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Semibullvalene and Diazasemibullvalene: Recent Advances in the Synthesis, Reaction Chemistry, and Synthetic Applications

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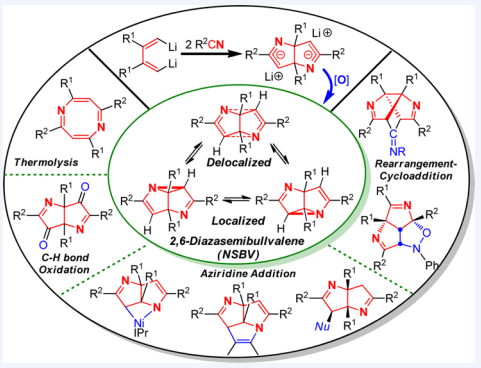
CONSPECTUS: Semibullvalene (SBV) and its aza analogue 2,6-diazasemibullvalene (NSBV) are theoretically interesting and experimentally challenging organic molecules because of four unique features: highly strained ring systems, intramolecular skeletal rearrangement, extremely rapid degenerate (aza-)Cope rearrangement, and the predicted existence of neutral homoaromatic delocalized structures. SBV has received much attention in the past 50 years. In contrast, after NSBV was predicted in 1971 and the first in situ synthesis was realized in 1982, no progress on NSBV chemistry was made until our results in 2012. We have been interested in the reaction chemistry of 1,4-dilithio-1,3-butadienes (dilithio reagents for short), especially for their applications in the synthesis of SBV and NSBV, because (i) the cyclodimerization of dilithio reagents could provide the potential eight-carbon skeleton of SBV from four-carbon butadiene units and (ii) the insertion reaction of dilithio reagents with C≡N bonds of two nitriles could provide a 6C + 2N skeleton that might be a good precursor for the synthesis of NSBV. Therefore, we initiated a journey into the synthesis and reaction chemistry of SBV and NSBV starting from dilithio reagents that has been ongoing since 2006. In this Account, we outline mainly our recent achievements in the synthesis, structural characterization, reaction chemistry, synthetic application, and theoretical/computational analysis of NSBV.



Two efficient strategies for the synthesis of NSBV from dilithio reagents and nitriles via oxidant-induced C−N bond formation are described. Structural investigations of NSBV, including X-ray crystal structure analysis, determination of the activation barrier for the aza-Cope rearrangement, and theoretical analysis, show that the localized structure of NSBV is the predominant form and that the homoaromatic delocalized structure exists as a minor component in the equilibrium. We also discuss the reaction chemistry and synthetic applications of NSBV. Several novel reaction patterns have been explored, including thermolysis, C−N bond insertion, rearrangement−cycloaddition, oxidation, and nucleophilic ring-opening reactions. Diverse and interesting N-containing polycyclic skeletons can be constructed, such as nickelaazetidine, 1,5-diazatriquinacenes, and triazabrexadienes, which are not available by other means.

Our results show that NSBV not only features a rapid aza-Cope rearrangement with a low activation barrier but also acts as unique synthetic reagent that is significantly different from aziridine. The strained rigid ring systems as a whole can be involved in the reactions. Our achievements highlight two significant advances: (i) the well-established efficient synthesis and isolation of NSBV has greatly accelerated the development of NSBV chemistry, and (ii) the previously unattainable molecules have become "normal" and routine starting materials for the synthesis of otherwise unavailable but interesting structures. We expect that our pursuits will inspire and help direct future chemical and physical research on NSBV.

1. INTRODUCTION

Semibullvalene (SBV, **1**) and its aza analogue 2,6-diazasemibullvalene (NSBV, **2**) are theoretically and experimentally interesting and important compounds (Scheme 1)[1−3] because they have four unique features: (i) highly strained ring systems, (ii) intramolecular skeletal rearrangement, (iii) rapid degenerate (aza-)Cope rearrangement,[4] and (iv) the predicted existence of homoaromatic delocalized structures.[1d,5] The synthesis, structural studies, and reaction chemistry of SBV and NSBV have been a great challenge in organic chemistry and have attracted much attention from both experimental and theoretical chemists.

