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Investigation of the Stereochemistry of Intermolecular Conjugate Additions of Nucleophiles to Acyclic Nitrosoalkenes

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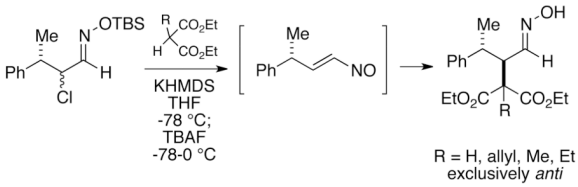
Abstract



Michael-type conjugate additions of γ-chiral aldehyde-derived acyclic nitrosoalkenes have been explored using a series of carbon and hetero nucleophiles. In all cases examined, these reactions are stereoselective, leading exclusively to the *anti* products.

Vinylnitroso compounds **1** are highly reactive, short-lived species which have found only sporadic use in organic synthesis.[1] To date, very few of these intermediates have actually been isolated and characterized, and they are usually generated and trapped in situ. One potentially valuable reaction of nitrosoalkenes involves intermolecular conjugate additions of hetero and carbon nucleophiles in a Michael-type of transformation to produce adducts such as **2** (eq 1). By this process nitrosoalkenes **1** can act as enolonium ion equivalents, thereby allowing a simple method for the umpolung of the usual enolate reactivity.[2] However, these vinylnitroso species have been the object of surprisingly little systematic study and have not seen application to the synthesis of complex molecules. We have recently been exploring the scope of both inter-[3] and intramolecular[4] conjugate additions of these reactive intermediates with a variety of nucleophiles. Recently, we have also begun to investigate various stereochemical issues relevant to these reactions which have never been addressed, and some of this work is the subject of this communication.

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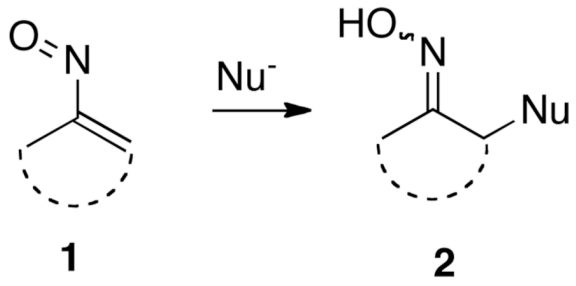
Supporting Information Available Experimental procedures for preparation of new compounds including spectral data. X-ray data for compounds **11, 15** and **19** are also provided. This material is available free of charge on the Internet at http://pubs.acs.org.



(1)

Our initial studies were designed to probe the stereoselectivity of conjugate additions of acyclic aldehyde-derived nitrosoalkenes bearing a γ-stereogenic center (Cf **4**, Scheme 1). It should also be noted that relatively few examples exist in the literature of reactions of nitrosoalkenes generated from aldehydes.[3,5] For this work, we have opted to generate the requisite nitrosoalkene by the Denmark method, which involves exposure of an *O*-TBS-α-chlorooxime to a fluoride source.6 Therefore, known α-chloro-γ-methyldihydrocinnamaldehyde[7] (racemic, mixture of diastereomers) was converted to *O*-TBS-oxime **3** with commercially available *O*-TBS-hydroxylamine (see Supporting Information). Conjugate additions to the vinylnitroso compound derived from **3** were then effected with a series of four malonate anions as the nucleophiles (Scheme 1). Thus, the malonate (2 equiv) was first deprotonated with potassium hexamethyldisilazide in THF at low temperature followed by addition of *O*-silyloxime **3** (1 equiv). Tetrabutylammonium fluoride (2 equiv) in THF was then added at −78 °C and the mixture was warmed to 0 °C to generate the nitrosoalkene **4**. We were pleased to find that in each case the malonate enolate addition was completely stereoselective, producing only the *anti* stereoisomeric adducts **5–8**. Oximes **7** and **8** appear to be single geometric isomers assumed to be (*E*), whereas **5** and **6** are ~9–10:1 (*E*/*Z*) mixtures.[8,9]

In order to establish the configuration of these adducts, α-allylmalonate oxime **5** was heated in toluene at 190 °C (sealed tube) to generate nitrone **9**, which then cyclizes via the conformation shown to afford *cis*-fused bicyclic isoxazolidine **10** (Scheme 2).5c,e,g Treatment of **10** with tosyl chloride gave sulfonamide **11**, whose structure was determined by X-ray crystallography, thereby proving the *anti* configuration of **5**. It seems quite reasonable to assume that the other adducts **6–8** also have this same *anti* arrangement.

