

Communications to the Editor

Conformational Transmission of Chirality: The Origin of 1,4-Asymmetric Induction in Michael Reactions of Chiral Imines

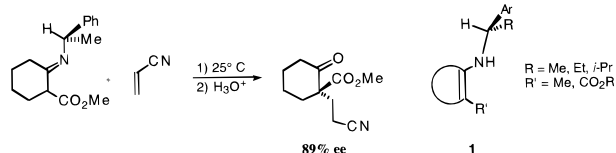
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Remarkable π -facial stereoselectivity has been documented for hundreds of examples of reactions of chiral imines with Michael acceptors.^{1,2} A typical example is illustrated in Scheme 1. The work of Pfau, d'Angelo, and others establishes the scope of these types of reactions.¹ Generally, a cyclic imine is involved, although some intramolecular cyclizations of acyclic systems are also known. Furthermore, these reactions proceed through the intermediacy of an enamine possessing the characteristics shown in **1**. Audia and co-workers studied related systems.^{2c}

Scheme 1

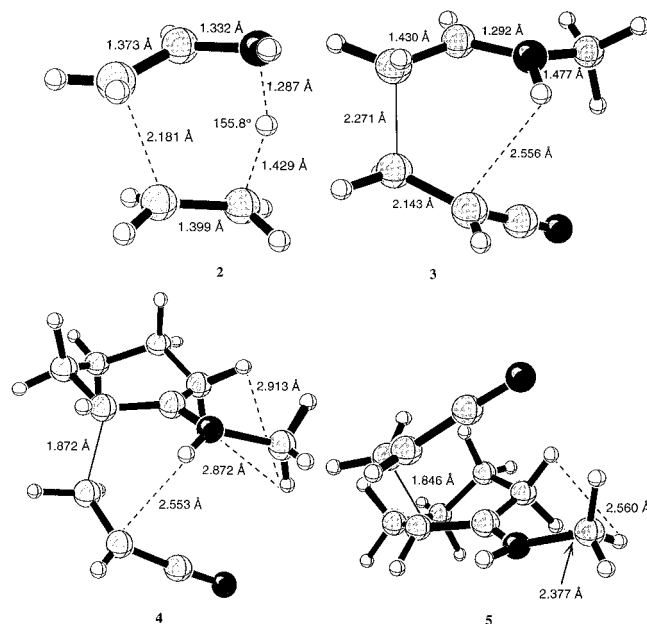


The (phenylethyl)amine moiety (Ar = Ph) has proven particularly effective as a chiral control element. Replacing the phenyl moiety with larger or alkyl-substituted aromatic groups does not affect the selectivity, whereas substituting an alkyl group, such as cyclohexyl, for Ar produces a considerable drop in stereoselectivity.³ However, exchanging the methyl for larger alkyl groups causes no change in stereoselectivity unless R = *t*-Bu, in which case the reaction becomes very sluggish and inefficient.⁴ Despite considerable computational effort,⁵ no explanation as to the origin of this intriguing stereoselectivity has been forthcoming, except for the generalization that the Michael acceptor avoids steric repulsions with the chiral group. We report a theoretical analysis of this reaction and a novel and general explanation for the observed stereoselectivity. Additionally, a new general principle of stereoselective synthesis, involving long-range conformational transmission through the cycloalkene skeleton, is proposed, and the consequences for related systems are outlined.

Theoretical studies of the reaction between simple enamines and electrophilic olefins by Sevin *et al.* indicate a preference for the *syn* arrangement of enamines and electron deficient

alkenes.^{5a} This is the result of favorable electrostatic interactions between the partially positive NH and the partially negative Michael acceptor terminus in the transition state.

The transition structure reported earlier for the reaction of vinylamine with ethylene (**2**) is typical for a concerted ene reaction, with partial hydrogen transfer in the transition state.⁶ We have now used ab initio RHF (restricted Hartree–Fock) calculations with the 6-31G* basis set to explore larger systems.⁷ (*N*-Methylamino)ethylene and acrylonitrile give transition structure **3**, which leads to the formation of a zwitterionic intermediate. Electrostatic attraction maintains the *syn* arrangement of the termini not involved in bonding. The reaction of (*N*-methylamino)cyclohexene with acrylonitrile has two *syn* transition states, **4** and **5**. The forming bond lengths are 1.872 and



1.846 Å, respectively, typical of a stepwise reaction leading to a zwitterionic intermediate.⁸ For this half-chair cyclohexene, axial attack (**4**) is 2 kcal/mol lower in energy than equatorial attack (**5**). This preference for axial attack arises primarily from a staggering of the forming bond with respect to the allylic bonds; in addition, 1,4-diaxial repulsion develops upon equatorial attack and exceeds the 1,3-diaxial repulsion accompanying axial attack. Axial attack on cyclohexenes,^{9a} enolates,^{9b} and related species is known to be favored for a variety of electrophiles, and this can be interpreted in terms of torsional strain.¹⁰