Since Zimmerman and Grunewald reported the first synthesis of SBV in 1966,[6a] there have been many reports on its synthesis, structures, and reaction chemistry[6c−j] as well as theoretical studies.[7] Several novel SBVs have been synthesized in the past five decades, such as 2,6-dicyano-1,5-dimethyl-4,8-diphenylsemibullvalene by Quast et al.[6e] and 2,4,6,8-semibullvalene tetracarboxylic dianhydride by Williams et al.[6f] Their major aims were to decrease the activation barrier of the Cope rearrangement and realize a neutral homoaromatic SBV.[6c−j]

In contrast to the numerous publications on SBV, little progress on NSBV chemistry has made, mainly because of the inherent structural instability of NSBV and the lack of efficient synthetic methods. However, NSBV has attracted much attention because it was theoretically predicted to undergo a more rapid aza-Cope rearrangement with a lower activation

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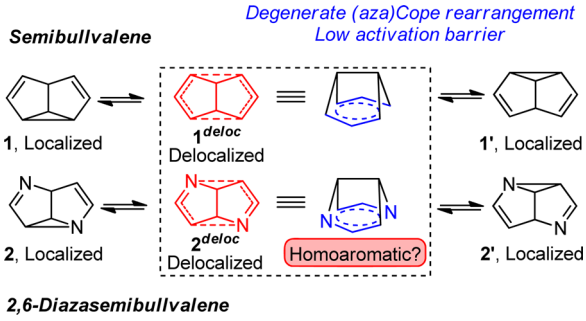
Scheme 1. Semibullvalene (SBV) and 2,6-Diazasemibullvalene (NSBV)



barrier than its all-carbon analogue SBV and to potentially approach a delocalized homoaromatic structure.[2,3] Before our studies, the only experimental report on NSBV was the in situ NMR identification and thermolysis of 1,5-dimethyl-3,7-diphenyl-2,6-diazasemibullvalene (**3**) in early 1980s by Müllen et al.[3a,b] NSBV **3** was generated in situ by reducing the dibromide precursor in [D_8]tetrahydrofuran (THF-d_8). During the past 30 years, no further report followed in the literature except our investigations, leaving the synthesis, structure, and reaction chemistry of NSBV almost unknown.

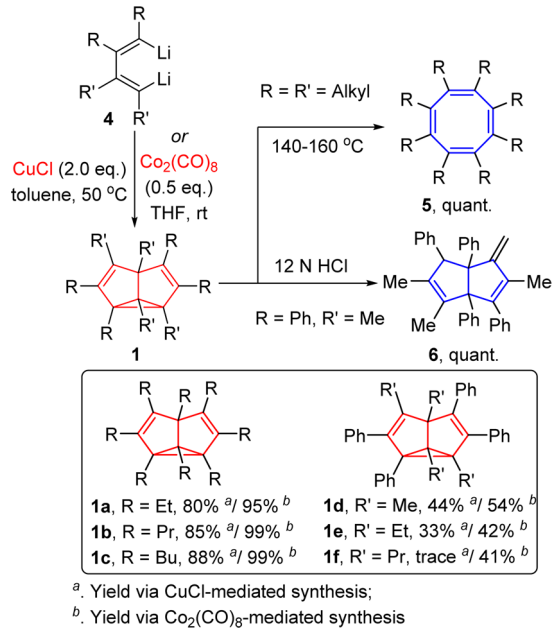
We are interested in the reaction chemistry of 1,4-dilithio-1,3-butadienes (dilithio reagents for short), especially their cyclodimerization and their insertion reaction with nitriles, because (i) the cyclodimerization of dilithio reagents could provide the potential eight-carbon skeleton of SBV from four-carbon butadiene units and (ii) the insertion reaction of dilithio reagents with C≡N bonds of two nitriles could provide a 6C + 2N skeleton that might be a good precursor for the synthesis of NSBV. This Account outlines our journey into the synthesis and reaction chemistry of NSBV from SBV chemistry based on dilithio reagents. Our well-established efficient synthesis and isolation of NSBV has been greatly beneficial for investigations into its structure and reaction chemistry. Thus, previously unattainable molecules have become "normal" and ready starting materials for further synthetic applications.