Since simple nitrosoalkenes such as **4** have never been isolated, the double bond configuration of these species has not been established, but we speculate that these reactions might well occur via the (*E*)-geometric isomer. If so, the outcome of these nitrosoalkene additions can be nicely rationalized based upon a Felkin-Ahn-type transition state (Figure 1). Thus, one would anticipate that the γ-phenyl group would be perpendicular to the olefinic double bond of the nitrosoalkene and the methyl substitutent would be “inside.” Burgi-Dunitz attack on this conformation as shown in the figure leads to the observed *anti* products **5–8**.

A good analogy for this process would be the conjugate additions of organometallics and other nucleophiles to acyclic γ-chiral α,β-unsaturated esters, which have been extensively studied both experimentally[10] and theoretically.[11] For example, with (*E*)-α,β-unsaturated esters having γ-substituents as in **4**, the reaction usually proceeds via a transition state similar to that in Figure 1 and therefore the major addition product is *anti* (with the corresponding (*Z*)-isomer, *syn* is usually preferred). However, in additions to related γ-

alkoxy systems, both *syn* and *anti* products have been observed, depending upon the nucleophile and substrate. The formation of the *syn* products has been rationalized using a modified Felkin-Ahn model with the alkoxy group perpendicular to the π-bond, or one involving metal chelation to the oxygen. We therefore decided to explore a conjugate addition of a vinylnitroso compound related to **4** bearing a γ-alkoxy group in place of methyl to see if this substitution leads to formation of any of the *syn* product.

For this work, substrate **12** was prepared,[12] and again using the Denmark protocol the potassium enolate of diethyl α-allylmalonate was added to the derived nitrosoalkene to give only the *anti* product **13** in 68% isolated yield (Scheme 3). The structure of this adduct was established as before by thermolysis to the isoxazolidine **14**, which was converted to the sulfonamide **15**. X-ray analysis of this compound indicated its composition to be as shown, thus confirming the *anti* configuration of **13**. In addition, to see if there are any chelation effects in the conjugate addition, the corresponding lithium salt of the allylmalonate was used, but the *anti* product **13** was again produced exclusively, albeit in somewhat lower yield (52%) than with the potassium salt.

In order to probe whether replacing the γ-phenyl substituent in nitrosoalkene **4** with a bulky alkyl group has any affect on the stereochemistry of the addition, the neopentyl system **16** was prepared.[13] Using the standard procedure, addition of potassium diethyl α-allylmalonate to the corresponding nitrosoalkene was totally stereoselective, giving the *anti* compound **17** as the only product (Scheme 4). Once again, the stereochemistry was established by thermal conversion to the isoxazolidine **18**, followed by X-ray analysis of the derived *p*-nosyl compound **19**.

Finally, we have examined the stereochemistry of a heteronucleophile addition to one of these nitrosoalkenes. Therefore, the potassium salt of *N*-methyl-*p*-toluenesulfonamide was first combined with α-chloro-*O*-silyoxime **16**, followed by addition of TBAF in THF, to produce a single stereoisomeric adduct **20** (Scheme 5). The oxime **20** was dehydrated with methanesulfonyl chloride/pyridine in methylene chloride to afford the corresponding nitrile **21**. Based upon NMR proton coupling data for **21** in comparison with some closely related compounds,[14,15] we have assigned the *anti* stereochemistry to the sulfonamide adduct as shown.

