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# Lewis Acid Catalyzed Site-Selective Cycloadditions of 2,6-Diazasemibullvalenes with Isocyanides, Azides, and Diazo Compounds for the Synthesis of Diaza- and Triazabrexadiene Derivatives**

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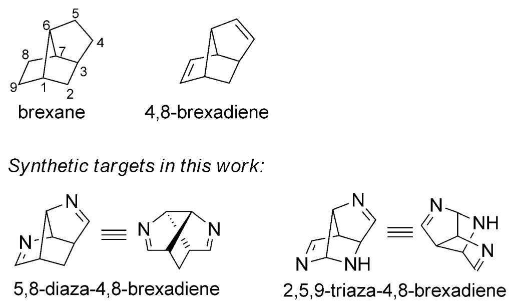
Organic cage compounds, such as adamantane and cubane, are important in both structural organic chemistry and synthetic chemistry, yet the development of new organic cage compounds has been limited owing to the difficulties associated with multistep syntheses and low yields.[1] Brexanes (tricyclo[4.3.0.0$^{3,7}$] nonanes), brexadienes, and their aza analogues have structurally interesting cage architectures and are important intermediates for organic synthesis (Scheme 1).[2,3] However, efficient synthetic methods toward brexane derivatives and their aza analogues are very rare.



**Scheme 1.** Brexane, brexadiene and their aza analogues.

2,6-Diazasemibullvalenes (NSBVs; **1**) undergo extremely rapid degenerate aza-Cope rearrangement and contain highly strained rings.[4–6] Such inherent features should be useful for synthetic applications and for consequent studies of the reaction mechanism. However, the structure, reactivity, and synthetic applications of NSBVs have been largely unexplored, mostly owing to lack of methods for their synthesis.

In 1982, Müllen and co-workers reported the first NSBV compound, 1,5-dimethyl-3,7-diphenyl-2,6-diazasemibullvalene, which was identified by NMR spectroscopy.[5] Very recently, we established efficient synthetic methods and isolation procedures for a series of NSBVs,[6] thus enabling us to study their chemical nature and synthetic applications, such as the construction of novel cage compounds.

Herein, we would like to report Lewis acid catalyzed diverse cycloaddition reactions of NSBVs **1** with a wide variety of isocyanides, azides, and diazo compounds. These reactions afforded 5,8-diaza- and 2,5,9-triazabrexadiene derivatives, having highly-fused nitrogen-containing polycyclic frameworks; these structurally and chemically interesting caged-shape compounds are not readily accessible by other methods.[2,3] Unique and unprecedented rearrangement/cycloaddition pathways are revealed. These reaction pathways are not only different from that of our previously reported reaction with DMAD or RNCO,[6] but most notably, very different from the reactions of common aziridines,[7–10] because of the active involvement of the whole ring skeleton of the NSBV compound.

The reaction of NSBV **1a** with *tert*-butyl isocyanide (*t*BuNC) in toluene was monitored by $^1$H NMR spectroscopy. No reaction took place even when the reaction mixture was heated to 120 °C for 12 h in a sealed tube. However, in the presence of a catalytic amount of zinc triflate (5 mol %), the reaction proceeded smoothly at room temperature and was complete within 2 h, to afford the 5,8-diaza-4,8-brexadiene derivative **2a**, as a tetracyclic triimine, in 93 % yield upon isolation (Scheme 2). None of the C–N bond insertion product **2a′** was detected.[6] Single-crystal X-ray structural analysis of **2a** revealed a cage skeleton containing a cyclopentanimine core fused with one cyclohexane ring and two pyrroline rings. The reaction scope was found to be very broad. Both aliphatic and aromatic isocyanides including those bearing bulky substituents, could undergo clean reactions with NSBVs under the $Zn(OTf)_2$-catalyzed reaction conditions to afford the corresponding products **2a**–**n** in good to excellent yields (Scheme 2). Tertiary, secondary, and primary alkyl isocyanides could all be used. Functional groups such as ester and sulfonyl groups were tolerated. NSBVs with different substituents were also tested and various diazabrexadiene derivatives were isolated in good yields (**2l**–**n**).