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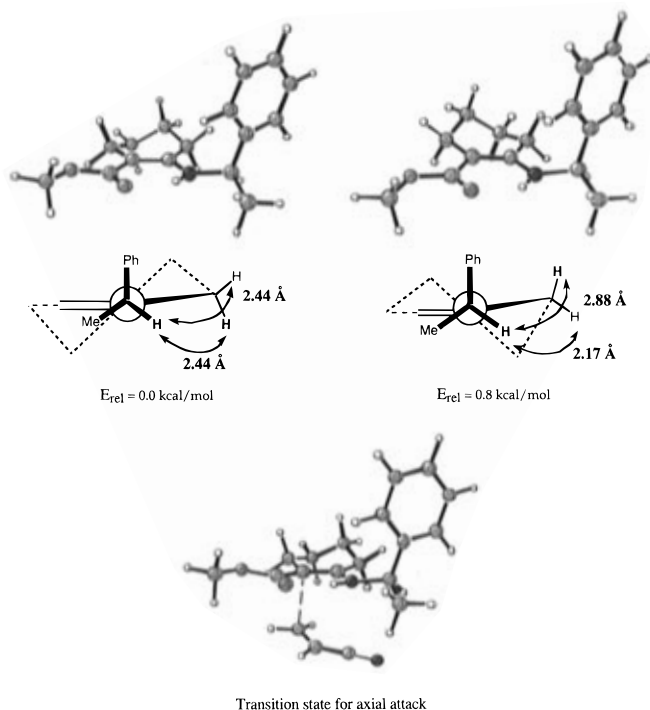


Figure 1.

For an achiral aminocyclohexene, the two enantiomeric half-chairs are equal in energy and axial attack on either chair is equally probable. With a chiral substituent, the two half-chairs are diastereomers. Is it possible that the chiral substituent causes one of these half-chairs to be favored significantly over the other? The two half-chairs of a chiral enamine computed with MM2¹¹ are shown in Figure 1. The example contains the enamine intermediate involved in the reaction shown in Scheme 1. The preferred conformation of the (phenylethyl)amine group directs the hydrogen of the chiral center toward the cyclohexene ring. The relevant H-H distances are shown below each model. Consequently, the first conformer is 0.8 kcal/mol more stable than the second.

Figure 1 also shows a force field model for the transition state for axial attack on the preferred chair conformer. Axial attack is favored by 1 kcal/mol over attack from the opposite face. This energy difference accounts for a 90:10 ratio of products, a typical value observed in the d'Angelo systems.¹

Conformational transmission of chirality, summarized in Figure 2, provides a general model for the observed high stereoselectivity and explains the apparently anomalous experimental observations. Structures **6** and **7** show the major and

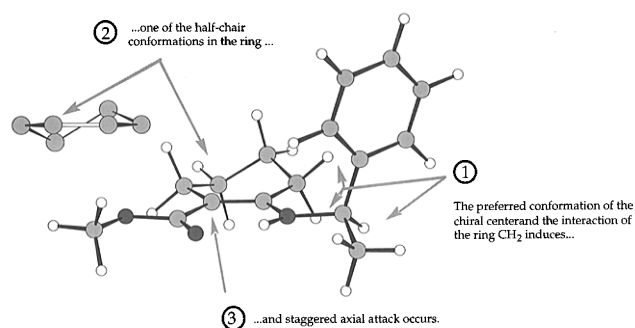
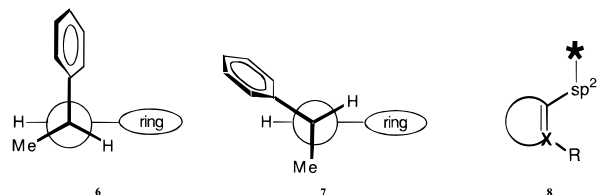


Figure 2.

minor conformers of the phenylethyl group. Replacing the phenyl group with bulkier groups like mesitylene or naphthalene results in no notable variation of ee, because steric interactions between the aromatic group and the electrophile are not the major source of induction; substitution of an isopropyl group for the methyl group fails to influence the selectivity because the preferred conformation, **6**, is unchanged by this substitution. The phenyl ring remains in the perpendicular position, and the difference between the energies of the half-chairs is unchanged.



Conformational transmission of chirality also explains the apparent insensitivity to electronic effects: substitution of the phenyl with electron-donating (NMe₂) or electron-withdrawing groups (*o*- or *p*-NO₂) does not markedly affect the distances between the chiral center and the ring. The dramatic drop in enantioselectivity (45% ee) observed upon exchange of the phenyl for cyclohexyl or norbornyl groups is understandable, because **6** and **7** are nearly identical in energy when Ph is replaced by a primary or secondary alkyl group.

Conformational transmission of chirality operates for many systems other than Pfau-d'Angelo-type cyclohexenes. In fact, the (phenylethyl)amine moiety successfully transfers chirality through 5-membered rings,¹² and chirality transmission is also observed when other rings are fused to the parent cyclohexene ring.² Any system resembling **8**, possessing an asymmetric center bound to an sp² center while at the same time in a 1,4-relationship to the site of reaction, should exhibit comparable selectivity. Examples include work² of Audia and nucleophilic additions to α,β -unsaturated cyclohexenyl ketones recently reported by Linderman.¹³ Studies to quantitate conformational transmission of chirality for such reactions are in progress.

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