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Annulation Reactions of Donor–Acceptor Cyclopropanes with (1-Azidovinyl)benzene and 3-Phenyl-2*H*-azirine

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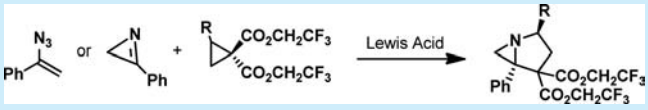
Supporting Information

ABSTRACT: Under the influence of heat and Lewis acid, donor/acceptor cyclopropanes underwent annulation reactions with (1-azidovinyl)benzene and 3-phenyl-2*H*-azirine to form an unusual azabicyclic scaffold with an imbedded aziridine. The mechanism of reaction is believed to proceed via a vinyl nitrene intermediate.

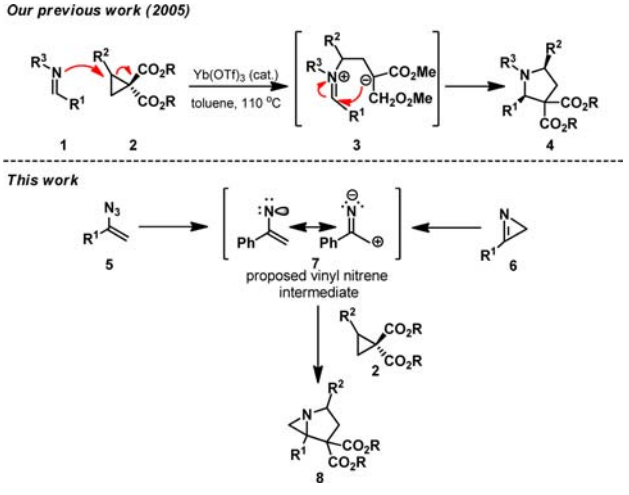


The field of donor–acceptor cyclopropane chemistry has seen a huge resurgence since the early work of Wenkert,[1] Danishefsky,[2] and Reissig.[3] The number of reacting partners is now quite wide, and research over the past decade has mainly focused upon annulation reactions for the formation of hetero- and carbocycles.[4] In addition, the new methods have seen applications in a number of total syntheses. Annulation partners include nitrones,[5] aldehydes,[6] imines,[7] azomethine imines,[8] allyl silanes,[9] acetylenes,[10] and more.[4]

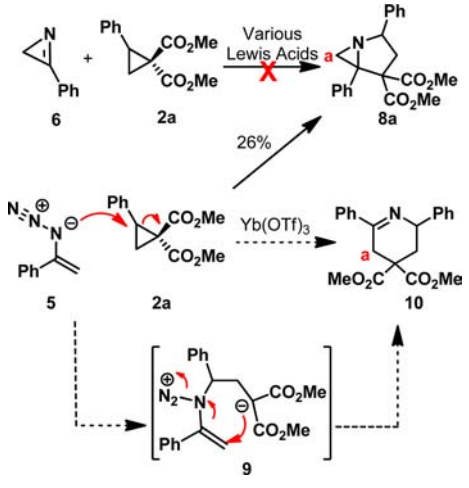
In an effort to expand our early work involving the annulation of DA cyclopropanes **2** with imines[7a] **1** to produce pyrrolidines **4**, a simple extension to (2*H*)-azirines **6** was envisaged (Scheme 1). The products would be a pyrrolidine **8** with an aziridine imbedded in the ring structure. Our motivation for this work was based on the potentially interesting transformations of the adducts via aziridine opening. Herein, we present the results of this research, which are anything but obvious. The implication is that azirines are not the reactive species but generate a reactive vinyl nitrene "dipole" in situ. Moreover, vinyl azides may also act as the precursor to the putative vinyl nitrene.

