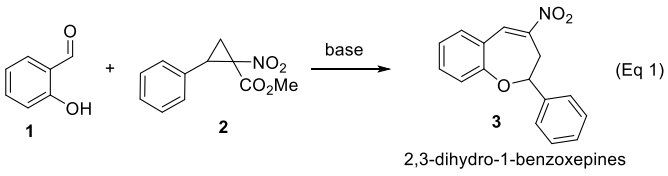
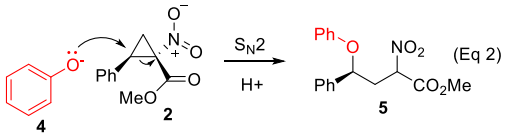
PRF# 55707-UR1
Organocatalytic Domino Reactions for the Synthesis of Highly Substituted Hetereocycles
Shanina Sanders Johnson PhD, Spelman College

Research Progress: The research topic for this grant has shifted to an exciting project that accesses 7-membered heterocycles efficiently from donor-acceptor nitrocyclopropanes. Donor-acceptor (D-A) cyclopropanes are known reaction partners in a variety of ring forming reactions.[1,2] The innate ring strain of the cyclopropane ring paired with vicinally substituted donor and acceptor groups make D-A cyclopropanes particularly susceptible to ring opening.[3] Nitrocyclopropane carboxylates have not been used as frequently as 1,1-diestercyclopropanes, although, the nitro functionality is a valuable tool in accessing other nitrogen functionalities.[4,5] The use of two different acceptor groups, a nitro and an ester, creates a stereocenter at this position which can racemize upon ring opening and create undesirable diastereomers. We proposed a one-pot S_N2/Henry cascade reaction between nitrocyclopropanes (**2**) and 2-hydroxy or 2-amino benzaldehyde derivatives as an efficient and innovative strategy to build complex 7-membered rings (Eq 1). Formal cycloadditions are common for donor-acceptor cyclopropanes to form 5 and 6-membered rings, however, examples of formal [4+3] cycloadditions to form 7-membered rings with D-A cyclopropanes are scarce. The 5-membered ring is often obtained in lieu of the 7-membered ring due to more favorable entropic forces and the absence of transannular interactions that can accompany the formation of 7-membered rings.[6-7]. Thus far, nitrocyclopropanes have seldom been used in any formal cycloadditions.[8] The combination of the nitrocyclopropane and the unique reaction cascade offer a new strategy to access novel, underrepresented benzoxepine and benzazepine compounds. A variety of natural products contain the 1-benzoxpine skeleton and quite a number of pharmacological properties have been observed in these compounds.[9] Reported biological activities include antiviral, antibacterial, anticancer, hypertensive, anti-implantation, and digestive agents.[9] 1-Benzazepines are also known to have a variety of biological activities and syntheses are currently being pursued by both organic and medicinal chemists.[10,11] The reagents typically used to access these structures are structurally complex and not commercially available in contrast to the reagents used in the current project.



(Eq 1)

We initially examined the reaction between phenol and nitrocyclopropane (**2**) with cesium carbonate under microwave irradiation to see if we could optimize the formation of the acyclic ring opened product **(4)** (Eq 2). The phenolate ion (**4**) was generated after deprotonation by cesium carbonate. This study was based on work by the Charette group where type (**5**) products were formed under conventional heating in 12 hours with 3 equivalents of phenol and 2.5 equivalents of cesium carbonate.[12] Our reaction went to completion in an hour with 3 equivalents of phenol and 3 equivalents of cesium carbonate. Microwave irradiation has been shown to increase reaction rates and yields in a variety of organic reactions while reducing reaction times.[13] This reaction is being optimized and a screen of other phenol derivatives is underway.



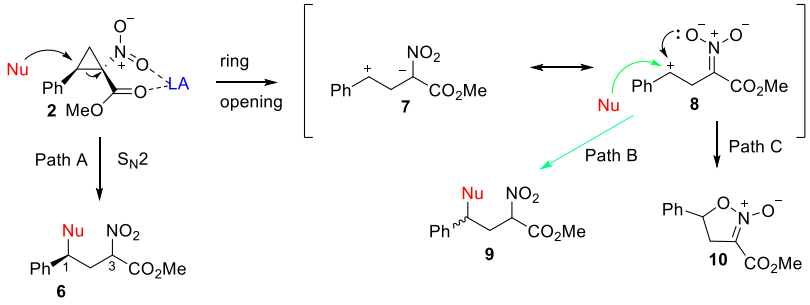
(Eq 2)

Since these conditions seemed to efficiently consume the nitrocyclopropane, we then tested the reaction of salicylaldehyde with nitrocyclopropane in the microwave. To our delight, we observed the formation of a sole cyclic product in one hour at 80 °C. The product was identified as a 2,3-dihydro-1-benzoxepine (**3**), specifically 2-phenyl-4-nitro-2,3-dihydro-1-benzoxepine, based on ^1H and ^{13}C NMR analysis (Eq 1). A characteristic singlet around 8 ppm was confirmation of the benzylic nitroalkene proton. The lack of the methyl group from the methyl ester confirmed a decarboxylation had occurred.

