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Examination of Homo-[3 + 2]-Dipolar Cycloaddition: Mechanistic Insight into Regio- and Diastereoselectivity

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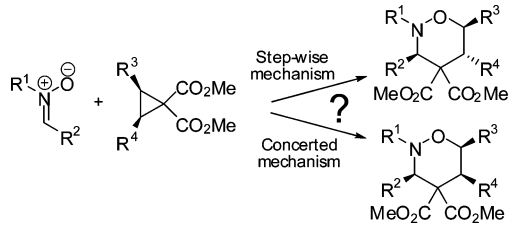
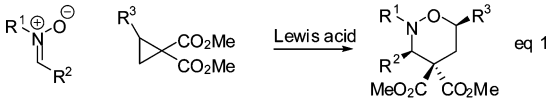


The reaction of 2,3-disubstituted-1,1-cyclopropanediesters with nitrones under Lewis acid conditions produces tetrahydro-1,2-oxazines in which the cis/trans relationship of the cyclopropanes is not conserved. Reacting nitrones with 2,3-cis-disubstituted cyclopropanes lead to 5,6-*trans*-oxazines, and 2,3-trans-disubstituted cyclopropanes lead to 5,6-*cis*-oxazines. This observed stereochemical inversion provides evidence for a stepwise annulation mechanism in the preparation of tetrahydro-1,2-oxazines.

Recently, we reported the reaction of nitrones **1** with 1,1-cyclopropanediesters **2** to form tetrahydro-1,2-oxazines **3** in what we termed a homo-[3 + 2]-dipolar cycloaddition.[1] This moniker (as opposed to a [3 + 3] cycloaddition) is preferred since one of the carbons in the cyclopropane is an electronic bystander in the reaction. While this reaction has been developed by us[2] and others[3] over the last several years, and has been shown to be a powerful tool in total synthesis,[4] the exact mechanism of the reaction remains unclear.



1 **2** **3**

We recently subjected the reaction to DFT analysis to probe the likely course of the reaction only to find global minima for both a concerted and a stepwise fashion, which were very close in energy.[5] Herein, we present a study of the reaction mechanism that relies on the use of a modified cyclopropane diester as a mechanistic probe.

Figure 1 shows a simple reaction/energy diagram of a stepwise and a concerted reaction between a nitrone and a 1,1-cyclopropanediester. In the concerted scenario, the cyclopropyl substituent R^3 would necessarily be exo to the nitrone to satisfy the observed 3,6-cis relationship observed in the adducts (since R^1 and R^2 are trans in the nitrone). If this mechanism was operational, R^3 and R^2 would end up cis to Ha in the adduct. In a stepwise mechanism, we envision a nucleophilic ring opening of the cyclopropane (with inversion) by the nitrone oxygen resulting in a zwitterionic intermediate. Ring closure of the malonic anion onto the iminium moiety would result in an adduct in which R^3 is cis to Hb. Of course, in our previous studies, the adducts from each mechanistic pathway were indistinguishable. We reasoned, then, that the positioning of an additional substituent on the cyclopropane vicinal to both R^3 and the diester moiety would allow, upon examination of the adducts, insight into the concerted or stepwise nature of the reaction.

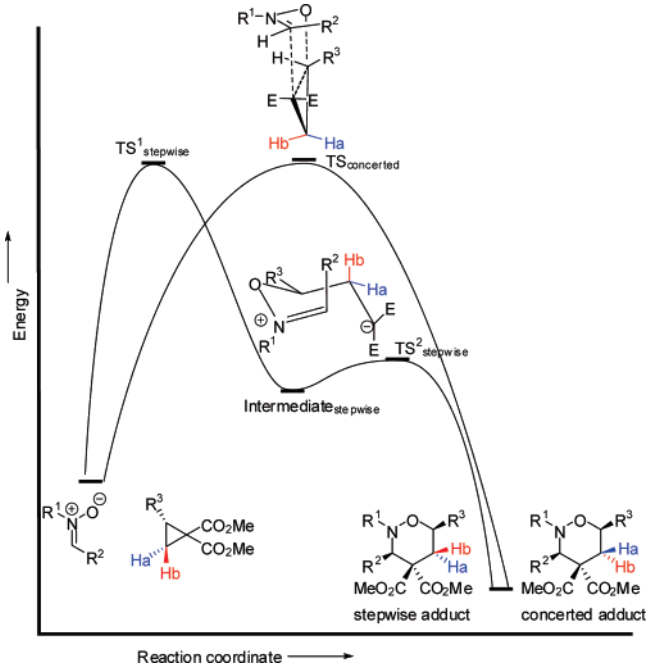


FIGURE 1. Stepwise and concerted mechanisms for cycloaddition.

