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The Intramolecular Salt Effect in Chiral Auxiliaries. Enhanced Diastereoselectivity in a Nitrile Oxide Cycloaddition via Rational Transition State Stabilization.

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Abstract: The use of ion pairs to control a nitrile oxide cycloaddition is demonstrated. A chiral phenylmaleimide derivative bearing an ionic group and an associated counterion provides enhanced selectivity in the cycloaddition of benzonitrile oxide. The intramolecular salt effect controls the orientation of the 1,3-dipolar reagent. The nature of the solvent is shown to be relevant in the selectivity of the reaction.

The electrostatic fields associated with charged and dipolar functional groups in the active site of enzymes may be central to the rate accelerations achieved by these molecules[1]. It is evident that appropriately placed charged groups in an enzyme or synthetic receptor can complement the electrostatic field presented by the transition state of a reaction and thereby reduce the activation energy for the reaction provided that the coulombic binding energy between the transition state and receptor exceeds that of the ground state and receptor.

In model experiments on the intramolecular salt effect we demonstrated that simple molecules with charged groups in their structure can be used to show the potential usefulness of this effect[2]. We have also demonstrated that the effect can be used catalytically and suggested that this provides a pathway for new selective catalysts[3]. In this paper we illustrate that dipolar cycloadditions can be controlled in a predictive manner through proper placement of ion pairs nearby the reaction site, and provide a model for other predictions.

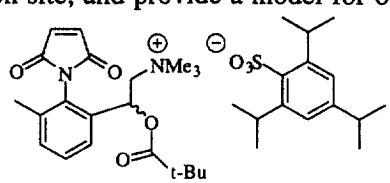

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Fig. 1. Structure for compound **1**.

The mechanism of 1,3-dipolar cycloadditions has been proposed to lie between a completely synchronous process and an alternative biradical zwitterionic process[4]. Both possibilities could be strongly affected by the presence of charged groups in the dipolarophile,

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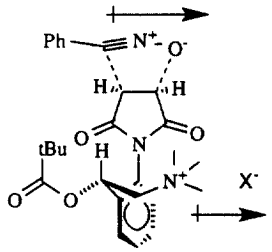
because 1,3-dipoles (and the transition states composed of such dipoles) are generally more polar than dipolarophiles. To explore this idea, we examined the diastereoselectivity of nitrile oxide addition to chiral racemic maleimide **1** (Fig. 1).

The presence of the stereogenic benzylic center in the chiral auxiliary of compound **1** renders the two methine carbon atoms of the maleimide diastereotopic. The substituents in the ortho positions of the phenyl ring raise the N-phenyl rotational barrier to over 22 kcal/mol, resulting in a sensible difference in the two faces of the maleimide[5]. The high barrier allows one to observe four possible products and to study the face selectivity of the reaction. The pivalate ester was introduced to reduce the number of possible conformations for the molecule, and to force the ammonium salt to be close to the maleimide ring.

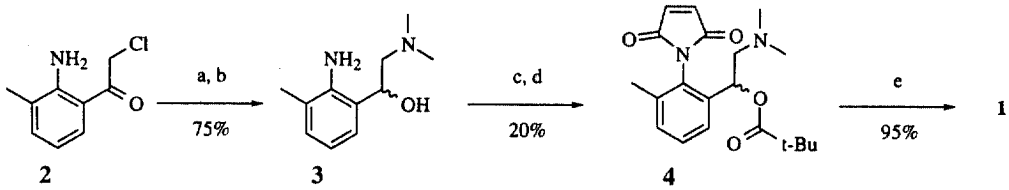


Our hypothesis was that the major diastereomer would arise from a transition state wherein the 1,3-dipole is on the more hindered side and is oriented to optimize electrostatic attractions to the ion pair.

Synthesis of compound **1** began with 2-methylaniline (Scheme 1). The reaction of the aniline with chloroacetonitrile afforded chloroderivative **2**[6].

Nucleophilic displacement by dimethylamine and reduction of the ketone afforded aminoalcohol **3**. Formation of the maleimide by reaction of the amine with maleic anhydride and ring closure by formation of the mixed anhydride with pivaloyl chloride was not optimized. It is likely that this reaction does not give a good yield because of the hindrance of the aniline and the enhanced reactivity of the alcohol caused by the nearby tertiary amine[7].

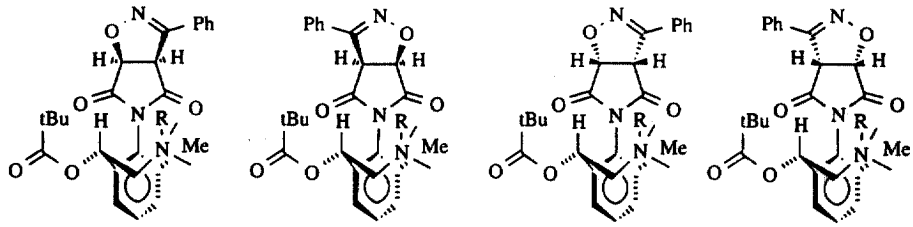
Methyl 2,4,6-triisopropylbenzenene sulfonate was used for the alkylation of amine **4**. The organic anion increases the solubility of the ammonium salt, allowing the use of a larger number of organic solvents for the study of the cycloaddition reaction. In fact, compound **1** is soluble in solvents as nonpolar as toluene and carbon tetrachloride.



a) dimethylamine, methanol; b) $NaBH_4$, methanol; c) maleic anhydride, dichloromethane; d) pivaloyl chloride, triethylamine, dichloromethane; e) methyl 2,4,6-triisopropylbenzenesulfonate, dichloromethane.

