me), 1.70-1.86 (m, 1H), 2.72 (quint., *J* 7.3, H-3), 2.94 (ddd, *J* 7.0, 10.4, 13.1, 1H), 4.75 (dq, *J* 6.7, 8.8, Ph-CH-Me), 7.20-7.45 (m, 8H), 7.65-7.75 (m, 2H), 10.90 (brd, *J* 8.8, NH) . ^{13}C-NMR ($CDCl_3$) δ: 17.61 (q), 24.74 (q), 29.01 (t), 31.49 (t), 37.59 (d), 53.77 (d), 103.40 (s), 125.28 (d), 127.03 (d) 127.20 (d), 127.64 (d), 128.68 (d), 129.33 (d), 142.01 (s), 144.48 (s), 173.65 (s), 188.40 (s). MS, m/z (%): 305 (M^+, 43), 290 (9), 200 (80), 105 (100).

(2*R*,3*R*)-1-benzoyl-3-methyl-2-[N-(1-phenylethyl)]-aminocyclopentene (2*R*,3*R*)-**2aa.** $[\alpha]_D^{20}$ = - 411.1 (c 0.71, $CHCL_3$). IR (film) 3350 (broad), 1585, 1515, 1315, 1265, 685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (d, *J* 7.3, Me-3), 1.57 (dd, *J* 6.7, 12.2, 1H), 1.62 (d, *J* 7.0, Ph-CH-Me), 3.60 (m, 1H), 2.50-2.60 (m, 1H), 2.96 (ddd, *J* 6.7, 10.7, 13.1, 1H), 3.06 (quint., *J* 7.3, H-3) 4.77 (dq, *J* 6.7, 9.8, Ph-CH-Me), 7.20-7.43 (m, 8H), 7.65-7.75 (m, 2H), 11.20 (brd, *J* 9.7, NH); ^{13}C-NMR ($CDCl_3$) δ: 17.35 (q), 25.46 (q), 29.03 (t), 31.91 (t), 37.55 (d), 54.26 (d), 102.98 (s), 125.42 (d), 127.10 (d) 127.22 (d), 127.63 (d), 128.62 (d), 129.33 (d), 141.92 (s), 143.76(s), 173.48 (s), 189.02 (s). MS, m/z (%): 305 (M^+, 54), 290 (11), 200 (83), 105 (100).

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