Scheme 1 shows the preparation of two cyclopropane substrates for our study. Dihydroxylation of *trans*-*β*-methylstyrene **4** gave diol **5**, which upon treatment with thionyl chloride gave cyclic sulfite **6**. Oxidation to sulfate **7** gave a suitable substrate for conversion to cyclopropane **8** via double displacement with the anion derived from dimethyl malonate. The diastereomeric cyclopropane **11** was prepared directly by carbenoid insertion of diazomalonate **10** to *cis*-*β*-methylstyrene **9**.

With cyclopropanes **8** and **11** in hand, we proceeded to subject them to cycloaddition reactions with two representative nitrones

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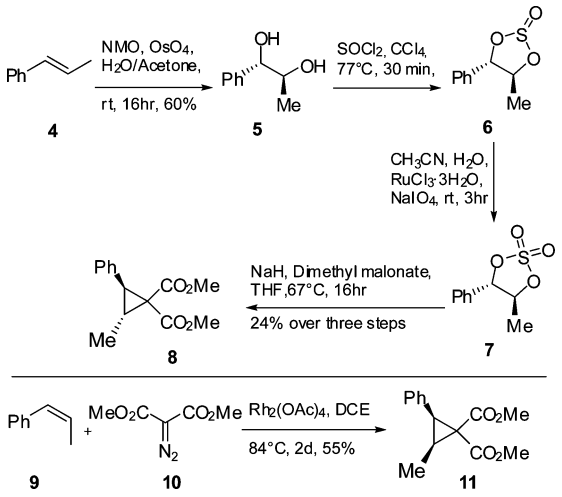
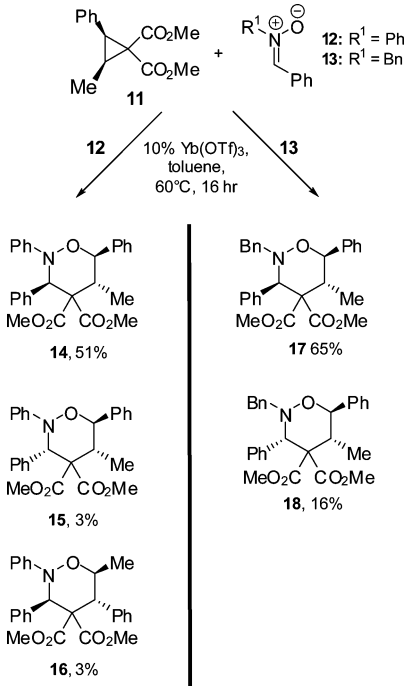
SCHEME 1. Synthesis of trans- and cis-Disubstituted Cyclopropanes



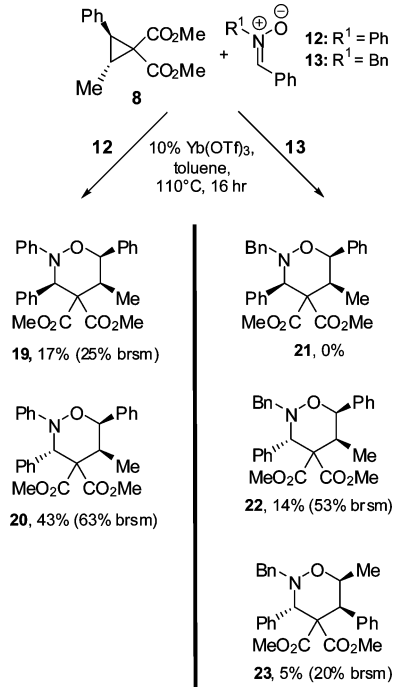
SCHEME 2. Reaction of Cyclopropane 11 with Nitrones 12 and 13



12 and **13**. Aside from their ease of preparation, these nitrones were chosen because they bear an aryl and an alkyl nitrogen substituent, respectively. Scheme 2 shows the reaction of cyclopropane **11** with nitrones **12** and **13**.

Several observations from Scheme 2 are worth noting. In all cases, the groups at the 5- and 6-positions of the tetrahydrooxazine ring had a trans relationship, indicating that ring opening of the cyclopropane had occurred with inversion of configuration.[6] Although slightly lower than usual for this transformation, the overall yields of adducts were reasonably good. As expected the 3,6-*cis* diastereomer was the major isomer although a significant amount of the 3,6-*trans* isomer **18** was isolated in the reaction with nitrone **13**. Last it is interesting that a small amount of regioisomer **16** was observed in reactions of nitrone **12**. This is surprising since we have come to expect that the carbocation-stabilizing ability of the cyclopropane substituent vicinal to the diester moiety is key to promoting ring opening at that position.

