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

Jennifer A. R. Luft, Kieche Meleson, and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095

houk@chem.ucla.edu

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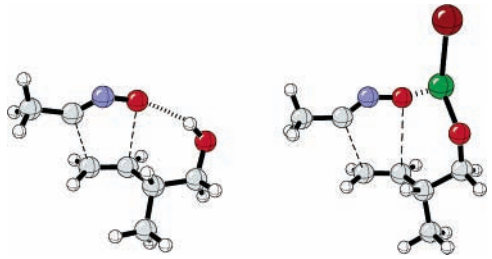
ABSTRACT



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 al-

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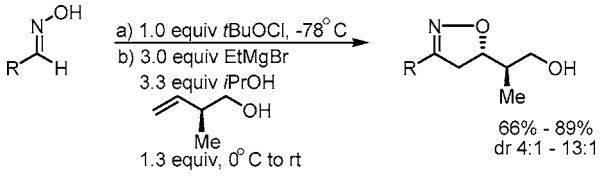
cohols have been investigated quantum mechanically by Fukuda et al.[8]

There are few literature examples 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 regioselectivities[9] and diastereoselectivities[10] are low. Kanemasa et al. first published the magnesium-mediated cycloaddition of homoallylic alcohols in 1994 but reported low yields and enantioselectivities.[9] Kociolek 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]

Scheme 1. Diastereoselective Dipolar Cycloaddition of Nitrile Oxides to Homoallylic Alcohols



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, and 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 enable hydrogen bonding with

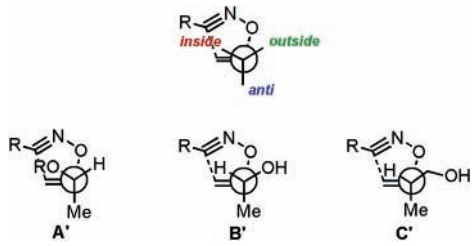


Figure 1. Model transition structures with alkoxy, **A′**, hydroxy, **B′**, and hydroxymethyl, **C′**, substituents.

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 enable hydrogen bonding 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 model[15] 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 considering 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

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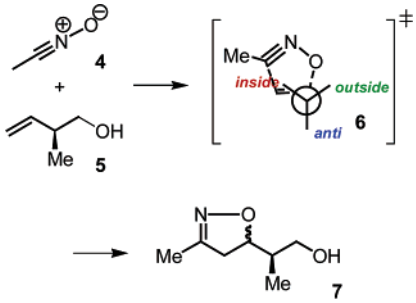
Table 1. Activation Energies of Transition State Geometries and Reaction Energies of Products for the Cycloaddition of **4** with **5**



compound		$E^{a,b}$	inside	outside	anti
$\mathbf{6}_{\mathbf{outside,anti}}$	anti	16.7 (14.3)	H	CH_2OH	Me
$\mathbf{6}_{\mathbf{outside,inside}}$	syn	17.7 (15.1)	Me	CH_2OH	H
$\mathbf{6}_{\mathbf{anti,inside}}$	anti	17.8 (18.0)	Me	H	CH_2OH
$\mathbf{6}_{\mathbf{anti,outside}}$	syn	17.9 (18.1)	H	Me	CH_2OH
$\mathbf{6}_{\mathbf{inside,anti}}$	syn	18.3 (18.2)	CH_2OH	H	Me
$\mathbf{6}_{\mathbf{inside,outside}}$	anti	18.9 (19.1)	CH_2OH	Me	H
7	syn	−34.9 (−35.5)	–	–	–
7	anti	−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.

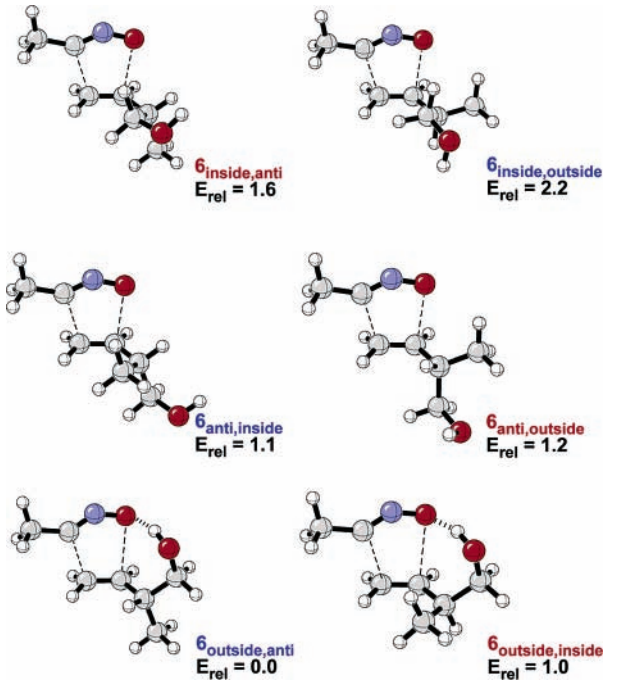


Figure 2. B3LYP/6-311+G(d,p)+CPCM(dichloromethane)//B3LYP/6-31+G(d) transition structures for dipolar cycloaddition of **4** to **5**. Energies are in kilocalories/mole.

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 ($\mathbf{6}_{\mathbf{outside,anti}}$ vs $\mathbf{6}_{\mathbf{outside,outside}}$).

