Published in final edited form as:

Org Lett. 2007 February 15; 9(4): 555–558. doi:10.1021/ol062751x.

Transition Structures of Diastereoselective 1,3-Dipolar Cycloadditions of Nitrile Oxides to Chiral Homoallylic Alcohols

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Abstract

Transition structures of the 1,3-dipolar cycloaddition of substituted nitrile oxides with chiral homoallylic alcohols were explored with density functional theory (B3LYP/6-311+G(d,p)+CPCM (dichloromethane)//B3LYP/6-31+G(d)). The diastereoselectivity observed in these reactions was explained. The anti product is favored in both the thermal and magnesium-mediated reactions. Selectivity is predicted to increase in the presence of magnesium, in agreement with experimental results. The energetics of the magnesium-mediated reaction are similar to those previously found for allylic alcohols.

The 1,3-dipolar cycloadditions of chiral alkenes are widely used in organic synthesis.¹ Control of diastereoselectivity in these cycloadditions is important for economical syntheses of natural products,² particularly for the synthesis of polyketides.³ Nitrile oxide cycloadditions with allylic alcohols have been thoroughly studied,⁴ and theoretical calculations have given insights into the origins of their selectivities.⁵

Magnesium salts have been shown to accelerate nitrile oxide cycloadditions to allylic alcohols.⁶ This methodology has been useful for the synthesis of enantiopure β -hydroxy ketones and γ -amino alcohols.⁷ The mechanism and energetics of magnesium-mediated cycloadditions with allylic alcohols have been investigated quantum mechanically by Fukuda *et al.*⁸

There are few literature example of dipolar cycloadditions with homoallylic alcohols, presumably due to the facile dimerization of aliphatic nitrile oxides in the absence of a reactive dipolarophile.^{9,10} Yields for the metal-free reaction are reasonable, but the observed regioselectivities⁹ and diastereoselectivities¹⁰ are low. Kanemasa *et al.* first published the magnesium-mediated cycloaddition of homoallylic alcohols in 1994, but reported low yields and enantioselectivities.⁹ Kociulek *et al.* published improved yields and enantioselectivities in 2003.¹⁰ Carreira and co-workers have extended this methodology to a variety of oximes

and monoprotected homoallylic diols to produce a range of Δ^2 -isoxazolines with reasonable yields, as shown in Scheme 1.¹¹

Selectivity in cycloaddition reactions has been explained using conformational analysis of transition structures.¹² Transition structures prefer a staggered orientation around the forming bonds. For nitrile oxide cycloadditions, this results in three possible locations for a substituent; *inside*, *outside*, or *anti* relative to the forming bonds of the cycloaddition transition structure (Figure 1).

Transition structures for α -substituted alkenes have been carefully examined.^{12d,e,13,14} Substrates with chiral α -alkoxy substituents prefer to orient the alkoxy group *inside* while large alkyl groups prefer to reside *anti*, **A'**. Our group has used this “inside alkoxy effect” to explain the stereoselectivities of cycloadditions of nitrile oxides with chiral allylic ethers.¹⁴ Hydroxyl groups, on the other hand, have a preference for the outside position in order to hydrogen bond with the incoming nitrile oxide oxygen; the large alkyl group continues to prefer the *anti* position, **B'**.^{5a,8} Steric interactions from *Z* alkenes have been found to alter the conformational preference of electronegative substituents.^{12d}

By analogy, the transition structures for nitrile oxide cycloadditions to homoallylic alcohols should prefer conformations such as **C'**. In this conformer, the hydroxymethyl group resides *outside* in order to hydrogen bond with the incoming nitrile oxide oxygen, and the methyl group resides *anti*. The addition of a Grignard reagent has been proposed to increase the preference for this conformer, as the magnesium will strongly coordinate to both oxygens.^{7–9}

