Tetrahedron Letters,Vol.30,No.20,pp 2645-2648,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE ASYMMETRIC MICHAEL PROCESS INVOLVING CHIRAL IMINES : THE DIASTEREOFACIAL DIFFERENTIATION ASPECT

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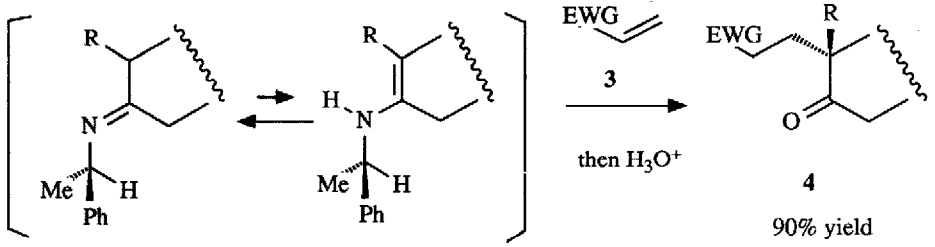
Summary : *A mechanism for the diastereofacial differentiation in the title reaction is proposed on the basis of the variation of the chiral auxiliary amines and of the examination of the crystal structure of enamino-ester* ***15****.*

We have recently disclosed that imines **1**, derived from *racemic* α-substituted cyclanones and optically active 1-phenylethylamine, react with electron-deficient alkenes **3** to produce, after hydrolytic work-up, regio- and stereoselectively, α-disubstituted cyclanones **4**, with high yields and excellent enantiomeric excesses[1]. We have also established that the reactive nucleophilic species involved in this process are, in fact, the secondary enamines **2**, in tautomeric equilibrium with imines **1**.

In this paper, we report on the influence of the nature of the chiral amine on the stereoselectivity, and discuss the mechanism of the diastereofacial differentiation of this process, on the basis of the examination of the crystal structure of enamino-ester **15**, a model compound for enamines **2**.



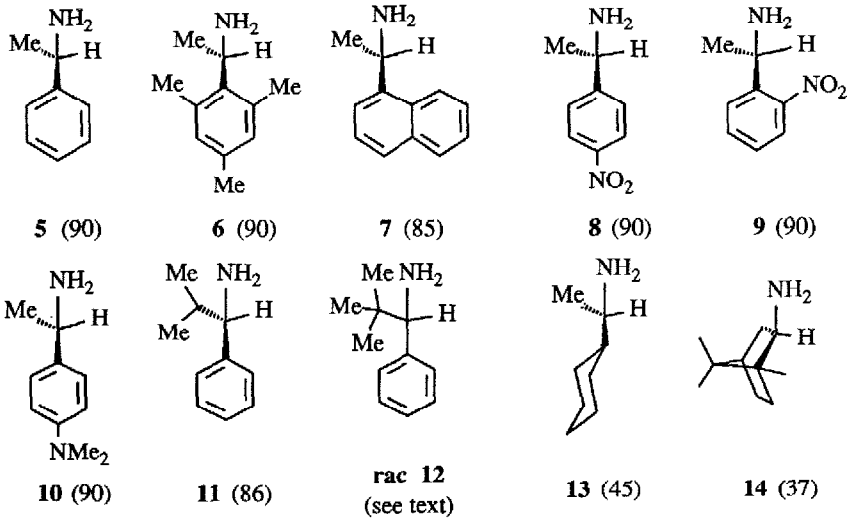
1 **2** **4**
90% yield
≥ 90% ee

Influence of the nature of chiral amines on the stereoselectivity

Ten different primary amines (**5** to **14**, **Table 1**) were tested[2] ; these chiral auxiliaries can be broadly classified into two categories : those bearing an aromatic nucleus in the α position to the amine group (**5** to **12**) and two others (**13** and **14**) containing no aromatic moiety.

Within the amines of the first category, no significant change of the diastereoisomeric excesses (de) was observed. Thus, when the phenyl group of 1-phenylethylamine **5** was replaced by more bulky aromatic nuclei (amines **6** and **7**) or when this phenyl was substituted, either by an electron-withdrawing group (amines **8** and **9**), or an electron-donating group (amine **10**), no notable variation of the de was detected. Likewise, the replacement of the methyl group in amine **5** by an isopropyl substituent (amine **11**) resulted in no substantial change of the de, while the imine derived from amine **12** (*ter*-butyl analogue to **5** and **11**) was found to be completely non-reactive (at least toward the electrophilic olefins which were used).