The above Lewis acid catalyzed reaction between NSBVs **1** and isocyanides represents a formal [5+1] cycloaddition.[11] This cycloaddition reaction has several notable features: 1) It is site selective as the cyclization occurred exclusively at the 4-

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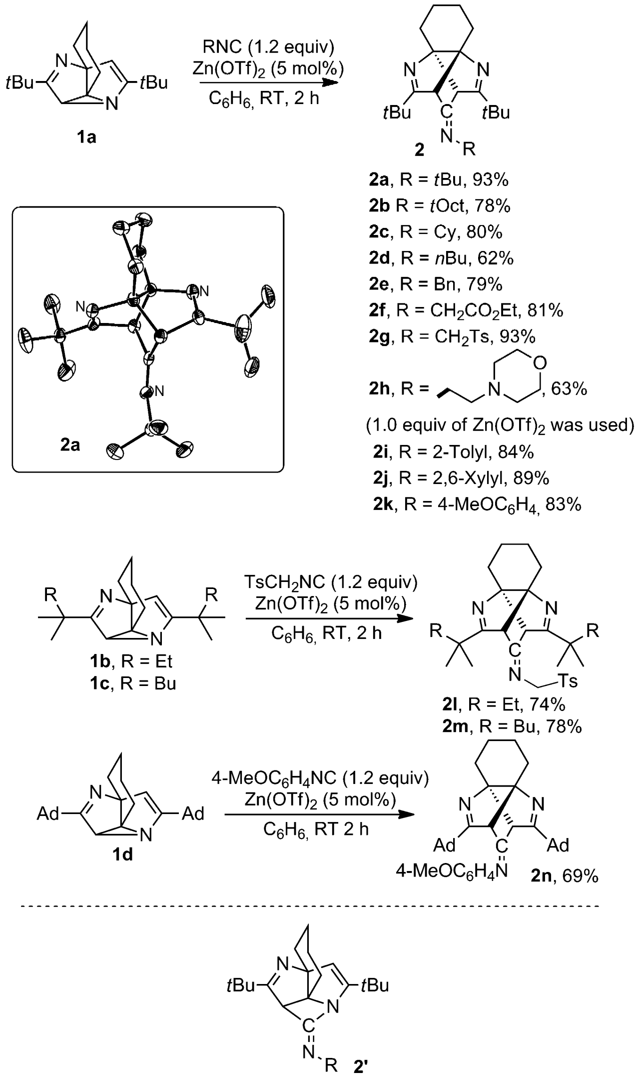
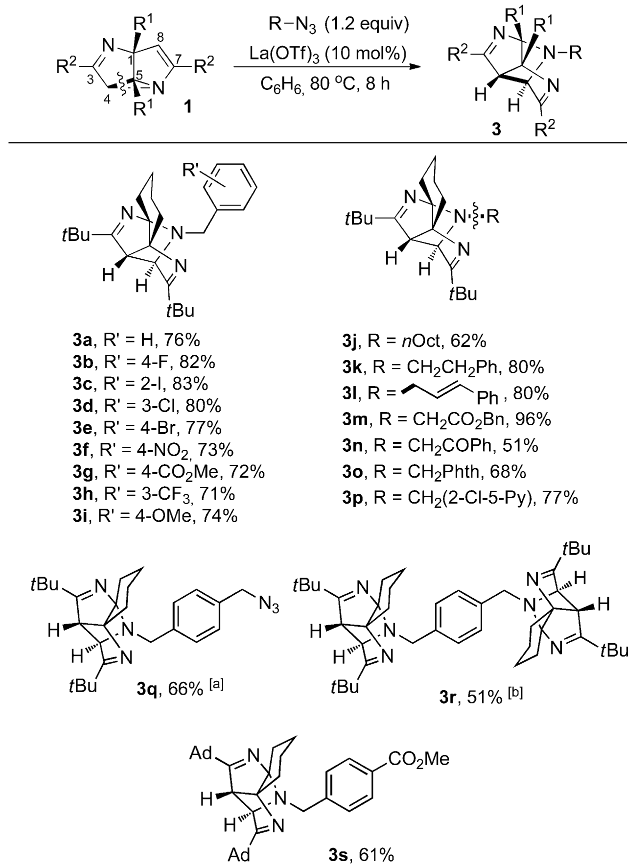