In conclusion, the stereochemical outcome of conjugate additions to a series of in situ-generated γ-chiral aldehyde-derived nitrosoalkenes has been examined using a number of malonate enolates as nucleophiles. These reactions are totally stereoselective in all of the examples tested, leading exclusively to the *anti* products. Moreover, a similar reaction using a sulfonamide anion as a heteronucleophile also cleanly led to the *anti* adduct. We are currently exploring extensions of this methodology as well as applications to synthesis of complex molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. Dehydration of the mixture of oxime geometric isomers of **6** to the corresponding nitrile with MsCl/pyr/CH_2Cl_2 led to a single *anti* diastereomer in 73% yield.
9. In a control experiment, α-chloro-*O*-silyloxime **3** was found to be unreactive towards potassium diethyl malonate at room temperature in the absence of TBAF.
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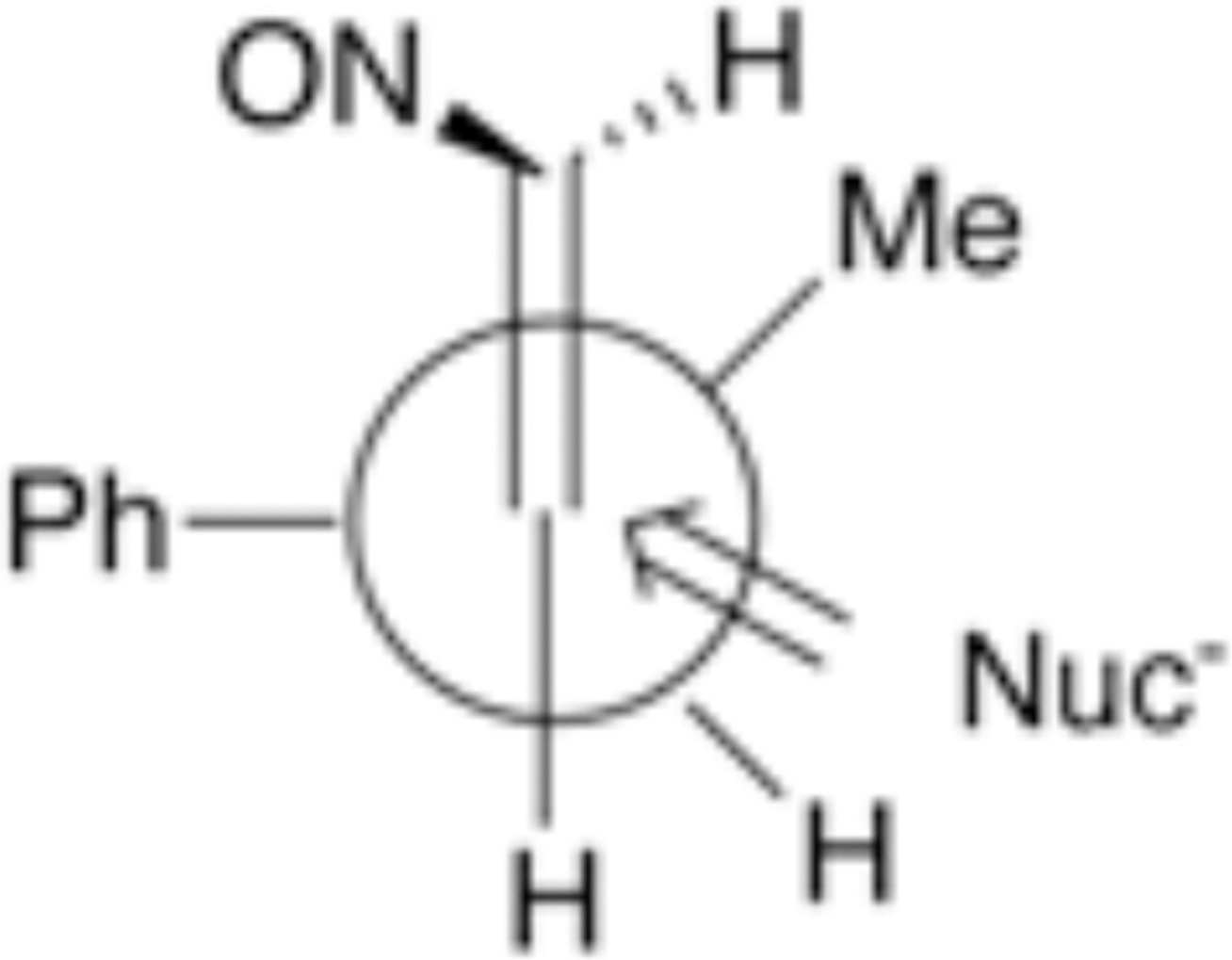
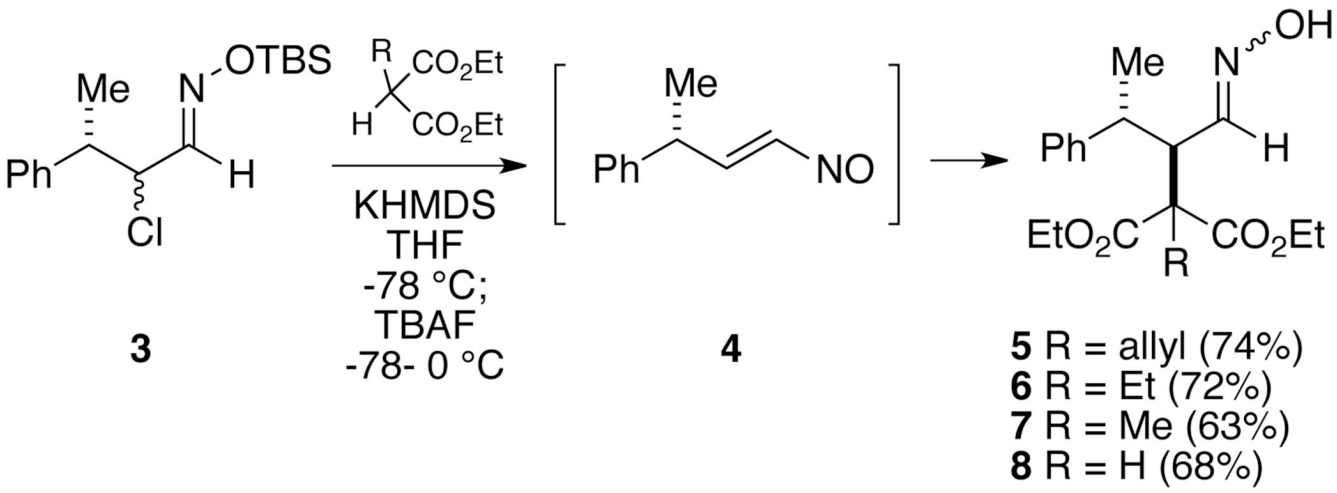
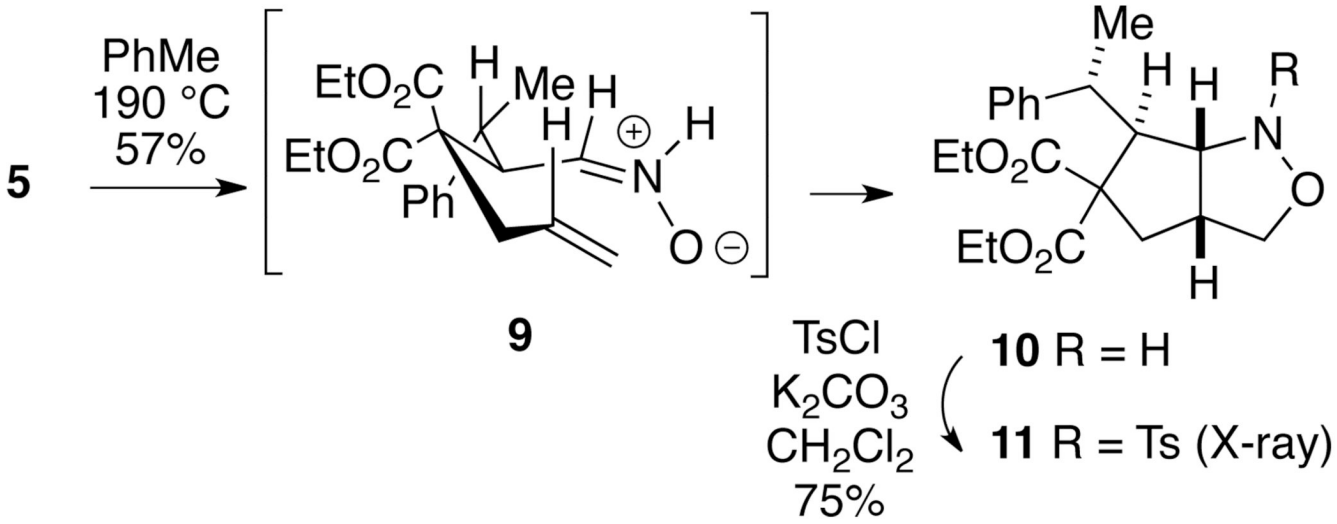