It is fortuitous that the cyclic nitroalkene formed because other possible products would have likely formed as a mixture of diastereomers. This is perhaps the primary reason that nitrocyclopropanes have not been used extensively both in acyclic and ring forming reactions. However, in this instance, the spontaneous decarboxylation conceals the diastereoselectivity issue. Only the cyclic nitroalkene has been observed in the crude NMR under the optimal conditions. We have also run this reaction with 2-bromosalicylaldehyde with similar results. Further work will reveal if this is a general phenomenon for other salicylaldehyde and 2-aminobenzaldehyde derivatives.

Analogous to the reaction with phenol and nitrocyclopropane, a similar reaction was published with aniline derivatives and nitrocyclopropanes by the Charette group. They used a mild Lewis acid, $Ni(ClO_4)_2$, at room temperature.[14] This reaction is believed to occur by an S_N2 type mechanism, which is suggested by the complete inversion of stereochemistry at C1, observed in the product, (**6**) (Scheme 1). In the presence of more highly activating Lewis acids a rearrangement product (**10**) was observed as well as the racemization of the stereogenic center at C1 which is illustrated in Path B (**9**). A range of electronically and sterically diverse amines worked well in the reaction

Scheme 1: Ring opening of nitrocyclopropanes with aniline derivatives



and in all cases a mixture of interconverting diastereomeric products were seen. The initial S_N2-type attack is a common mechanistic pathway for D-A cyclopropanes in reactions with nucleophiles.[15] This reaction is a milder version of a thermal reaction the group developed at 90 °C for 17 hours using 1.5 equivalents of aniline with acetonitrile. The high temperature over the prolonged time frame did not work well for sterically hindered compounds, thus the adaptation of Lewis acid catalysts. Our group tested the thermal reaction conditions in the synthetic microwave to examine its efficiency under microwave irradiation. It was found that the reaction proceeded in 3 hours at 90°C with two equivalents of aniline. The reaction time was reduced by 14 hours; an 80% yield of the acyclic diastereomers was observed. The scope of this reaction with other aniline and nitrocyclopropane derivatives is being explored in preparation for publication.

Impact from Grant: This past year funds from the grant directly supported two students and another student in the lab benefited from the supplies purchased with grant funds. Both students receiving support presented their work at the National Organization of Black Chemists and Chemical Engineers and the current work is expected to yield publications with additional student co-authors. Over the course of the grant, 8 undergraduate students have been supported to participate in research projects. All were Black women. Six are graduates of Spelman College. Three of the graduates are currently in graduate school and two are employed in STEM fields. Their involvement in undergraduate research exposed them to the research process, scientific literature, scientific communication, instrumentation, and norms of the field. The challenges faced in the lab allowed them to engage in real-world problem solving and enhanced their critical thinking and analytical skills. These skills and experience ultimately made them more competitive for internships, entry level workforce positions, and graduate programs in STEM fields. The expected publications are the most impactful for both the students and the PI because they provide clear evidence of the scholarly work that has been accomplished and highlight its significance in the field. This scholarship will be imperative in obtaining tenure and promotion and creating long-term research goals for the group.

(1) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chemie - Int. Ed.* **2014**, *53* (22), 5504.
(2) Reissig, H.-U.; Werz, D. B. *Isr. J. Chem.* **2016**, *56* (6–7), 367.
(3) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103* (4), 1151.
(4) Ballini, R.; Palmieri, A.; Fiorini, D. *Arkivoc* **2006**, *2007* (7), 172.
(5) Averina, E. B.; Yashin, N. V; Kuznetsova, T. S.; Zefirov, N. S. *Russ. Chem. Rev.* **2009**, *78* (10), 887.
(6) Ghosh, A. K.; Tomaine, A. J.; Cantwell, K. E. *Org. Lett.* **2016**, *18* (3), 396.
(7) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14* (4), 95.
(8) Hardman, A. M.; So, S. S.; Mattson, A. E. *Org. Biomol. Chem.* **2013**, *11* (35), 5793.
(9) Kuntala, N.; Telu, J. R.; Anireddy, J. S.; Pal, S. *Lett. Drug Des. Discov.* **2017**, *14* (9).
(10) Lowe, J. A.; Hageman, D. L.; Drozda, S. E.; McLean, S.; Bryce, D. K.; Crawford, R. T.; Zorn, S.; Morrone, J.; Bordner, J. *J. Med. Chem.* **1994**, *37* (22), 3789.
(11) Suh, C. W.; Kwon, S. J.; Kim, D. Y. *Org. Lett.* **2017**, *19* (6), 1334.
(12) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73* (17), 6838.
(13) Leadbeater, N.; Torenius, H. *J. Org. Chem.* **2002**, *67* (9), 3145.
(14) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10* (13), 2809.
(15) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130* (27), 8642.