*Scheme 2.* Zinc-triflate-catalyzed [5+1] cycloaddition of 2,6-diazasemibullvalenes and isocyanides. ORTEP drawing of **2a** is shown with thermal ellipsoids shown at 30% probability and hydrogen atoms omitted for clarity.[26] Ad = adamantyl, *t*Oct = 1,1,3,3-tetramethylbutyl, Ts = *p*-toluenesulfonyl, 2,6-Xylyl = 2,6-$Me_2C_6H_3$.

and 8-positions, rather than the 4- and 6-positions. 2) The strained ring tension remarkably weakens the C−N bond in **1** making this compound highly reactive. In comparison, insertion of isocyanides with simple aziridines is very rare.[12,13] 3) The active involvement of the whole ring skeleton of the NSBV compound makes this reaction unusual. 4) Synthetically useful poly-*N*-heterocyclic skeletons are constructed efficiently in one pot.

In addition to isocyanides, azides were found to react with NSBVs **1** cleanly and efficiently in the presence of a catalytic amount of $La(OTf)_3$, to afford multiply substituted 2,5,9-triaza-4,8-brexadienes **3** as single diastereomers in good to excellent yields (Scheme 3). $La(OTf)_3$ was found to be the most efficient catalyst; $Zn(OTf)_2$ gave slightly lower yields. Substrate decomposition was observed when $Sc(OTf)_3$ was used.[14] Single-crystal X-ray structural analysis of **3e** revealed its novel cage skeleton (Figure 1).



*Scheme 3.* Lanthanum-triflate-catalyzed ring-opening/rearrangement/cycloaddition reaction of 2,6-diazasemibullvalenes and azides.
[a] 1.5 equivalents of bisazide were used. [b] 0.4 equivalents of bisazide were used. Phth = phthalimide, Py = pyridyl.

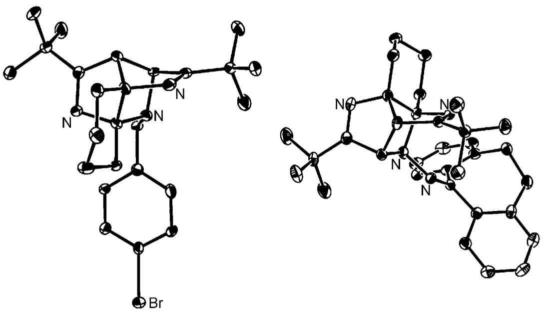
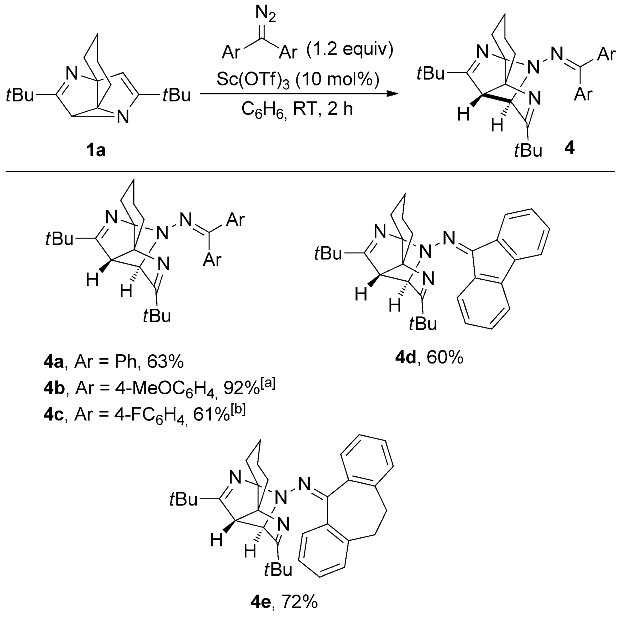