Conformational analyses of reagents, products and transition structures were computed with B3LYP/6-311+G(d,p)//B3LYP/6-31+G(d). Gas phase energetics and energetics incorporating the CPCM solvation model¹⁵ are reported. All calculations were performed using Gaussian 03.¹⁶ Computational details and references are given in supporting information. Density functional theory has been shown to be an effective method for modeling dipolar cycloadditions.^{11e–g,12f–h,17} Previous computational work on the magnesium-mediated 1,3-dipolar cycloaddition of nitrile oxides with allylic alcohols implemented the MP4(SDTQ)/6-31G**/RHF/6-31G* and RHF/6-31G**//RHF/6-31G* levels of theory.⁸

There are six possible transition structures that can be formed with three staggered rotamers and involving attack on the two pro-chiral faces of the alkene. Without magnesium salts present, the hydroxymethyl group prefers to reside *outside*, Table 1. The outside orientation allows the hydroxymethyl group to hydrogen bond with the incoming nitrile oxide oxygen. Figure 2 shows the most stable conformers of the six transition structures of **6**. With the hydroxymethyl group *outside*, the alkyl group prefers to reside *anti* by 1 kcal/mol for steric reasons (**6_{outside,anti}** versus **6_{outside,outside}**).

Transition structures **6_{outside,inside}**, **6_{anti,inside}**, **6_{anti,outside}**, and **6_{inside,anti}** are essentially equal in energy when solvation effects are taken into account. The two transition structures that orient the hydroxyl group *outside* and enable hydrogen bonding, **6_{outside,anti}** and **6_{outside,inside}**, are significantly lower than the other transition structures in the gas phase calculations. Rotamer **6_{inside,outside}**, the only rotamer that does not contain a hydrogen bond or an alkyl group *anti*, is the least stable transition structure.

Selectivities for the thermal reaction were calculated using a Boltzmann average based on the computed relative energies from the solvation single point calculations. The thermal reaction is predicted to favor the *anti* diastereomeric product over the *syn* diastereomer by a ratio of 1.7:1. Experimentally, little selectivity is observed. Our calculations overestimate the selectivity of the thermal reaction. The conformational preference for transition structure

6_{outside,anti} is similar in magnitude and direction to the conformational preference of allylic alcohols.⁸

Transition structures for the magnesium-mediated case show similar conformational preferences, Table 2. The Grignard reagent deprotonates the homoallylic alcohol and produces a magnesium complex **9**. Energies in Table 2 are given relative to **4** and **9**. Figure 3 contains the most stable conformers of the six possible transition structures for the magnesium-mediated process.

The magnesium ether shows a strong preference for chelation (**10_{outside,anti}** and **10_{outside,inside}**). This is similar to the trend exhibited by hydroxymethyl, but with the magnesium alkoxide, the preference for the oxygen substituent to reside *outside* has increased to 3 kcal/mol. In the gas phase calculations, the preference for magnesium alkoxide *outside* is very large but inclusion of solvation stabilizes the bisligated magnesium oriented *anti* or *inside*.

With the magnesium ether *outside*, the alkyl group prefers to reside *anti* by 3.4 kcal/mol (**10_{outside,anti}**), which is a larger preference than that observed in the thermal reaction (**6_{outside,anti}** and **6_{outside,inside}**, where **6_{outside,anti}** is preferred by 1.0 kcal/mol). Gas phase energetics suggest no preference for methyl *anti* versus methyl *inside*. Conformers with magnesium ether either *inside* or *anti* are less stable by 7 to 8 kcal/mol.

In both **10_{outside}** conformers, the magnesium ether is stabilized by coordination with the incoming nitrile oxide oxygen. This interaction withdraws electron density from the dipolar cycloaddition transition structure. Since these transition structures are more electron-deficient, there is a greater preference for methyl *anti* to stabilize the transition structure through hyperconjugation.

This preference is not observed in gas phase calculations due to electrostatic interactions. Transition state **10_{outside,inside}** aligns the electron deficient oxygen and the methyl group *gauche*, enabling a stabilizing electrostatic interaction. This interaction is minimized when solvation interactions are taken into consideration.

