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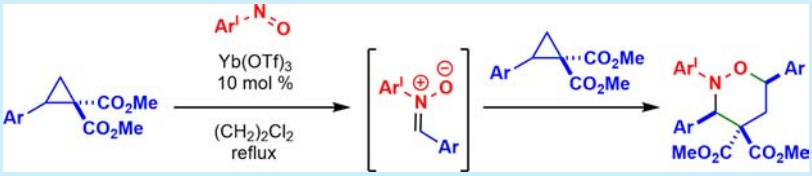
Cascade Reaction of Donor–Acceptor Cyclopropanes: Mechanistic Studies on Cycloadditions with Nitrosoarenes and *cis*-Diazenes

Tristan Chidley, Naresh Vemula, Cheryl A. Carson, Michael A. Kerr, and Brian L. Pagenkopf*

Department of Chemistry, The University of Western Ontario, 1151 Richmond Street, London, ON N6A 5B7, Canada

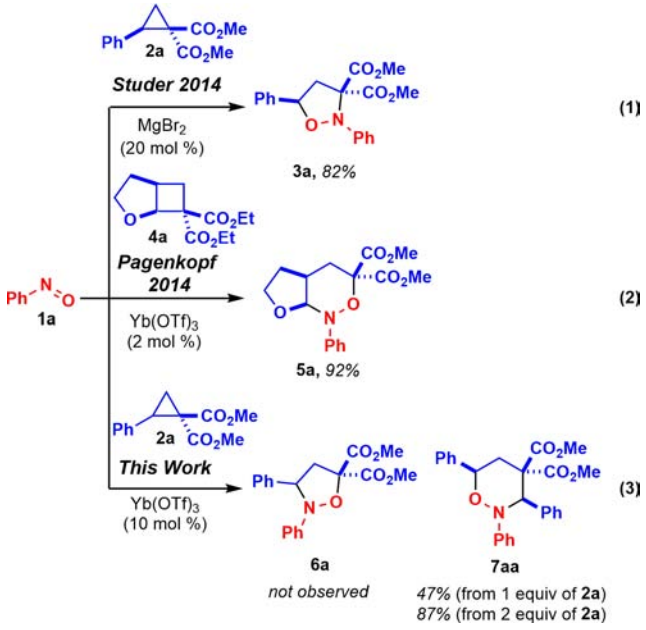
Supporting Information



ABSTRACT: Tandem ring opening, elimination, and cycloaddition of donor–acceptor cyclopropanes were observed in $Yb(OTf)_3$-catalyzed cycloaddition with nitrosoarenes. The reaction results in formation of tetrahydro-1,2-oxazine instead of the normal cycloadduct isoxazolidine via in situ nitrone formation. A similar cascade sequence was observed with *cis*-diazines. Mechanistic studies on this unique transformation offer an entirely new approach for reaction design with donor–acceptor cyclopropanes.

Exploitation of ring strain in donor–acceptor (DA) cyclopropanes to generate 1,3-zwitterionic intermediates has been extensively studied, and a number of reactive partners have been found to undergo cycloaddition reactions.[1] Most recently, the Studer group described a stereospecific [3 + 2] cycloaddition of DA cyclopropanes with nitrosoarenes under $MgBr_2$ catalysis (eq 1, Scheme 1).[2] That work was preceded by our disclosure of a $Yb(OTf)_3$-catalyzed [4 + 2] cycloaddition of DA cyclobutanes with nitrosoarenes, in which we observed opposite regioselectivity (eq 2, Scheme 1).[3]

Scheme 1. Cycloaddition of Nitrosobenzene 1a with DA Cyclopropane 2a and DA Cyclobutane 4a



Inspired by this reaction and our ongoing interest in $Yb(OTf)_3$-catalyzed cycloadditions of DA cyclobutanes,[4] we were interested in investigating the reactivity of DA cyclopropanes with nitrosoarenes under $Yb(OTf)_3$ catalysis, aiming to secure the opposite regioisomer **6a**. To our surprise, the reaction resulted in the formation of tetrahydro-1,2-oxazine **7aa** instead of the anticipated isoxazolidine **6a** (eq 3, Scheme 1). Interestingly, the yield of the reaction was slightly below 50%, but rose to 87% when 2 equiv of cyclopropane was used. After some experimentation, it appeared that the reaction was consuming 2 equiv of the cyclopropane. A plausible mechanism that accounts for the observed stoichiometry requirements is shown in Scheme 2.[5]