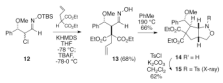
Figure 1.
Felkin-Ahn-type Attack of Nucleophiles on Nitrosoalkene **4**



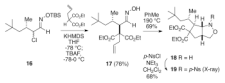
Scheme 1.
Conjugate Additions to a γ-Chiral Aldehyde-Derived Nitrosoalkene



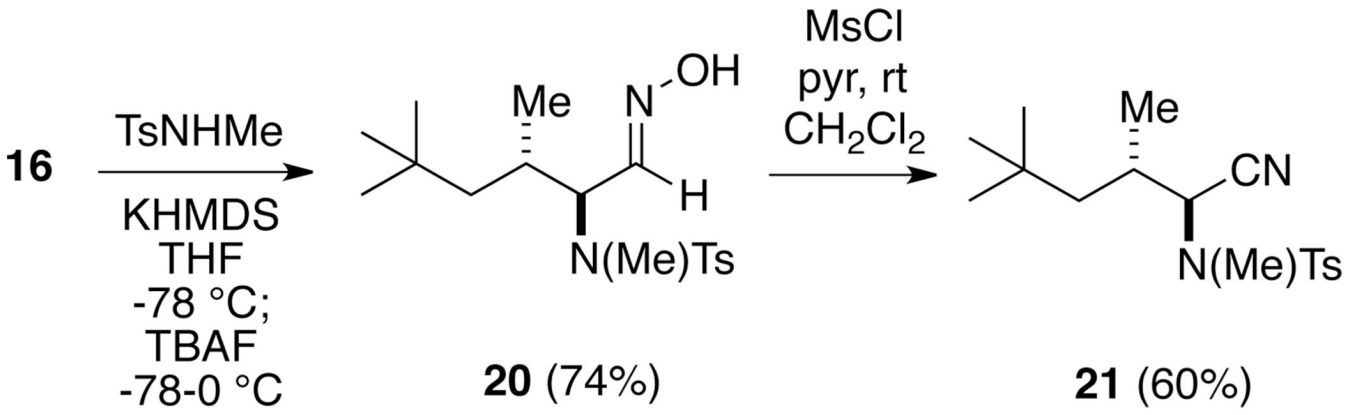
Scheme 2.
Intramolecular Nitrone/Olefin Cycloaddition of Allyl Oxime **5** to Isoxazolidine **10**



Scheme 3.
Conjugate Additions to a γ-Methoxy Nitrosoalkene



Scheme 4.
Conjugate Additions to a γ-Neopentyl Nitrosoalkene



Scheme 5.
Conjugate Addition of a Sulfonamide Nucleophile to a Nitrosoalkene