Diastereoselectivities were predicted using a Boltzmann average based on the calculated potential energies from the solvation single point calculations. The magnesium-mediated reaction is predicted to favor the *anti* product over *syn* by over 99:1. Carreira and coworkers report diastereoselectivities between 4:1 and 13:1. Our calculations overestimate the selectivity of the magnesium-mediated process, most likely due to the absence of explicit solvation of the magnesium in these calculations.

Diastereoselectivity of the dipolar cycloadditions of nitrile oxide to homoallylic alcohols is increased by the addition of Grignard reagents. The *anti* product is favored kinetically and thermodynamically, in both cases. The most stable transition structures prefer to orient the hydroxymethyl or the magnesium ether *outside* to maximize stabilizing interactions with the incoming nitrile oxide oxygen. The alkyl group prefers to reside *anti*, which minimizes steric effects and enables the C-C σ bond to hyperconjugate with the π^* of the alkene.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are grateful to the National Institute of General Medical Sciences, National Institutes of Health (GM 36700 to K.N.H.) for financial support. We also thank the NSF-PACI and UCLA-ATS for computing resources.

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Figure 1.
Model transition structures with alkoxy, **A'**, hydroxy, **B'**, and hydroxymethyl, **C'**, substituents.

Figure 2.
B3LYP/6-311+G(d,p) + CPCM (dichloromethane)//B3LYP/6-31+G(d) transition structures for dipolar cycloaddition of 4 to 5. Energies are in kcal/mol.

Figure 3. B3LYP/6-311+G(d,p) + CPCM (dichloromethane)//B3LYP/6-31+G(d) transition structures for dipolar cycloaddition of **4** to **5** in the presence of MeMgBr (**8**). Energies are in kcal/mol.

Scheme 1.

Diastereoselective Dipolar Cycloaddition of Nitrile Oxides to Homoallylic Alcohols

Table 1
Activation Energies of Transition State Geometries and Reaction Energies of Products for the Cycloaddition of **4** with **5**

compound	$E_s^{a,b}$	inside	outside	anti
6 _{outside,anti}	16.7 (14.3)	H	CH ₂ OH	Me
6 _{outside,inside}	17.7 (15.1)	Me	CH ₂ OH	H
6 _{anti,inside}	17.8 (18.0)	Me	H	CH ₂ OH
6 _{anti,outside}	17.9 (18.1)	H	Me	CH ₂ OH
6 _{inside,anti}	18.3 (18.2)	CH ₂ OH	H	Me
6 _{inside,outside}	18.9 (19.1)	CH ₂ OH	Me	H
7	-34.9 (-35.5)	-	-	-
7	-36.2 (-36.7)	-	-	-

^a Energies relative to **4** + **5** in kcal/mol

^b B3LYP/6-311+G(d,p)+CPCM(dichloromethane)//B3LYP/6-31+G(d) and B3LYP/6-311+G(d,p)//B3LYP/6-31+G(d) in parentheses

Table 2
Activation Energies of Transition State Geometries and Reaction Energies of Products for the Cycloaddition of **4** with **5** in the Presence of MeMgBr (**8**)

compound	E_a^{ab}	inside	outside	anti
10 _{outside,anti}	8.4 (4.1)	H	CH ₂ OMgBr	OMgBr
10 _{outside,inside}	11.8 (4.4)	CH ₃	CH ₃ OMgBr	H
10 _{anti,inside}	15.2 (23.5)	CH ₃	H	CH ₃ OMgBr
10 _{inside,anti}	15.4 (24.2)	CH ₃ OMgBr	H	CH ₃
10 _{anti,outside}	15.6 (23.3)	H	CH ₃	H
10 _{inside,outside}	16.7 (24.5)	CH ₃ OMgBr	CH ₃	CH ₃ OMgBr
11	-40.2 (-46.6)	-	-	-
11	-45.6 (-47.6)	-	-	-

^a E_a Energies relative to **4** + **9** in kcal/mol

^b B3LYP/6-311+G(d,p)+CPCM(dichloromethane)//B3LYP/6-311+G(d) and B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d) in parentheses