2. OCTASUBSTITUTED SEMIBULLVALENES: SYNTHESIS, STRUCTURAL CHARACTERIZATION, AND SKELETAL REARRANGEMENT

Traditional synthetic methods for SBV featured the multistep construction of complicated poly-fused-ring skeletons and the utilization of strong reducing agents.[6] After we carefully surveyed the eight-carbon skeleton of SBV and the reaction chemistry of dilithio reagents, we envisioned that cyclodimerization of dilithio reagents might lead to an efficient synthesis of SBV. Interestingly, after screening metal salts, we found that CuCl-mediated cyclodimerization of dilithio reagents **4** in toluene afforded the octasubstituted SBVs **1** in high yields (Scheme 2).[8,9] This is the first example of metal-mediated synthesis of SBVs via a C−C bond-forming process. 1,4-Dicopper-1,3-butadienes are proposed as reactive intermediates.[10] Alternatively, $Co_2(CO)_8$-promoted cyclodimerization of **4** in THF also gave SBVs in higher yields (Scheme 2).[11]

SBVs **1** showed some intriguing reaction chemistry. Octaalkyl SBVs readily underwent thermal rearrangement to give cyclooctatetraene (COT) derivatives **5**.[6h,8] In contrast, thermolysis of 1,2,5,6-tetramethyl-3,4,7,8-tetraphenyl SBV **1d** did not afford COT derivatives but rather gave a mixture of

Scheme 2. Synthesis of Semibullvalenes 1 via CuCl- or $Co_2(CO)_8$-Mediated Cyclodimerization of 1,4-Dilithio-1,3-butadienes and Skeletal Rearrangement



a. Yield via CuCl-mediated synthesis;
b. Yield via $Co_2(CO)_8$-mediated synthesis

products. Acid-mediated isomerization of **1d** in 12 N aqueous HCl afforded pentalene **6**.[8] Acid-mediated isomerization of **1a−c** was not observed. These results suggest that the substitution pattern on the SBV core has an impact on the reactivity of SBVs.

Both the ^{1}H and ^{13}C NMR spectra of octaalkyl SBVs **1a−c** showed averaging of signals at room temperature, indicating a rapid equilibrium of the degenerate Cope rearrangement between two localized structures **1** and **1′**. The X-ray crystal structure of octapropyl SBV **1b** showed a C_{2v}-symmetric structure at room temperature but an unsymmetrical localized structure at low temperature.[8,11] As different structural models, SBV **1d** displayed degenerate signals in the NMR spectra and a C_{2v}-symmetric X-ray structure at room temperature. In contrast, the ethyl analogue **1e** showed unsymmetrical, nondegenerate NMR signals as well as a localized X-ray structure, indicating a relatively slow degenerate Cope rearrangement in solution. Despite the fact that both **1b** and **1d** feature symmetrical structures in the crystalline phase, they are considered to be results of temperature-dependent dynamic or static disorder of two nondegenerate SBV molecules at room temperature rather than having a neutral homoaromatic nature.[6f] Our results showed that both the substituents on the SBV core and the temperature have significant effects on the structure as well as the rate of the Cope rearrangement, which have also been reported on other SBVs.[6f]

3. 2,6-DIAZASEMIBULLVALENES: SYNTHESIS, STRUCTURAL CHARACTERIZATION, REACTION CHEMISTRY, AND THEORETICAL ANALYSIS

3.1. Synthesis

After we successfully developed the synthesis of SBV via cyclodimerization of dilithio reagents **4** in 2006, we turned our interest to the preparation of its aza analogue NSBV from dilithio reagents and N-containing starting materials. In 2008, we reported that reactions of 1,4-unsubstituted dilithio reagents

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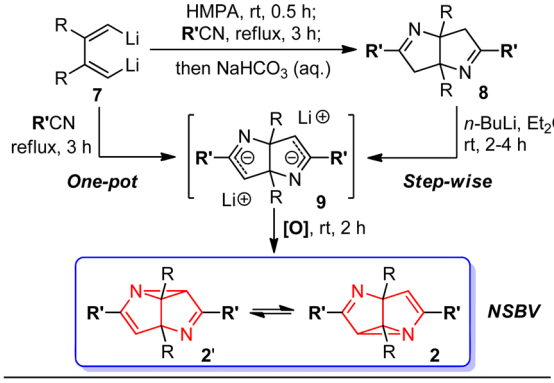
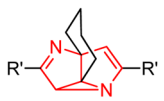
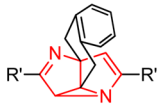
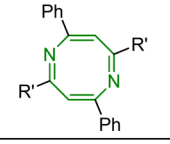
7 with two nitrile molecules afford Δ^1-bipyrrolines **8**. This finding prompted us to explore the synthesis of NSBV because of the analogous 6C + 2N skeletons of NSBVs **2** and Δ^1-bipyrrolines **8**. The difficulty in this strategy lies in how to construct the key strained C−N bond of Δ^1-bipyrrolines **8**. The progress of oxidant-induced intramolecular C−N bond formation inspired us to try the reaction of **8** with oxidants.[12]