Transition structures $\mathbf{6}_{\mathbf{outside,inside}}$, $\mathbf{6}_{\mathbf{anti,inside}}$, $\mathbf{6}_{\mathbf{anti,outside}}$, and $\mathbf{6}_{\mathbf{inside,anti}}$ 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, $\mathbf{6}_{\mathbf{outside,anti}}$ and $\mathbf{6}_{\mathbf{outside,inside}}$, are significantly lower than the other transition structures in the gas-phase calculations. Rotamer $\mathbf{6}_{\mathbf{inside,outside}}$, 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 $\mathbf{6}_{\mathbf{outside,anti}}$ 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 ($\mathbf{10}_{\mathbf{outside,anti}}$ and $\mathbf{10}_{\mathbf{outside,inside}}$). 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

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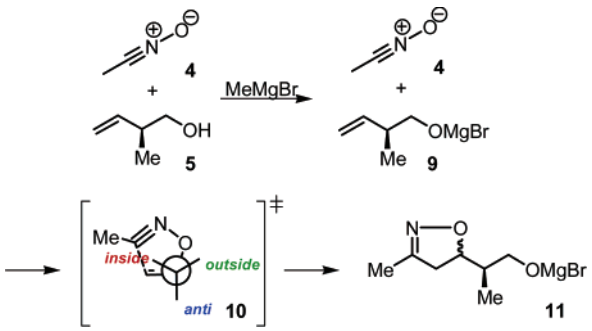
Table 2. Activation Energies of Transition State Geometries and Reaction Energies of Products for the Cycloaddition of **4** with **5** in the Presence of MeMgBr (**8**)



compound		$E^{a,b}$	inside	outside	anti
$\mathbf{10}_{\mathbf{outside,anti}}$	anti	8.4 (4.1)	H	Ether[c]	CH_3
$\mathbf{10}_{\mathbf{outside,inside}}$	syn	11.8 (4.4)	CH_3	Ether[c]	H
$\mathbf{10}_{\mathbf{anti,inside}}$	anti	15.2 (23.5)	CH_3	H	Ether[c]
$\mathbf{10}_{\mathbf{inside,anti}}$	syn	15.4 (24.2)	Ether[c]	H	CH_3
$\mathbf{10}_{\mathbf{anti,outside}}$	syn	15.6 (23.3)	H	CH_3	Ether[c]
$\mathbf{10}_{\mathbf{inside,outside}}$	anti	16.7 (24.5)	Ether[c]	CH_3	H
11	syn	−40.2 (−46.6)	–	–	–
11	anti	−45.6 (−47.6)	–	–	–

[a] Energies relative to **4** + **9** 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. [c] Refers to CH_2OMgBr.

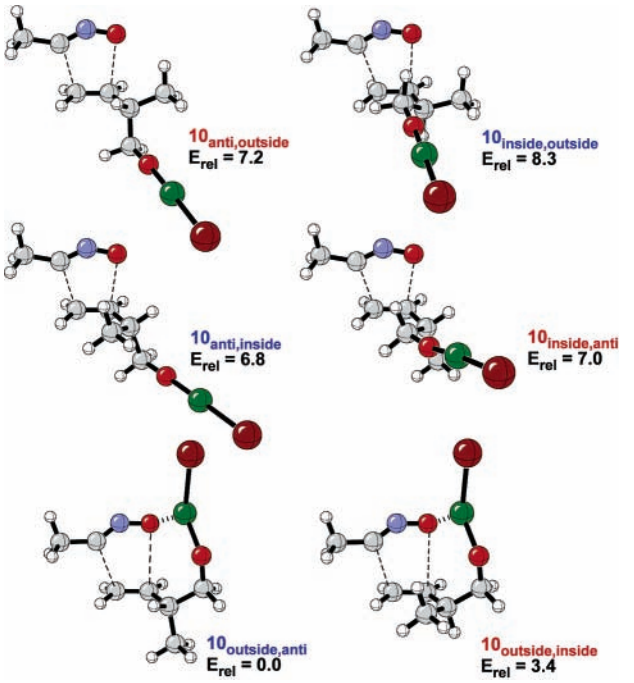


Figure 3. B3LYP/6-311+G(d,p)+CPCM(dichloromethane)//B3LYP/6-31+G(d) transition structures for dipolar cycloaddition of **4** to **5** in the presence of MeMgBr (**8**). Energies are in kilocalories/mole.

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 ($\mathbf{10}_{\mathbf{outside,anti}}$), which is a larger preference than that observed in the thermal reaction ($\mathbf{6}_{\mathbf{outside,anti}}$ and $\mathbf{6}_{\mathbf{outside,inside}}$, where $\mathbf{6}_{\mathbf{outside,anti}}$ is preferred by 1.0 kcal/mol). Gas-phase energetics suggest no preference for methyl anti vs methyl inside. Conformers with magnesium ether either inside or anti are less stable by 7−8 kcal/mol.

In both $\mathbf{10}_{\mathbf{outside}}$ 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. Because 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 $\mathbf{10}_{\mathbf{outside,inside}}$ aligns the electron-deficient oxygen and the methyl group gauche, enabling a stabilizing electrostatic interaction. This interaction is less stabilizing 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 the syn product by over 99:1. Carreira and co-workers 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.

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Supporting Information Available: Cartesian coordinates of all reported structures, as well as the total electronic (B3LYP) and zero-point vibrational (ZPE) enthalpies and computational references. This material is available free of charge via the Internet at http://pubs.acs.org.

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