In sharp contrast with "benzylic" amines **5** to **11**, a striking decrease of the de was observed with the amines of the second category (**13** and **14**) ; thus, *the presence of an aromatic nucleus in the α position to the amine group in the auxiliary chiral amine appears crucial to ensure a good diastereofacial differentiation in this process.*



5 (90) **6** (90) **7** (85) **8** (90) **9** (90)

10 (90) **11** (86) **rac 12** (see text) **13** (45) **14** (37)

Table 1 de in brackets (see footnote 2 for experimental details).

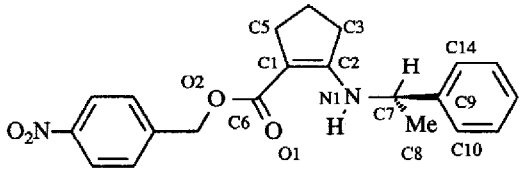
Discussion

Although we have clearly demonstrated that a cyclic transition state -and hence a compact approach of reactant partners **2**+**3**- is implied in the present Michael addition reaction (the transfer of the proton borne by the nitrogen atom of enamines **2** to olefins **3** occuring in concert with the creation of the new C-C bond)[1d], no definitive answer to the intriguing question concerning the mechanism of the diastereofacial differentiation has been given until today.

A tentative explanation, relevant to the present problem, was proposed in 1978 by Dunitz and Eschenmoser, in a rather related asymmetric process, the so-called "Hajos-Parrish reaction"[3]. According to these authors, the nitrogen atom of chiral enamines could provide a "switch for relaying the chiral information", *a pyramidal nitrogen atom* seeming essential for an efficient transmission of this information, and then, the π-facial discrimination. A quite similar interpretation was recently given by Oppolzer in an asymmetric alkylation reaction involving sultam derivatives[4]. In both cases, the Dunitz-Eschenmoser hypothesis was supported by X-ray structure determinations of enamines (and enamides), the nitrogen atom of the latter indeed exhibiting generally a substantial degree of pyramidality.

In order to prove the validity of this proposal, the crystalline enamino-ester **15**,[5] structurally closely related to enamines **2**, was prepared and submitted to an X-ray analysis. In contrast with the aforementioned observations, *the enamine nitrogen atom of this compound was found to be perfectly planar*[6] **(Fig. 1 and 2)**. It might be argued that the flattening of the enamine moiety in enamino-ester **15** originates from the additional π-π overlap contribution of the ester function ; nevertheless, this compound constitutes a valuable model for tautomeric secondary enamines **2** since, albeit less reactive, *it provides the same order of magnitude of π-facial discrimination toward electrophilic alkenes as imines* **1** *(R = alkyl)*[5].

A careful examination of molecular structure **15** reveals that the conformation of the substituents around the two enamine C-N bonds (N1-H and C7-H bonds roughly eclipsing C1-C6 and C2-C3 bonds, respectively) is, in fact, virtually identical to the one we have previously evoked for enamines **2**, minimizing the main steric interactions[1d] (in this respect, the additional intramolecular hydrogen bond, (N1)H...O1, stabilizes this conformation in enamino-ester **15**). If we now consider the two diastereotopic approaches of an electrophilic alkene to this molecule (assuming, in view of the important energy barrier to internal rotation around the two C-N bonds found in enamines **2**[1d], that the main conformational features involved in the enamino-ester ground state are preserved in the transition state), it is manifest that attack on the lower π-face should greatly predominate, due to the fact that the upper face is dramatically sterically hindered by the bulky phenyl ring, *nearly perpendicular*[7] to the plane defined by the enamine triad atoms C1-C2-N1 **(Fig. 2)**.