Our study commenced with the readily available and highly studied 3-phenyl-2*H*-azirine **6** (generated by heating (1-azidoviynl)benzene **5**).[11] Treatment under our previously defined conditions, which involved catalytic $Yb(OTf)_3$ in toluene, failed to yield a clean product and certainly no appreciable amount of a compound resembling **8a**. After much frustration at what seemed to be a straightforward extension of our previous work, we decided to examine the reaction of vinyl azides with the DA cyclopropanes. One might imagine vinyl azides behaving in a 1,3-dipolar manner. Our hypothetical reaction is shown in Scheme 2. Under Lewis acid conditions, attack by nitrogen on the vinyl azide would yield intermediate **9**, which may undergo a formal S_N' attachment with loss of

Scheme 1. Hypothetical Reaction of DA Cyclopropanes with Vinyl Azide and 3-Phenyl-2*H*-azirine



Scheme 2. Hypothetical Reaction of Vinyl Azide with DA Cyclopropanes and a Surprising Result



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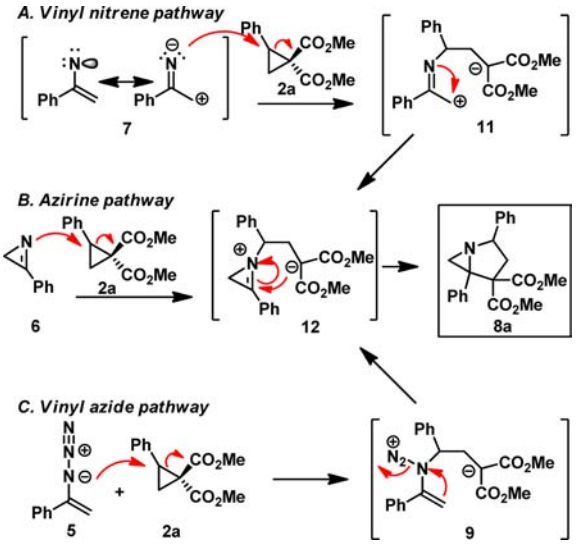
nitrogen. The result would be the formation of the dehydropiperidine **10**.

In the event, treatment of **5** with cyclopropane **2a** gave what appeared to be **10** in a meager 26% yield. We were delighted that a proof of principle was achieved and were confident that yields could be improved. While the ^{1}H NMR spectrum looked consistent with **10**, several aspects of the data bothered us, particularly the absence of any geminal coupling of the methylene at carbon **a**. In addition, the ^{13}C NMR spectrum showed no resonance for an imine carbon. Upon closer inspection of the NMR data (1D and 2D), it was determined to our surprise that the product was not **10** but in fact **8a**. This was later borne out by X-ray analysis.

Three possible mechanistic explanations for the observed transformation are shown in Scheme 3. Option A involves a

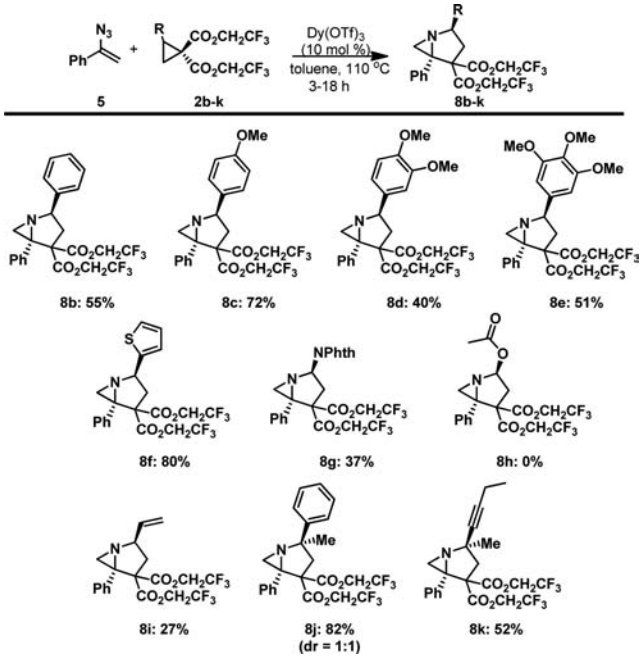
Scheme 3. Possible Mechanistic Pathways



vinyl nitrene formed by the known thermolysis of the vinyl azide. Nitrene **7**, acting as a dipolar species, may engage in Lewis acid mediated ring opening of the cyclopropane **2a** to yield **11**. Conversion of **11** to the more stable iminium ion **12** sets up a Mannich style ring closure to the observed product **8a**. Option B involves an azirine formed by the known thermolysis of the vinyl azide **5** via a putative nitrene **7**. Ring opening of the cyclopropane by the nucleophilic nitrogen produces the same intermediate **12**. Finally, option C has the vinyl azide itself nucleophilically opening the cyclopropane **2a** to yield intermediate **9**.