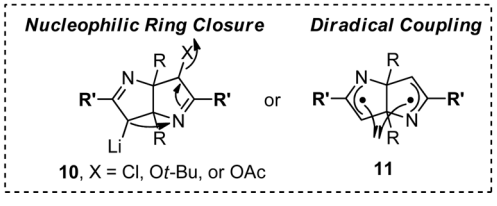
Treatment of dianions **9** (generated in situ from dilithiation of Δ^1-bipyrrolines **8**) with phenyliodine diacetate ($PhI(OAc)_2$) or *tert*-butyl hypochlorite (*t*-BuOCl) resulted in intramolecular C−N bond formation to afford NSBVs **2** in high yields.[13] Alternatively, the NSBVs could be prepared by a one-pot synthesis via the reaction of dilithio reagent **7** with 2.4 equiv of nitrile without an α-hydrogen followed by the addition of di-*tert*-butyl peroxide as the oxidant. NSBVs **2a−h** bearing different substituents are summarized in Scheme 3.[14] The oxidative formation of NSBVs **2** might proceed via nucleophilic ring closure of intermediate **10** or intramolecular C−N bond coupling of (bis)allyl diradical **11**.

Scheme 3. Synthetic Strategies toward NSBVs 2



NSBV/1,5-Diazocine		Isolated Yield (%) One-pot	Step-wise
	**2a**, R' = *t*-Bu	66 [a]	83 [b]
	2b, R' = Ad	53 [a]	68 [b]
	2c, R' = Et_2MeC	43 [a]	72 [b]
	2d, R' = $BuMe_2C$	30 [a]	83 [b]
	2e, R' = $EtMe_2C$	51 [a]	72 [b]
	**2f**, R' = *t*-Bu	51 [c]	
	**2g**, R = Me, R' = *t*-Bu		72 [c]
	2h, R = Bu, R' = *t*-Bu		73 [c]
	2i, R = Ph, R' = *t*-Bu		0 [d]
	**12a**, R' = *t*-Bu	53 [c]	73 [c]

a. [O] = $(t\text{-BuO})_2$ (4.0 equiv); *b*. [O] = $PhI(OAc)_2$ (1.0 equiv); *c*. [O] = *t*-BuOCl (1.0 equiv); *d*. Not isolated



However, when 2,3-diphenyl-1,4-dilithio-1,3-butadiene was applied, the 1,5-diphenyl NSBV **2i** was not isolated. Instead, 1,5-diazocine **12a** was obtained. We assumed that the expected NSBV **2i** might be unstable at room temperature and readily transformed into the thermodynamically more stable **12a**.[3c]

3.2. Structural Studies

We utilized several characterization methods in both the solid state and the solution phase as well as computational results to study the structural features and homoaromaticity of NSBV.

Single-crystal X-ray analysis of **2a** revealed a localized structure[14] that features a strained aziridine ring with an elongated C4−N6 bond (1.628 Å), indicating enhanced ring strain in the NSBV molecule (Figure 1).[15] Thus, this NSBV

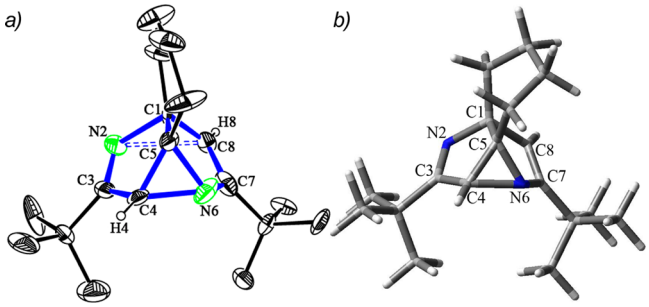


Figure 1. (a) Single-crystal X-ray structure of **2a**. (b) B3LYP/6-31G*-optimized localized structure of **2a**.

molecule **2a** does not have C_2 symmetry in the crystal phase. Solid-state ^{13}C NMR spectroscopy of **2a** at room temperature also showed its unsymmerical and localized structure, indicating that the degenerate aza-Cope rearrangement was "frozen" in the solid state.