*Figure 1.* ORTEP drawings of **3e** (left) and **4e** (right) with thermal ellipsoids shown at 30% probability. Hydrogen atoms are omitted for clarity.[26]

A wide variety of azides could be used in this reaction. Good functional-group tolerance was demonstrated. Satisfactory yields were obtained when of benzyl azides bearing halogen atoms (F, Cl, Br, and I), electron-withdrawing groups ($CO_2Me$, $NO_2$, and $CF_3$) and electron-donating groups (OMe) were used (products **3a–i**). Cinnamyl azide and alkyl azides bearing ester or carbonyl groups showed good reactivity as well, to give products **3j–n**. The use of azides bearing heterocycles, such as phthalimide and pyridine, also afforded the corresponding products (**3o**–**p**) in good yields. 1,4-Bis(azidomethyl)benzene reacted chemoselectively with 1 or 2 equivalents of NSBV **1a** to afford the corresponding highly fused mono(diazabrexadiene) **3q** and bis(diazabrexadiene) derivatives **3r** in 66 and 51 % yields, respectively. An NSBV with an adamantyl substituent could also be used (product **3s**).

To the best of our knowledge, the reaction of organic azides with simple aziridines has not been reported.[15] Obviously, during this present reaction process, skeletal rearrangement of NSBV **1** and loss of $N_2$ from the azide took place. Normal reactions, such as [3+2] cycloaddition of azide 1,3-dipole,[16] or [2+1] cycloaddition of nitrene, did not occur.[15] Also, this reaction features cleavage of the unstrained C4–C5 bond of NSBV **1** as well as C4–C8 coupling. All these transformations are different to those that occur in the reaction of **1** with isocyanides.

The unusual reactivity of NSBVs **1** was further demonstrated by their reaction with diazo compounds (Scheme 4). The use of diazo compounds as carbene precursors has been well developed and reviewed.[17] However, transition metal or Lewis acid catalyzed cyclization of diazo compounds with standard aziridines is very rare.[18] The few examples include copper-catalyzed coupling of 2-acylaziridines or 2-vinylaziridines with diazo compounds, to give bicyclic aziridines, indolizidines, or seven-membered lactams as products.[18]

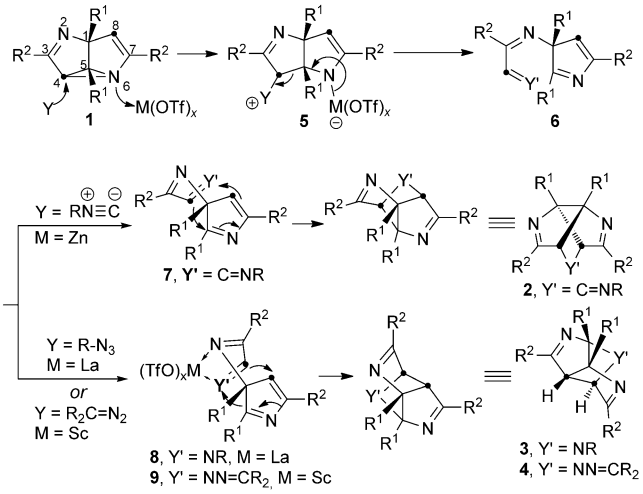


***Scheme 4.*** Scandium-triflate-catalyzed ring-opening/rearrangement/cycloaddition reaction of 2,6-diazasemibullvalenes and diazo compounds. [a] Reaction time: 0.5 h. [b] Reaction time: 12 h.