Efforts were then undertaken to optimize the reaction for the formation of the interesting azabicyle **8a**. The most obvious hurdle to overcome was the tendency of the vinyl azide to dimerize. This is a known process, presumably proceeding via a vinyl nitrene.[11] Variation of all the normal parameters failed to suppress the dimerization, which occurred competitively with the desired process. Even addition of the vinyl azide via syringe pump in order to lower the concentration in the reaction mixture failed to improve the situation. At this time, we became aware of the work of Waser,[12b,c] who used donor−acceptor cyclopropanes bearing trifluoroethyl esters[12] in place of the more common methyl esters. This, in effect, makes the cyclopropane more electrophilic toward ring opening. In short, this provided a solution to the dimerization issue, making the desired annulation more favorable than dimerization. The results of a substrate study are shown in Scheme 4. It was found during the screening of catalysts that dysprosium(III)triflate ($Dy(OTf)_3$) provided superior results to other Lewis acids.

Scheme 4. Reaction of (1-Azidovinyl)benzene with DA Cyclopropanes: Substrate Scope



The optimized conditions worked reasonably well, producing the adducts in fair to excellent yields. The range of cyclopropanes was fairly wide with aryl, heteroaryl, vinyl, alkynyl, and phthalimido substituents tolerated. Several observations are worthy of note. Cyclopropanes bearing an aryl moiety with a highly electron-withdrawing group (ester, nitrile) failed to undergo a successful reaction. When the aryl moiety bore an electron-donating group such as a methoxy group, the fate was much better. Two or three methoxy groups made the cyclopropane too reactive and prone to decomposition, thus the diminished yields. It is also important to note that cyclopropanes bearing a quaternary center vicinal to the diester moiety also produced the expected azabicycles **8j** and **8k**. The adducts (with the exception of **8j**) were produced as single diastereomers, the identity of which remained unclear until satisfactory crystals were grown for X-ray analysis. The structure obtained via X-ray diffraction is shown in Figure 1.

The source of the diastereoselectivity is somewhat unclear at this time; however a rationale which predicts the observed

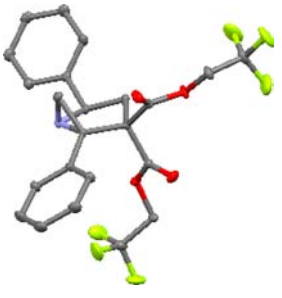


Figure 1. X-ray structure of **8b**.

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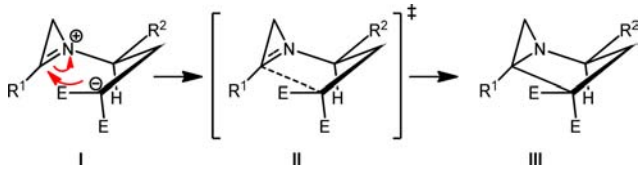
results is shown in Scheme 5. Zwitterionic species I may undergo Mannich-style ring closure via transition state II

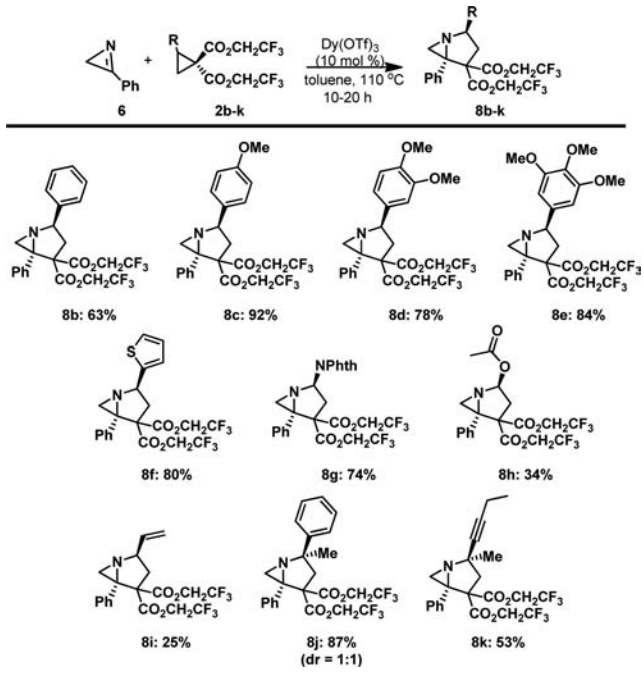
Scheme 5. Rationale for the Observed Diastereoselectivity



resulting in the formation of the observed diastereomer III. Transition state II would have the R^2 in a pseudoequatorial position in the newly formed five-membered ring.

