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On the Stereochemical Course of Asymmetric Mannich Reactions

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Abstract: In the $TiCl_4$-mediated Mannich reaction, β-amino ketones are obtained with diastereoselectivities of 70–95%. The configuration of the major isomer obtained from benzaldehyde, piperidine, and cyclohexanone [2-(α-piperidinobenzyl)cyclohexanone **1**] is shown by X-ray crystallography to be *unlike* (*u*, cf. Fig. 1). Thus, the trigonal centers combine to form the C–C bond with relative topicity *like* (*lk*, **3**). Possible mechanisms of the reaction are briefly discussed.

The Mannich reaction (a), Scheme 1, is of similar importance to organic synthesis as the aldol addition; mechanistically, the former is the imino analogue of the latter reaction. Only recently, a diastereoselective Mannich reaction – with so-called open-chain stereocontrol – was discovered: the $TiCl_4$-mediated version (b)[2].

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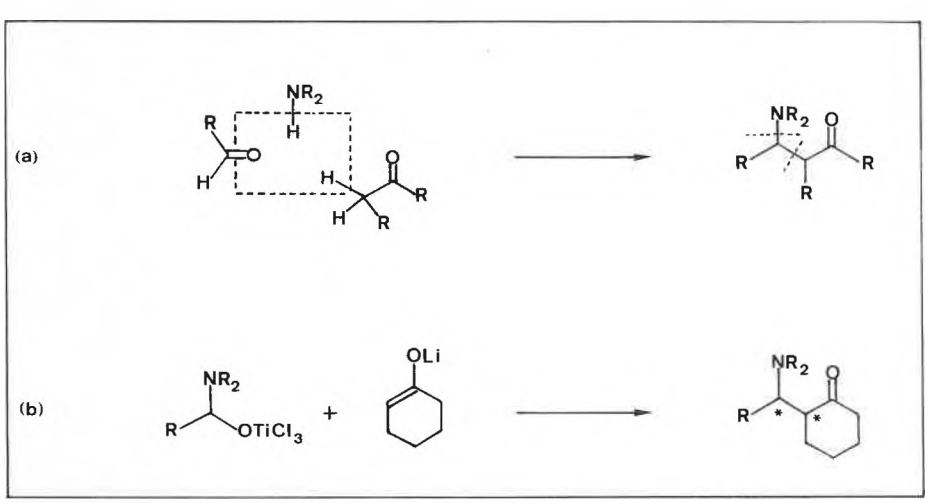
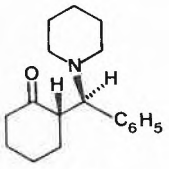
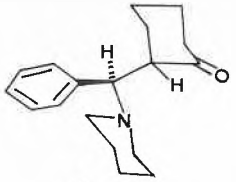
Although several examples were presented, and although it was established by NMR spectroscopy that the major diastereomers obtained with aromatic aldehydes were all of the same configuration, no assignment could be made at that time[2]. We have now been able to determine the crystal structure of 2-(α-piperidinobenzyl)cyclohexanone **1** by X-ray analysis (see Fig. 1 for a stereoview). The aminoketone **1** is prepared from benzaldehyde, piperidine, and cyclohexanone by the published procedure[2], it predominates





1 (*u*)



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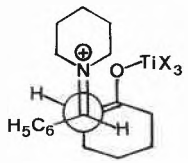
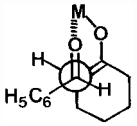
by a factor of 4:1, its configuration is *u*[3], and its conformation in the crystal is as depicted in formula **2**.

