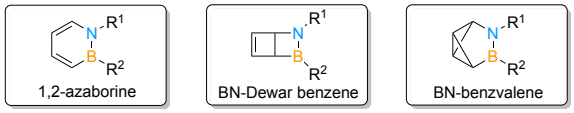
A. Introduction

"Isosterism" is a valuable concept for broadening chemical diversity. In our efforts to expand the chemical space of boron-nitrogen heterocycles, we employ BN/CC isosterism, which is defined as a replacement of two carbon atoms with one boron and one nitrogen atom. In particular, we employ the BN-isomer of benzene, 1,2-azaborine, as a 4C + 1N + 1B synthon for organic synthesis.[1] My research aims to develop the valence isomers of 1,2-azaborine[2], namely BN-Dewar benzene and BN-benzvalene, as new synthetic building blocks to access previously unexplored chemical territory (Scheme 1.).

Scheme 1. Three key compounds



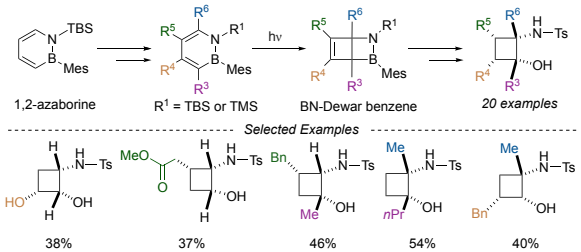
B. Completed Research

Topic 1. Modular and Stereoselective Synthesis of Cyclobutane β-Amino Alcohols

Publications: X. Yang‡, T. Ozaki‡, B. Li, N. Wei, S.-Y. Liu. *Manuscript in preparation.*

Cyclic *β*-amino alcohols are important building blocks for the synthesis of biologically active molecules and chiral catalysts. Cyclopentane and cyclohexane *β*-amino alcohols have been well investigated and have found applications in areas such as HIV drugs[3] and chiral ligands for enantioselective synthesis[4]. In contrast, cyclobutane cis-*β*-amino alcohols are less explored. We utilized BN-Dewar benzene as a building block to access this motif. Specifically, hydrogenation of the cyclobutene and oxidation of boron on BN-Dewar benzene were conducted to prepare the cyclobutane *cis-β*-amino alcohols (Scheme 2). Combined with the facile late-stage functionalization of 1,2-azaborine, this method has been extended to access diversely functionalized tri- and tetra-substituted cyclobutane *cis-β*-amino alcohols (20 examples, 8 substitution patterns).

Scheme 2.

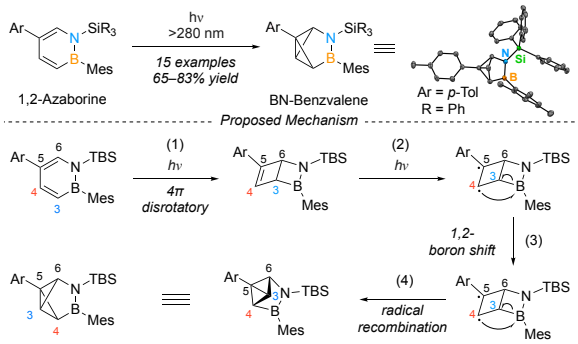


Topic 2. Synthesis and Characterization of BN-Benzvalene

Publications: T. Ozaki, S. Bentley, N. Rybansky, B. Li, S.-Y. Liu, *JACS* ***2024****, 146, 24748. For Overview:* T. Ozaki, S.-Y. Liu, *Chem. Eur. J.* ***2024****, e202402544.*

Benzvalene, first isolated in 1967, has captured the attention of synthetic chemists due to its unique bonding and reactivity.[5] In addition to carbonaceous benzvalene, numerous phosphorus-[6] and silicon[7] containing heteroatom benzvalenes have been developed to date. However, hetero-benzvalenes containing second-row elements (B, N, O) have remained elusive. During the investigation of Topic 1, we serendipitously discovered that a C5-aryl-1,2-azaborine yields benzvalene isomers after the photoisomerization of 1,2-azaborine (Scheme 3). To our delight, this is the first example of a light-element hetero-benzvalene in the literature.[8] Through an intermediacy study and deuterium labeling studies, a mechanism shown in Scheme 6 is proposed.