With optimized conditions in hand for the reaction of vinyl azides with donor−acceptor cyclopropanes, it was decided to reinvestigate the failed reactions of azirines. To our great surprise, with the more activated cyclopropanes bearing the trifluoroethyl esters, the formation of the azabicycles proceeded rather smoothly. Scheme 6 illustrates the results. The same

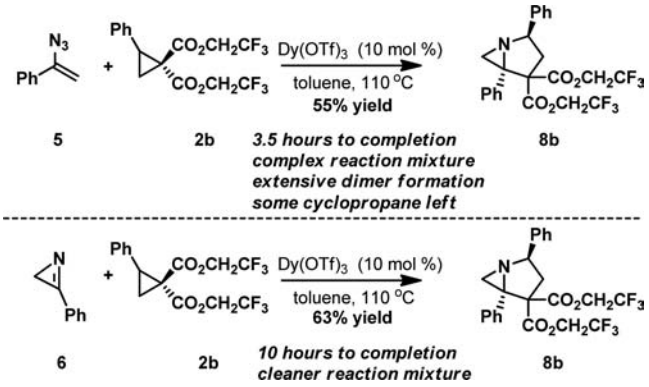
Scheme 6. Reaction of 3-Phenyl-2*H*-azirine with DA Cyclopropanes: Substrate Scope



cyclopropanes were used as substrates, and in general, the yields were much improved. While the yields were higher, the reactions took longer to complete. The reactions were also cleaner with little or no dimerization product.

The success of the reaction of azirines with the donor−acceptor cyclopropanes was both welcome and puzzling. Perhaps the more reactive cyclopropanes underwent reaction with the imino moiety of the azirine as postulated initially (Scheme 3, pathway B). A simple side-by-side experiment was conducted to compare the reaction profiles of the azirine and the vinyl azide. The results are shown in Scheme 7. Under identical reaction conditions carried out in the same heating bath, azirine **6** and vinyl azide **5** were subjected to reaction with cyclopropane **2b**. The vinyl azide reacted at a much faster rate with the reaction reaching completion in 3.5 h. The reaction

Scheme 7. Parallel Study of the Two Reactions



mixture was complex, with extensive dimerization leaving some cyclopropane unreacted. On the other hand, the azirine took 10 h to react to completion, resulting in a much cleaner reaction mixture.

We believe that the above results argue against an azirine as the active reactant in the reaction of vinyl azides with donor−acceptor cyclopropanes. If this was the case, providing the reaction preformed azirine should result in lower reaction times. Both azirines and vinyl azides are known to form vinyl nitrenes on heating. It is our working hypothesis that the vinyl azide provides the rapid formation of vinyl nitrene, which may engage in the reaction with the cyclopropane or with itself. The azirine may provide a slower formation of vinyl nitrene resulting in a lower concentration in solution, suppressing dimerization, and allowing reaction with the cyclopropane to dominate. Admittedly, there is the possibility that two reaction pathways are in operation: a vinyl nitrene pathway for the vinyl azide and an imine annulation for the azirine. Finally, we should note that the direct involvement of the azide functional group in the cyclopropane ring opening (Scheme 3, option c) cannot be completely discounted.

In summary, we have described a new annulation reaction forming an unsual azabicycle with an imbedded aziridine unit. The potential reactivity of this type of compound toward ring expansions and other transformations is being investigated, with the results forthcoming in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02409.

Full experimental procedures and spectroscopic data for all new compounds and crystal data for compounds **8b** and **8g** (PDF)

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Notes

The authors declare no competing financial interest.

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Hairsine of the University of Western Ontario Mass spectrometry facility for performing MS analyses.

DEDICATION

Dedicated to the memory of Aaron Kinsman.

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