Furthermore, the solution-phase structure and activation barrier for the aza-Cope rearrangement of NSBV were demonstrated by variable-temperature NMR spectra. At room temperature, all of the isolated NSBV **2a−2h** showed averaging signals, suggesting rapid equilibrium between two localized structures **2** and **2′** in solution.[14] For example, the aziridinyl H4 and vinyl H8 in **2a** displayed only one singlet at δ = 4.79 ppm in the ^1H NMR spectrum in THF-d_8. At −110 °C, line broadening of the C4/C8 resonance suggested that the aza-Cope rearrangement had slowed down. By line-shape analysis, the upper limit of the activation barrier for the aza-Cope rearrangement, $\Delta G^{\ddagger}_{163K}$, was determined to be 4.4 kcal/mol, which is lower than the values for the corresponding all-carbon analogues.[6b,g] Thus, in solution **2a** shows a dynamic equilibrium of the rapid degenerate aza-Cope rearrangement rather than a static homoaromatic form.

The structures of both localized **2a** and delocalized $\mathbf{2a}^{deloc}$ were optimized and found to be energy minima using DFT calculations at the B3LYP/6-31G* level.[16] The transition state for the aza-Cope rearrangement, **2a***, was also optimized. The Gibbs free energy of $\mathbf{2a}^{deloc}$ at 163 K was 1.8 kcal/mol higher than the value calculated for **2a**.[14] Greve's computational results showed that the localized structure of unsubstituted NSBV also has a lower calculated energy at the MP2/cc-pVDZ level.[2b] We calculated the activation barrier for the aza-Cope rearrangement at 163 K as 2.1 kcal/mol, which is comparable to the experimental value. These results show that **2a** is the predominant form in solution or the gas phase and that the

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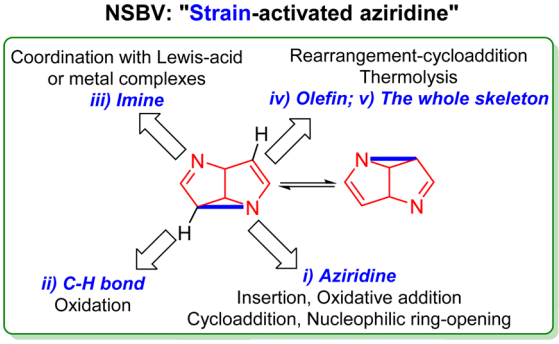
homoaromatic delocalized **2a**^{deloc} exists as a minor component in the equilibrium.

3.3. Reaction Chemistry

The structure−reactivity relationship of theoretically interesting NSBV not only plays an important role in the in-depth understanding of its structural and bonding natures but is also useful for the development of new synthetic methods for functional architectures. However, because of the limitation of synthetic methods for NSBVs **2**, the reaction chemistry of NSBVs was unknown except for their thermolysis to give 1,5-diazocines as reported by Müllen and co-workers.[3b]

Generally, all isolated NSBVs **2** are stable in an inert atmosphere, but they are sensitive to acid, base, and silica gel and decompose slowly when exposed to moisture. Our further efforts showed that NSBVs **2** are highly reactive and useful in organic and organometallic synthesis because of their unique strained ring system, multiple reaction sites, and intramolecular aza-Cope rearrangement. The multiple reaction sites in **2** include (i) the aziridine ring, (ii) C−H bonds, (iii) the imine C═N bond, (iv) the olefin (or enamine) C═C bond, and (v) the polycyclic skeleton as a whole (Scheme 4).