SCHEME 3. Reaction of Cyclopropane 8 with Nitrones 12 and 13



Cyclopropane **8** behaved quite differently in the cycloaddition reactions, most notably in its sluggishness. The results are shown in Scheme 3.[6] In contrast to reactions with **11**, conditions involving refluxing toluene were necessary to effect appreciable reaction and the yields were somewhat diminished. In these reactions, all isolated adducts bore a cis relationship between substituents at the 5- and 6-positions, indicating again that the reaction had proceeded with inversion of configuration during the cyclopropane ring opening event. The most striking result to us, however, was the fact that for the first time ever, the 3,6-trans adduct was the major diastereomer isolated. In essence, then, the extra substituent, which is on a carbon not electronically involved in the reaction, influenced the stereochemical relationship.

Figure 2 presents a reasonable rationale for the stereochemical distribution of products from both cyclopropane **8** and **11**. In the case of cyclopropane **11**, nitrone attack on the cyclopropane results in intermediate **I**, in which the phenyl and methyl groups originating from the cyclopropane can both be equatorial in the proposed chair-like conformation. Intermediate **I** then proceeds uneventfully to the product with the expected and observed stereochemical outcome.

Cyclopropane **8**, on the other hand, would result in intermediate **II** upon reaction with the nitrone, necessarily putting the methyl group in an axial orientation. This should result in an unfavorable 1,3-diaxial interaction with the phenyl substituent from the nitrone. The formation of this higher energy intermediate would imply a slower rate of reaction. Relief of the unfavorable 1,3-diaxial interaction could be achieved upon changing to a boat conformation **III**. Ring closure from **III** would produce the unusual 3,6-*trans*-tetrahydro-1,2-oxazines observed.[7]

(6) Stereochemistry of all compounds was unambiguously confirmed by either X-ray crystallographic analysis or NOE analysis. See Supporting Information for details.

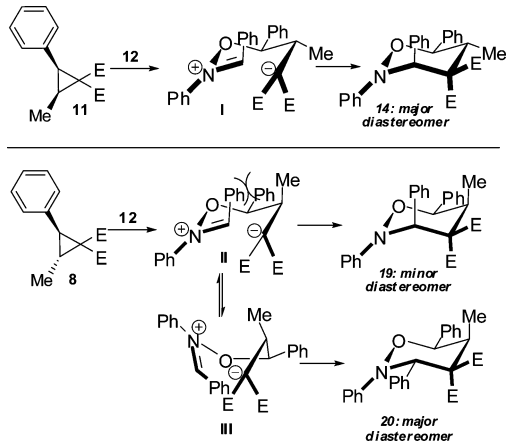
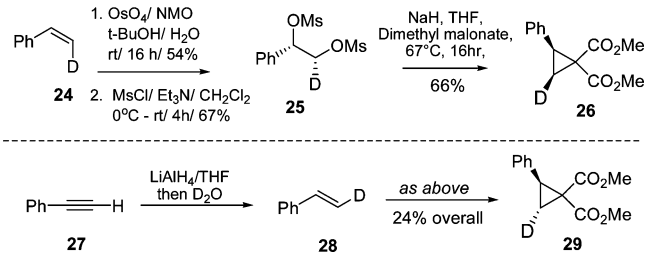


FIGURE 2. Mechanistic rationale for observed product mixture.

SCHEME 4. Preparation of Cyclopropanes 26 and 29



To remove the steric effects imposed by the methyl group on the cyclopropanes, we prepared two cyclopropanes **26** and **29**, which bore a deuterium label cis and trans to the phenyl moiety, respectively (Scheme 4). Dihydroxylation of *cis*-*β*-deuterostyrene **24**[8] followed by bis-mesylation provided **25**, which was a suitable substrate for cyclopropane formation with dimethylmalonate and sodium hydride. Cyclopropane **29** was prepared in the same manner, however, from *trans*-*β*-deuterostyrene **28**, which in turn was available from hydride reduction of phenylacetylene **27** and a deuterium quench.