Scheme 1. Synthesis of compound **1**.

To reveal the effect of the charged groups, a cycloaddition was first carried out between the uncharged amine **4** and benzonitrile oxide[8] (10 mM each) in THF. As expected, these conditions lead to four products (**5**-**8**). Isolation of the products by column chromatography allows assignment of the structures by NMR spectroscopy for compounds **5** and **6**. Unfortunately no thermal isomerization of compounds **5** or **6** could be achieved before decomposition occurred. Therefore we were unable to confirm the assignment of **7** and **8**. However, because **7** and **8** are always observed in equal amounts, the conclusions of the study are not compromised by this ambiguity. The reaction of the neutral amine provided four diastereomers in a ratio 1:4:4:4 (**5**:**6**:**7**:**8**) (Fig. 2).



R=lone pair **5** **6** **7** **8**

R=methyl **9** **10** **11** **12**

Fig. 2. Products for the cycloaddition reaction.

In the central experiment, the cycloaddition reaction was performed under the same conditions as used for the neutral amine, but using the salt **1**. ^{1}H NMR integration of the crude product mixture revealed that the ratio of **9:10:11:12** was 0:4:1:1 (Fig. 2). The correspondence of these products with **5-8** was established by methylation of **5-8**, which afforded **9-12**. It is a remarkable success of the design that the major compound in this ionic case comes from the *more hindered* face of the molecule. This reveals the direct influence of the charge in the reaction. The disappearance of compound **9** can be attributed to a higher steric hindrance due to the new methyl group on the amine nitrogen or to electrostatic repulsion attending non-favorable approach of the dipole in the presence of the charge. For **9** to be formed, the part of the dipole with the higher positive charge must be closer to the ammonium ion, and this would be electrostatically unfavorable.

To prove that the presence of the ammonium salt increases the speed of the reaction, a competitive experiment was carried out. To a 10^{-2} M solution of compounds **1** and **4** in THF, 1.25 equivalents of the benzonitrile oxide solution in THF was added. ^{1}HNMR of the reaction mixture showed an excess of compound **4** over **1** (in a ratio 2 to 1), so the speed of the reaction of the uncharged maleimide is slower. In less polar solvents, the difference is expected to be greater.

In order to examine the effect of reactant concentration in this reaction, new experiments were carried out in THF at different concentrations of salt **1**, keeping the concentration of nitrile oxide constant. The reaction was also carried out in toluene and acetonitrile, and in all the cases the same selectivity was observed (Table 1).

Table 1. Ratio of Products for salt **1** in THF, Toluene and Acetonitrile.

Solvent	Salt concentration (M^{-1})	Ratio of products **9:10:11:12**
THF	$1.0x10^{-2}$	0:4:1:1
THF	$5.0x10^{-3}$	0:4:1:1
THF	$1.0x10^{-3}$	0:4:1:1
toluene	$1.0x10^{-2}$	0:4:1:1
acetonitrile	$1.0x10^{-2}$	0:4:1:1
acetonitrile	$1.0x10^{-3}$	0:4:1:1

Triethylammonium chloride remains soluble in acetonitrile, so more of this salt is present during the reaction than when THF is used. However, it has no effect on the ratio of products obtained. This fact made it possible to carry out the reaction in other solvents, such as chloroform and dichloromethane. A new control experiment was performed using amine **4** in chloroform with DBU as the base to ensure that this tertiary amine remains essentially unprotonated. The ratio of products observed in this new control experiment remained

unchanged, (1:4:4:4), but when the reaction was performed with the salt **1**, the selectivity was greatly enhanced (Table 2) and the reaction product contained only one major isomer.

Different bases were used during the experiments with the salt **1** to ensure that this higher selectivity was not due to the presence of triethylammonium chloride. A hydrogen bond based catalytic effect was ruled out by the use of "proton sponge"[9] which does not allow the formation of any intermolecular hydrogen bond. A general acid catalysis was also proven unlikely by the use of the stronger base DBU. For both bases, the product distribution was the same as with triethylamine. The ratio of products is also independent of the concentration of the salt. To test the possible effect of the chloride ion, a new reaction was run using the same conditions as before but including additional tetraethylammonium chloride ($2x10^{-2}$M). Again the same ratio was obtained. Dichloromethane also showed an enhanced selectivity with respect to THF, but it was smaller than chloroform (0:7:1:1).

Table 2. Ratio of Products for salt **1** in halogenated solvents.

Solvent	Base	Salt concentration (M^{-1})	Ratio of products
chloroform	triethylamine	$1.0x10^{-2}$	0:20:1:2
chloroform	triethylamine	$5.0x10^{-3}$	0:20:1:2
chloroform	triethylamine	$1.0x10^{-3}$	0:20:1:2
chloroform	proton sponge	$1.0x10^{-2}$	0:20:1:2
chloroform	DBU	$1.0x10^{-2}$	0:20:1:2
dichloromethane	triethylamine	$1.0x10^{-2}$	0:7:1:1

We conclude that ion pairs can be used as effective control elements to direct that stereoselectivity and chemoselectivity of nitrile oxides. The control is predictable based on evaluations of the position and orientation of the ion pair dipole relative to the transition state dipole.

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