Scheme 3.



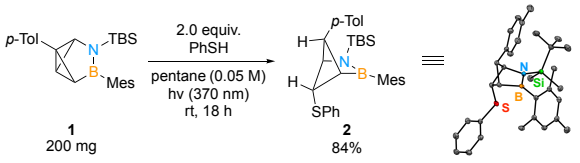
C. Ongoing Research

Topic 3. Synthetic Applications of BN-Benzvalene

In Progress: N. Pugliano, T. Ozaki, S. Diamandis

All carbonaceous benzvalene has been utilized in the synthesis of strained hydrocarbon scaffolds including bicyclo[1.1.1]pentane and bicyclo[2.1.1]hexane derivatives that are of interest as 3D bioisosteres of benzene in medicinal chemistry.[5b] Similarly, BN-benzvalene **1** reacts with thiophenol under purple light irradiation to cleanly produce BN-bicyclo[2.1.1]hexane **2** (Scheme 4). Efforts in this direction are ongoing in our laboratory.

Scheme 4.

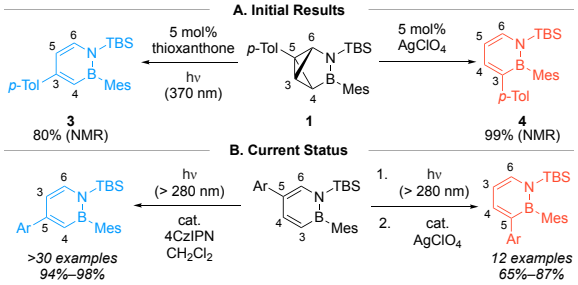


Topic 4. Positional Isomerization of 1,2-Azaborine through BN-Benzvalene

Publications: T. Ozaki‡, S. Diamandis‡, N. Rybansky, X. Yang, B. Li, S.-Y. Liu* *Manuscript in preparation.*
T. Ozaki, B. Li, S.-Y. Liu* *Manuscript in preparation.*

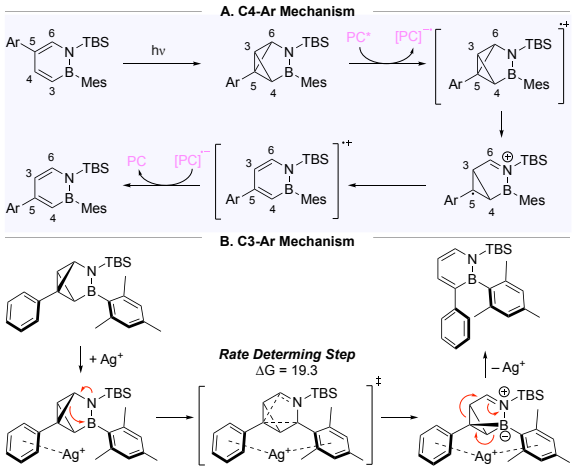
During our exploration of BN-benzvalene's reactivity, we discovered that BN-benzvalene **1** undergoes selective cycloreversion to produce C4-*p*-Tol-1,2-azaborine **3** by photocatalysts under purple light irradiation. In contrast, **1** reacts with $AgClO_4$ catalyst to selectively produce C3-*p*-Tol-1,2-azaborine **4** (Scheme 5A). We further optimized these reactions to enable the formation of C3-aryl- and C4-aryl-1,2-azaborine products in a one-pot manner from C5-aryl-1,2-azaborine (Scheme 5B).

Scheme 5.



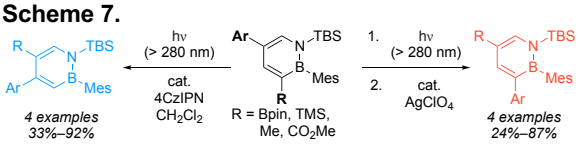
Through deuterium labeling studies and DFT calculations, a mechanism for each transformation shown in Scheme 6A and 6B was proposed.

Scheme 6.



Finally, additional functional groups can be incorporated at the C3-position, selectively moving to the C5-position (Scheme 7). To our delight, this stands as the first method to access C4C5-difunctionalized 1,2-azaborine.

Scheme 7.