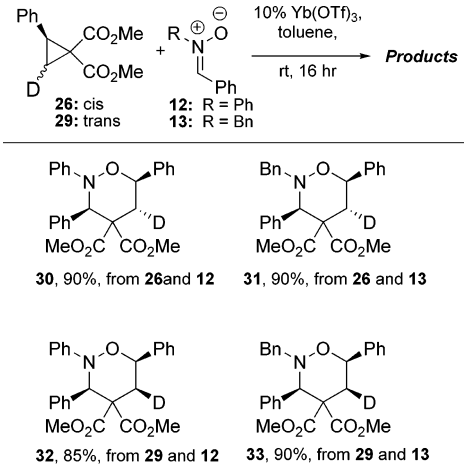
As expected, cycloadditions employing cyclopropanes **26** and **29** proceeded in excellent yields as seen from our previous work. Chart 1 summarizes the results. In all cases, the cyclopropane ring opening proceeded with inversion of configuration. That is, the *trans*-cyclopropane **29** resulted in cis adducts **32** and **33**, while *cis*-cyclopropane **26** yielded trans adducts **30** and **31**.

In conclusion, by utilizing cis/trans-disubstituted cyclopropanes in cycloadditions with nitrones, we have shown that the reaction proceeds through a stepwise mechanism with inversion of stereochemistry at the cyclopropane carbon undergoing attack by the nitrone oxygen. The adducts obtained from *cis*-cyclopropane **11** yield a cis 3,6-substituted adduct, while those obtained from *trans*-cyclopropane **8** yield adducts with a trans 3,6 relationship as the major products. This observation is attributed to the unfavorable nature of a chair-like transition

(7) It should be noted that we are assuming that the stereochemical integrity of the nitrone iminium bond (Z-geometry) is maintained during the course of the reaction. While the Z-geometry is preferred for nitrones, it cannot be ruled out that the iminium geometry is fluxional under the reaction conditions.

(8) Dolbier, W. S.; Wicks, G. E. *J. Am. Chem. Soc.* **1985**, *107*, 3626.

CHART 1. Cycloadducts from Deuterium Labeled Cyclopropanes



forcing the adoption of a boat-like transition state. When the cycloadditions were repeated with deuterium labeled cyclopropanes, thus removing the steric effects, the expected adducts were formed in excellent yields where clean inversion of stereochemistry had occurred at the cyclopropyl carbon undergoing attack. These findings further strengthen the postulation of a stepwise mechanism as being the mode of reaction for the cycloaddition.

Experimental Section

cis-Cyclopropane **11** (0.1 g, 0.4 mmol) and nitrone **12** (0.16 g, 0.8 mmol) were dissolved in 5 mL of toluene. $Yb(OTf)_3$ (0.025 g, 0.04 mmol) was added to the solution, and the reaction mixture was heated to 60 °C for 16 h. The reaction was poured into water and extracted with EtOAc, and the combined layers were washed with brine and then dried with anhydrous $MgSO_4$. The crude mixture was purified by flash column chromatography, and a mixture of diastereomers (1:0.06:0.06, totaling 0.102 g, 57%) was isolated as a yellow solid. The major isomer was recrystallized from a solution of EtOAc/hexanes as large white crystals. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.63$ (d, 2H, $J = 7.2$ Hz), 7.54 (d, 2H, $J = 6.6$ Hz), 7.46 (t, 2H, $J = 7.2$ Hz), 7.41 (t, 1H, $J = 6.6$ Hz), 7.25 (t, 2H, $J = 7.2$ Hz), 7.21 (t, 1H, $J = 7.2$ Hz), 7.10 (t, 2H, $J = 7.2$ Hz), 6.99 (d, 2H, $J = 7.8$ Hz), 6.77 (t, 1H, $J = 7.2$ Hz), 5.67 (s, 1H), 4.82 (d, 1H, $J = 10.8$ Hz), 3.90 (s, 3H), 3.42 (s, 3H), 3.25 (dq, 1H, $J = 10.8$, 6.6 Hz), 0.92 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.2$, 168.7, 148.3, 137.9, 135.6, 130.2, 128.7, 128.6, 128.4, 128.1, 128.02, 127.98, 121.2, 115.5, 85.0, 67.4, 62.6, 52.5, 52.2, 35.6, 14.2; IR (thin film): $\nu_{max} = 3063$, 3032, 3002, 2979, 2952, 2917, 2887, 2849, 1735, 1598, 1492, 1456, 1436, 1253, 1230, 1043, 910, 754, 733, 700, 650, 605; HRMS calcd for $C_{27}H_{27}NO_5$ 445.1889, found 445.1882 amu, mp = 161−163 °C.

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Supporting Information Available: Complete experimental procedures as well as ^{1}H NMR and ^{13}C NMR, IR, MS, and crystal structure data for **14**, **17**, **20**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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