With the structure of one of the benzaldehyde-derived Mannich products elucidated, it is possible to specify the relative topicity[3] of the asymmetric induction leading to it as *lk* and, thus, to discuss the mechanism of the reaction. Formally, the two centers joining to give the new carbon carbon bond approach each other like those in the aldol addition[4] of cyclohexanone lithium, sodium, magnesium, or boron enolate to benzaldehyde[4b,5], compare **3** with **4**, and see the general discussion of reactions in which trigonal centers combine to form two new asymmetric carbon atoms[6]. This result is by no means trivial or expected: (1) Ti-enolates, which may be involved here, add to aldehydes preferentially with relative topicity *ul* (see **5**), and not *lk*[7], and (2) the approach of the two centers with *synclinal* (see **3** and **5**) and not *antiperiplanar* arrangement (see **6**)



3 (rel. topicity *lk*)



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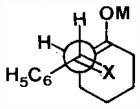
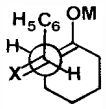


5 (rel. topicity *ul*)



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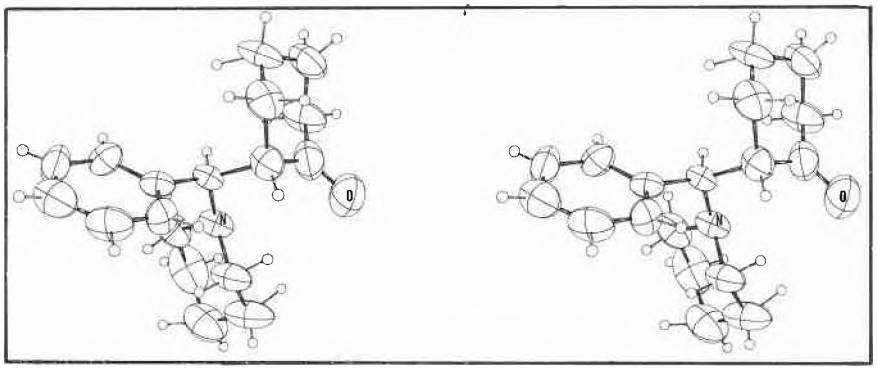

Fig. 1. ORTEP stereoview of **1**. *Ellipsoids are drawn at the 50% probability level*[11].

of the double bonds is often attributed to chelation between the heteroatoms and a metal atom (cf. **4**)[4b]; the nitrogen of an iminium ion, however, is no donor for a metal. Thus, electrostatic forces may be decisive. On the other hand, the reaction occurs at low temperature (−75°C), in non-polar solvents, and with a heavy precipitate present, so that the actual mechanism may not involve free ions in solution at all. Obviously, further investigations are necessary to reach definite conclusions.

X-ray analysis of **1**:

Single crystals of the major diastereoisomer (*m.p.* 109–110°C) from the reaction of Li-cyclohexenolate, benzaldehyde, and piperidine, as prepared by the published procedure[2], were obtained by four recrystallizations from pentane (+20 to −20°C).

Monoclinic space group $P2_1/n$, $a = 8.990$, $b = 10.734$, $c = 16.628$ Å, $\beta = 92.42°$, $V = 1603.2$ Å^3, $Z = 4$, $\rho_x = 1.13\ g \cdot cm^{-3}$, $C_{18}H_{25}NO$. 2817 independent reflexions of a crystal (rather wide mosaic spread, 1164 with $I > 3\sigma(I)$) were measured with an Enraf Nonius CAD-4 diffractometer at room temperature out to $\sin\theta/\lambda \leq 0.6$ Å^{-1} ($Mo_{K\alpha}$ radiation, $\lambda = 0.71069$ Å). The structure was solved by direct methods[8] and refined by full-matrix least-squares analysis[9]. All H-atoms except for three were located in a Fourier difference synthesis. The refinement (non-H-atoms anisotropically, H-atoms located in difference Fourier isotropically, three H-atoms with calculated positions) with a modified weighting scheme[10] ($w = \sigma(F)^{-2} \cdot \exp(r \cdot (\sin\theta/\lambda)^2)$, $r = 6$ Å^2) converged with $R = 0.098$ ($R_w = 0.113$)[11, 12].

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[11] Atomic coordinates are deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.
[12] The present X-ray analysis also establishes the configuration of the known epimer of **1** as being *l*. [P.B. Russel, R. Baltzly, *J. Am. Chem. Soc. 77* (1955) 629].