As described in Scheme 2, the nitrogen of the nitrosobenzene **1a** opens the $Yb(OTf)_3$-activated DA cyclopropane **2aa**, resulting in intermediate **8a**, which instead of undergoing ring closure to give the expected cycloadduct isoxazolidine **6a** (path A) expels dimethyl 2-methylenemalonate **10a**, producing nitrone **9a** (path B).[6] This in situ generated nitrone **9a** then undergoes a well-known [3 + 3] cycloaddition with another equivalent of $Yb(OTf)_3$-activated DA cyclopropane **2aa** to furnish tetrahydro-1,2-oxazine **7aa**.[7] Interestingly, no evidence of recombination of nitrone **9a** and dimethyl 2-methylenemalonate **10a** to form isoxazolidine **11a** was observed. This could be due to the rapid polymerization of dimethyl 2-methylenemalonate **10a** under $Yb(OTf)_3$ conditions.

To substantiate the proposed mechanism and gain insights into this unique reaction, a crossover experiment was designed

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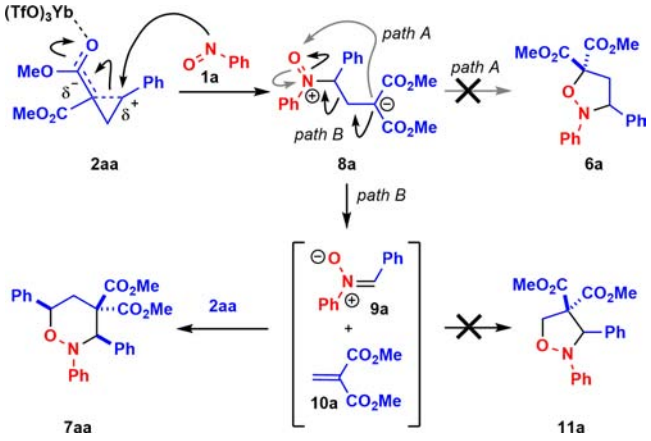
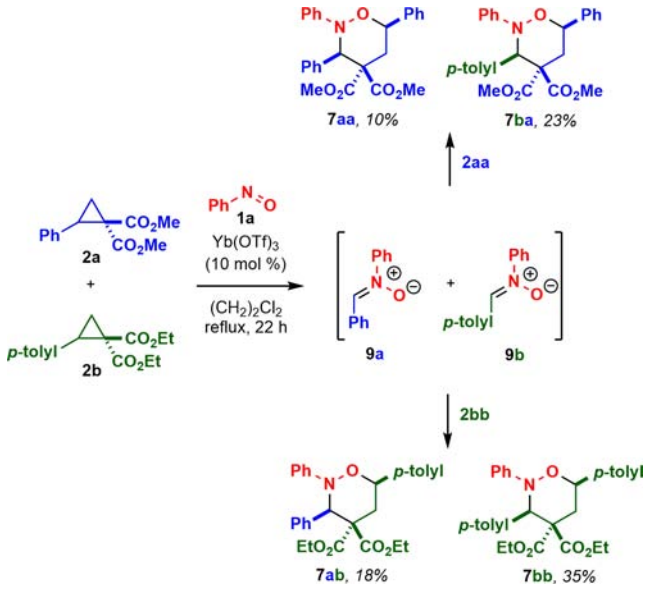
Scheme 2. Plausible Mechanism for the Formation of Tetrahydro-1,2-oxazine 7aa



with two similar cyclopropanes, **2a** and **2b**, with nitrosobenzene **1a** (Scheme 3).

Scheme 3. Crossover Experiment for the reaction of DA cyclopropanes, 2a and 2b, with nitrosobenzene 1a

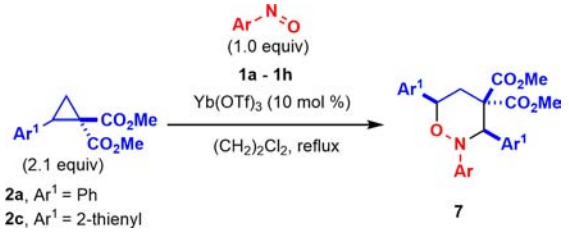


As expected, crossover products **7ba** and **7ab** were observed, supporting the formation of nitrone intermediates **9a** and **9b** (Scheme 3).[8] These products were identical to standards independently synthesized from literature procedures.