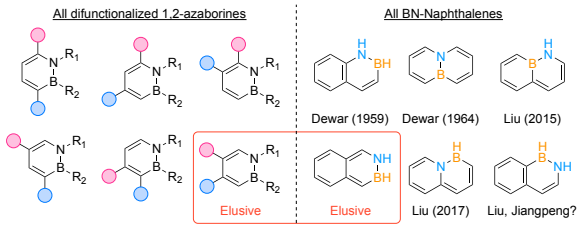


Topic 5. The development of C4C5-Difunctionalized 1,2-Azaborines

In Progress: T. Ozaki, N. Rybansky

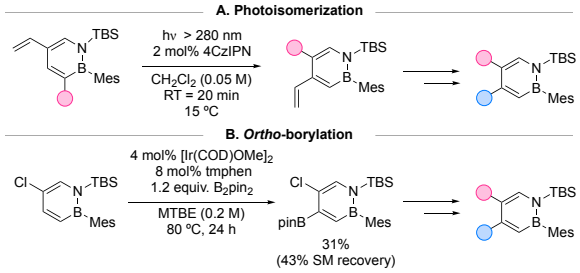
Accessing C4C5-difunctionalized 1,2-azaborines has long been a significant challenge in 1,2-azaborine functionalization, with no general methodologies currently available for this substitution pattern. Establishing a reliable synthetic route to this motif could expand the chemical space of BN-heterocycles. Once this general approach is developed, our goal is to synthesize parent-2,3-BN-naphthalene, the final and previously inaccessible parent isomer among the six possible BN-naphthalenes (Scheme 8).

Scheme 8.



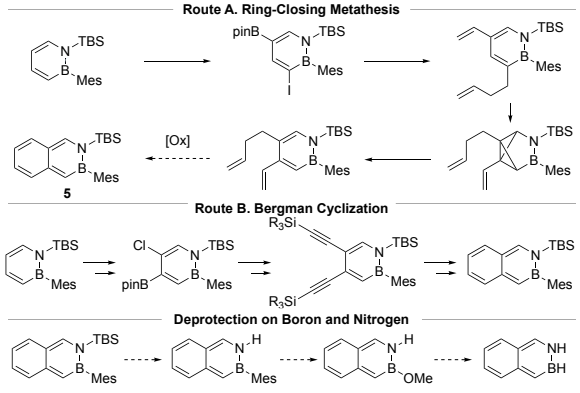
We have identified two distinct strategies to access C4C5-difunctionalized 1,2-azaborines (Scheme 9).
A.) Photochemical positional isomerization of C3C5-difunctionalized 1,2-azaborines via BN-benzvalenes.
B.) *Ortho*-borylation of C4- or C5-Cl-1,2-azaborine.

Scheme 9.



To synthesize parent-2,3-BN-naphthalene, we are employing the two strategies above to first access N-TBS-B-Mesityl-protected product. This will then undergo sequential deprotection at the boron and nitrogen (Scheme 10).

Scheme 10.



Reference:

[1] Burford, R. J.; Li, B.; Vasiliu, M.; Dixon, D. A.; Liu, S.-Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 7823–7827.
[2] Ozaki, T.; Liu, S.-Y. *Chem. Eur. J.* **2024**, e202402544.
[3] Gallou, I.; Senanayake, C. H. *Chem. Rev.* **2006**, *106*, 2843–2874.
[4] Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815–3818.
[5] (a) Wilzbach, K. E.; Ritscher, J. S.; Kaplan, L. *J. Am. Chem. Soc.* **1967**, *89*, 1031–1032. (b) Christl, M. *Angew. Chem. Int. Ed.* **1981**, 20, 529–546.
[6] Pioneer work of phospha-benzvalene: Kobayashi, Y.; Fujino, S.; Hamana, H.; Kumadaki, I.; Hanzawa, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8511.
[7] Pioneer work of sila-benzvalene: Ando, W.; Shiba, T.; Hidaka, T.; Morihashi, K.; Kikuchi, O. *J. Am. Chem. Soc.* **1997**, *119*, 3629–3630.
[8] Ozaki, T.; Bentley, S.; Rybansky, N.; Li, B.; Liu, S.-Y. *J. Am. Chem. Soc.* **2024**, *146*, 24748–24753.