Interestingly, in the presence of a catalytic amount of $Sc(OTf)_3$, the reactions between NSBV **1a** and a variety of diaryl diazomethanes were all completed in 2 h at room temperature without loss of dinitrogen. The structure of the product was confirmed as *N*-ylideneamino-2,5,9-triazabrexadiene **4**, which is similar to the cycloaddition product from the reaction of NSBV **1** with azides. The electronic effects of the substituents on diaryl diazomethane have a remarkable influence on this reaction. When a methoxy-substituted diaryl diazomethane was used, the reaction was completed within 0.5 h, affording the product **4b** in 92 % yield upon isolation. However, when a diazo compound bearing an electron-withdrawing group, such as a fluorine atom, was used, the reaction was slower and the yield of the product **4c** was 61 % after 12 h. Thus, a nucleophilic ring opening of NSBV **1** with diazo compounds is believed to be the key step.

Notably, the diaryl diazomethane here displayed the reactivity of a nitrene, rather than a carbene, thus two C–N bonds were formed in one cycloaddition reaction.[19–21] This result is probably because the α-C atom in diaryl diazomethane is less nucleophilic and sterically hindered, and the γ-N atom behaves as a nucleophile and initiates the ring opening of NSBV **1a**.[22] Although [3+2] cycloaddition of diazo compounds with other unsaturated compounds with preservation of the dinitrogen moiety have been reported,[23] there has only been a few reports of nitrene-type cycloadditions of diazo compounds that involve the formation of two C–N bonds.[19]

Proposed reaction pathways for the cycloaddition of NSBVs **1** with isocyanides, azides and diazo compounds catalyzed by different Lewis acids are shown in Scheme 5. All these pathways involve a tandem ring-opening/rearrangement/cyclization process. First, coordination of the Lewis acid with the aziridine nitrogen atom in NSBV **1** promoted nucleophilic ring opening to give the zwitterionic intermediate **5**.[8] Fragmentation of the C–C bond and ring opening of one pyrroline ring in **5** would give various forms of *N*-3-pyrrolylimine **6** as a key intermediate, depending on the nature of nucleophilic reagents Y. For isocyanide, azide, and diazo compounds, the structures of their corresponding intermediates **6** are ketenimine **7**, diimine **8**, and hydrazone **9**, respectively. Finally, an intramolecular [4+2] cycloaddition



***Scheme 5.*** Proposed mechanisms for Lewis acid catalyzed cycloaddition of 2,6-diazasemibullvalenes with isocyanides, azides, and diazo compounds.

of 3*H*-pyrrole ring and $C{=}Y'$ moiety would construct the cyclopentanimine or pyrroline core in polycyclic skeletons of **2**, **3**, and **4** in a regio- and diastereo-specific fashion.[24,25] The regiospecificity of the [4+2] cycloaddition depends on the nature of the $C{=}Y'$ moiety.

For the cycloaddition of NSBV with isocyanide, an alternative concerted chelotropic cycloaddition mechanism could be proposed. Moreover, a ring-opening/ring-closure process might be also possible, if the reaction site is considered as an *N*-alkenyl aziridine moiety (see the Supporting Information for details).[10] Nucleophilic cyclization of zinc enamide with the nitrilium moiety in **5** ($Y = RN{\equiv}C$) would give **2**. Although this pathway cannot be ruled out, we believe the mechanism given in Scheme 5 is more likely, because it could also explain the regio- and- diastereospecificity of the cycloaddition reaction.

In summary, we have developed Lewis acid-catalyzed diverse ring-opening/rearrangement/cyclization reaction of NSBV **1** with isocyanides, azides, and diazo compounds, leading to the efficient synthesis of cage diaza- and triazabrexadiene derivatives. A unique rearrangement/cycloaddition reaction pathway is revealed. Further investigation into the reaction mechanism and synthetic applications are in progress.

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