It is interesting to note that this remarkable transformation has a reasonable substrate scope and could be used as a general method for the synthesis of tetrahydro-1,2-oxazines (Table 1).[9] Nitrosoarenes with halogen substituents resulted in good yields regardless of the position on the aryl ring (entries 2–4). Nitrosoarenes with a moderately electron-withdrawing ketone (entry 5) or ester (entries 6 and 7) substituent were also found to be good reaction partners. Disappointingly, nitrosoarenes with a strong electron-withdrawing (entry 8) or electron-donating (entry 9) substituent resulted in decomposition products.[10] Finally, a thiophene-substituted cyclopropane **2c** was also shown to be a suitable reaction partner (entry 10).

With the fresh mechanistic insight in hand, we began to reconsider the curious products isolated by the de Meijere group

Table 1. Reaction Scope

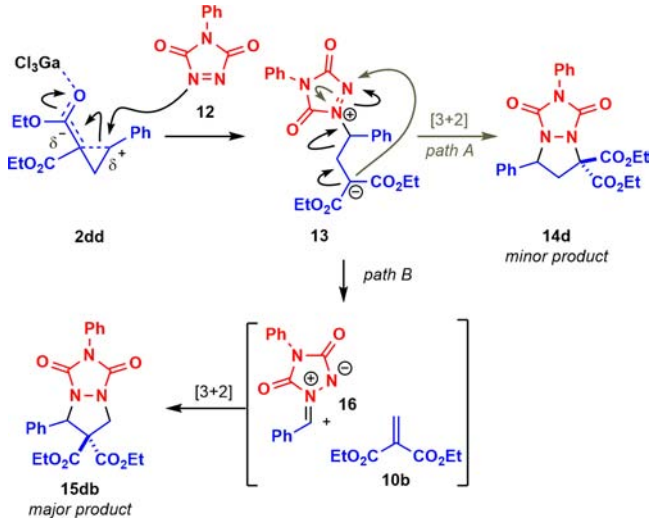


entry[a]	Ar^1	Ar	time (h)	yield (%)[b]
1	Ph	**1a**, C_6H_5	13	87
2	Ph	**1b**, 3-C_6H_4Br	24	73
3	Ph	**1c**, 4-C_6H_4Br	24	75
4	Ph	**1d**, 3,4-$C_6H_3Cl_2$	12	91
5	Ph	**1e**, 3-$C_6H_4C(O)Me$	20	68
6	Ph	**1f**, 3-$C_6H_4CO_2Et$	24	80
7	Ph	**1g**, 4-$C_6H_4CO_2Et$	23	78
8	Ph	**1h**, 4-C_6H_4CN		
9	Ph	**1i**, 4-C_6H_4OMe		
10	2-thienyl	**1a**, C_6H_5	7	69

[a]Reaction conditions: to a solution of cyclopropane **2** and nitrosoarene **1** in $(CH_2)_2Cl_2$ at room temperature was added $Yb(OTf)_3$ and then heated at reflux for the specified time. [b]Isolated yields.

in $GaCl_3$-catalyzed cycloadditions of diazene derivatives with DA cyclopropanes (Scheme 4).[11] We believe that the unusual

Scheme 4. Our Proposed Mechanism for de Meijere's Report on Cycloaddition of *cis*-Diazene 12 with $GaCl_3$-Activated DA Cyclopropane 2dd



product **15db** formed from *cis*-diazene 4-phenyl-1,2,4-triazoline-3,5-dione **12** (PTAD) and DA cyclopropane **2d** might have resulted through a similar mechanism via azomethine imine intermediate **16**. As depicted in Scheme 4, one of the nitrogens of PTAD **12** opens the $GaCl_3$-activated cyclopropane **2dd** to form zwitterionic intermediate **13**. This intermediate could then either undergo a cyclization to yield normal cycloadduct **14d** (path A) or fragment into azomethine imine **16** and diethyl 2-methylenemalonate **10b** (path B). Recombination of these latter two fragments would provide cycloadduct **15db**.