15

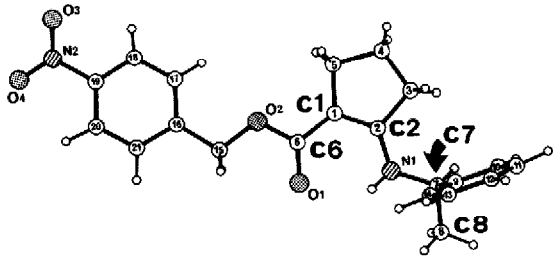


Fig 1 Molecular structure of enamino-ester **15**

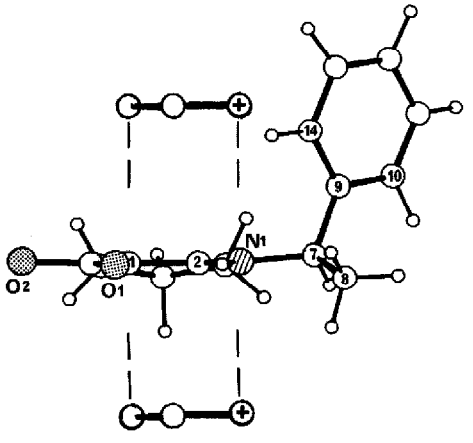


Fig 2 Projection of molecule **15** (the atoms of the ester part are omitted) showing the two diastereotopic, compact approaches (dotted lines) of an electrophilic alkene [symbolized by C=C-C$^+$, in interaction (perpendicular attack mode), at 3Å, with the C1-C2-N1 enamine system].

Though essentially qualitative, this model for rationalizing facial recognition is, in fact, highly consistent with the observed stereochemical outcome : *we have indeed established that attack on the π-face opposite the aromatic moiety of the chiral auxiliary amines (5 to 11) is always strongly preferred.*

In connection with this topic, theoretical calculations, involving the approach of reactants **2+3**, have recently been made[8]. Interestingly, a good agreement was obtained when the calculated energy differences between the two diastereotopic approaches were compared to the experimental values. It is apparent that such a method of investigation, taking into account *both reactant protagonists*, should provide an accurate description of the present stereochemical phenomenon.

Acknowledgments. *We thank Drs. M. Pfau and D. Desmaele (ESPCI, Paris), Dr. A. Sevin (Université Paris 6) and Profs. D. Arigoni and J.D. Dunitz (ETH, Zürich, Switzerland) for stimulating discussions.*

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2. The imines derived from amines **5-14** and 2-methylcyclohexanone were added to methyl acrylate and/or methylvinylketone. The de were established by measuring the optical rotation of the adducts (the *R* enantiomers, *in all cases*, predominating), after hydrolytic work-up[1a].

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5. A. Guingant, unpublished results. **15** : mp 75°C, $[\alpha]_D^{20}$ -355° (c = 1.5, $CHCl_3$).

6. **15** : crystal structure, pertinent data. bond valences (Å, σ = 0.005) O2-C6 (1.364) C6-O1 (1.229) C6-C1 (1.429) C1-C2 (1.374) C2-N1 (1.340) (N1)H-N1 (0.80) (N1)H...O1 (2.19) N1-C7 (1.462) C7-C8 (1.524) C7-C9 (1.510) C9-C10 (1.397) C9-C14 (1.384) bond angles (°, σ = 0.4) O2-C6-O1 (120.8) O1-C6-C1 (126.1) C6-C1-C5 (126.6) C6-C1-C2 (121.3) C1-C2-C3 (110.1) C1-C2-N1 (127.3) C2-N1-H(N1) (116.5) C2-N1-C7 (125.0) (N1)H-N1-C7 (118.5) N1-C7-C8 (109.3) N1-C7-C9 (113.2) C8-C7-C9 (110.1) (C7)H-C7-C8 (106.3) C7-C9-C10 (120.2) C10-C9-C14 (118.3) torsion angles (°, σ = 0.8) O1-C6-C1-C2 (-1.6) C1-C2-N1-H(N1)(5.7) C3-C2-N1-C7 (6.0) C2-N1-C7-H(C7) (-46.4) C2-N1-C7-C9 (75.5) C8-C7-C9-C10 (98.8).

7. The crucial role of a "perpendicular" phenyl ring in determining diastereofacial selectivity has recently been emphasized : C. Siegel, E.R. Thornton, Tetrahedron Lett., **29**, 5225 (1988). Such a peculiar conformation of a phenyl ring engaged in the 1-phenethylamino moiety has been pointed out by Schöllkopf : U. Schöllkopf, H.S. Hausberg, M. Segal, U. Reiter, I. Hoppe, W. Saenger, K. Lindner, Liebigs Ann. Chem., 439 (1981) ; see also M. Bogucka-Ledóchowska, A. Konitz, A. Hempel, Z. Dauter, E. Borowski, Tetrahedron Lett., 1025 (1976), S.K. Burley, G.A. Petsko, J. Am. Chem. Soc., **108**, 7995 (1986), and X-ray structure of compound **6** in paper **1d**.

8. A. Sevin, unpublished results.

(Received in France 21 February 1989)