Scheme 4. Reaction Modes of NSBV

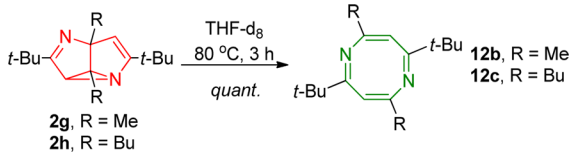


Once the whole polycyclic skeleton is targeted for further transformation, the multiple reaction sites of NSBV might induce more types of reactions than the reaction on the aziridine ring only. Moreover, the rigid ring skeleton as well as the substituents might result in unprecedented regioselectivity and diastereoselectivity. The introduction of nitrogen atoms into SBV changes the electronic effects and polarity of the resulting C−N and C═N bonds, which are prone to nucleophilic attack. Thus, reaction patterns and selectivities that differ from those of standard aziridine or the all-carbon analogue SBV are generated.[17−19]

On the basis of our analysis of the structural features of NSBV, we designed and explored several types of reactions of NSBVs, including thermolysis, insertion, rearrangement−cycloaddition, oxidation, and nucleophilic ring-opening reactions. These afforded diverse and novel ring-expansion products and bowl- or cage-shaped N-containing polycyclic frameworks that could be difficult to access by other means.

3.3.1. Thermolysis of NSBVs 2g and 2h To Give 1,5-Diazocines 12. Nonbridged NSBVs **2g** and **2h** could be quantitatively converted to the corresponding 1,5-diazocines **12b** and **12c** at 80 °C. This thermolysis reaction involves whole ring skeleton and is in good accordance with Müllen's study (Scheme 5).[3b,6h] On the contrary, 1,5-bridged NSBVs **2a−f** showed good thermostability under 200 °C and did not undergo the transformation. These results demonstrated that

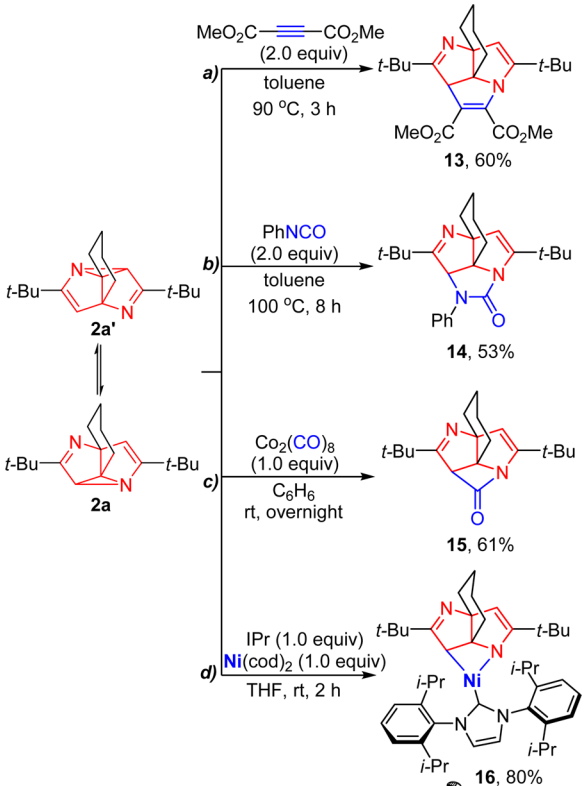
Scheme 5. Thermolysis of NSBVs 2g and 2h To Give 1,5-Diazocines 12

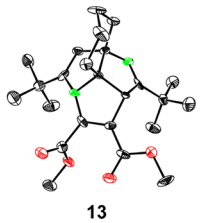


the substituents at the 1- and 5-positions of **2** play an important role in their thermostability.

3.3.2. "Insertion" of Unsaturated Compounds or Low-Valent Metal Complexes. As demonstrated by the elongated C−N bond of the aziridine ring in the X-ray structure of NSBV **2a**, the C−N bond is weakened and thus was expected to show rich reaction chemistry. Insertion of unsaturated compounds as well as a zero-valent Ni center results in interruption of the rapid aza-Cope rearrangement and the formation of a variety of ring-expansion products (Scheme 6).[14] Regiospecific cycloaddition of **2a** with the activated alkyne dimethyl acetylenedicarboxylate (DMAD) readily afforded bowl-shaped 1,5-diazatriquinacene **13**.[17a,20,21] Direct cycloaddition of **2a** with phenyl isocyanate gave tetracyclic imidazolidinone **14**. Carbonylation of **2a** with $Co_2(CO)_8$ at room temperature gave