To validate this hypothesized mechanism, another crossover experiment was designed with two similar cyclopropanes, **2d** and **2e**, with PTAD **12** (Scheme 5).[12]

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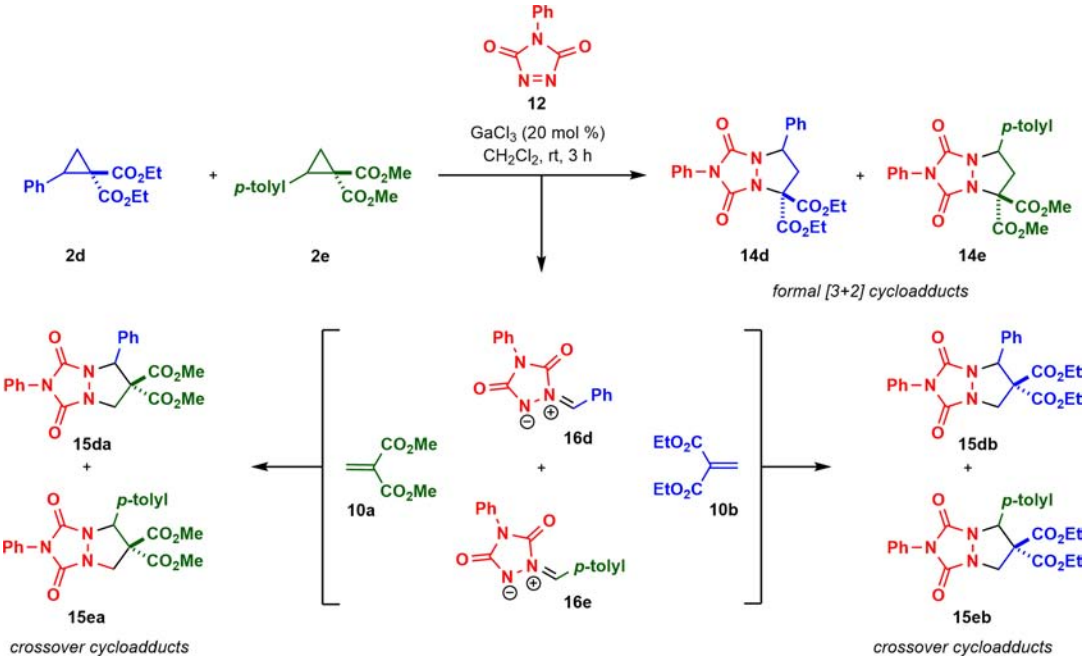
Scheme 5. Crossover Experiment for the Reaction of DA Cyclopropanes 2d and 2e with *cis*-Diazene 12



As anticipated, the reaction did yield crossover products **15da**, **15ea**, **15db**, and **15eb**, thus providing strong evidence for the formation of azomethine imines **16d** and **16e** in the reaction. All of the crossover products were identical with standards independently synthesized from de Meijere's method. The gas chromatogram in Figure 1 shows relative ratios of all six products in the crude mixture of a representative crossover experiment.[13]

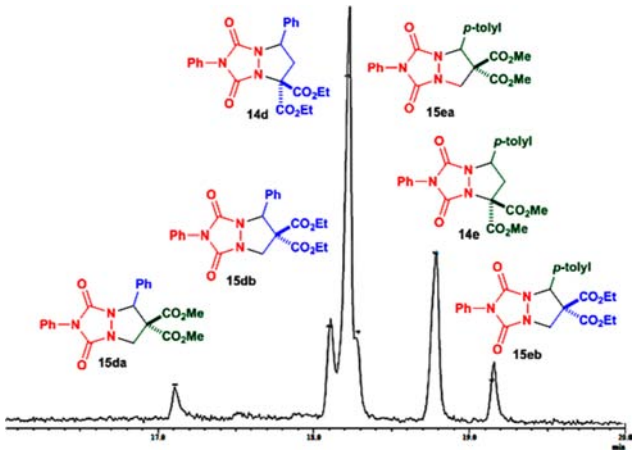


Figure 1. Gas chromatogram of the crude product of crossover experiment of cycloaddition of DA cyclopropanes **2d** and **2e** with *cis*-diazene **12**.

In conclusion, we discovered unusual reactivity in cycloadditions of DA cyclopropanes with nitrosoarenes to form tetrahydro-1,2-oxazines via a nitrone intermediate in good to excellent yields as single diastereomers. Mechanistic insights gained by crossover experiments on this unique transformation enabled a better rationale for peculiar products formed in $GaCl_3$-catalyzed cycloaddition of PTAD with DA cyclopropanes. Additionally, this study reveals new opportunities for reaction design in DA cyclopropane chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01269.

Experimental procedures, characterization data, and copies of NMR spectra and GC−MS data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bpagenko@uwo.ca.

Notes

The authors declare no competing financial interest.

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(12) Different cyclopropanes were chosen for experimental convenience.

(13) GC/MS was used to analyze the products due to separation problems in flash chromatography. See Supporting Information for complete details.

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