Scheme 6. Insertion of Unsaturated Compounds or Low-Valent Metals into the Weakened C−N Bond of 2a

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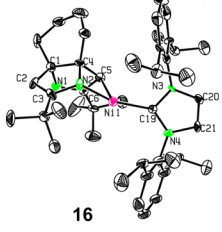
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tetracyclic β-lactam **15** as the product of "insertion" of a CO moiety into the C−N bond. These results show the higher reactivity of NSBVs compared with standard aziridines. Generally the reactions of standard aziridines with isocyanates and carbonylation require a transition-metal catalyst,[22] elevated temperatures, or high pressures of CO gas.[23]

The reaction of **2a** with $Ni(cod)_2$ in the presence of 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) led to the formation of the three-coordinate four-membered azanickelacycle **16** (Scheme 6).[14] Only one NHC carbene ligand coordinates to the Ni(II) center, probably because of steric hindrance. We suggest that the mechanism might be concerted or involve a diradical pathway, in contrast to the S_N2 mechanism proposed by Hillhouse for oxidative addition of Ni(0) complexes with standard aziridines.[24]

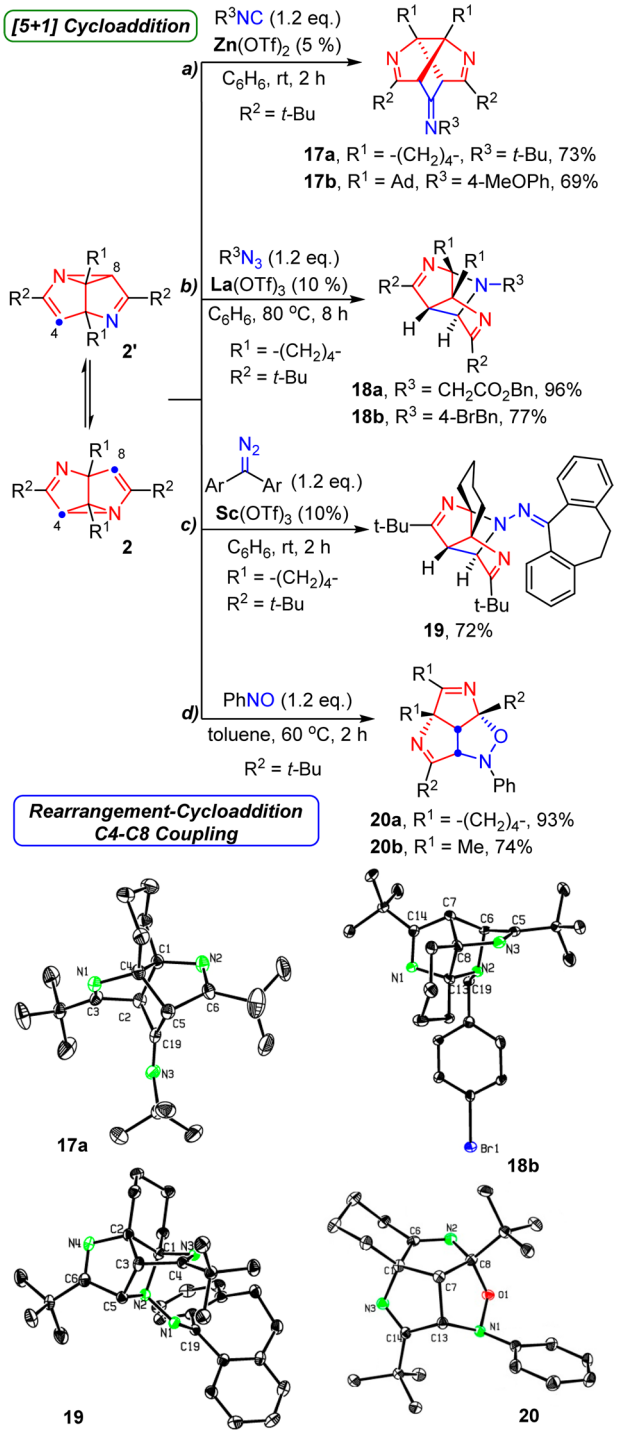
3.3.3. Rearrangement−Cycloaddition Reactions with Isocyanides, Azides, Diazo Compounds, and Nitroso Compounds. The reactions of NSBVs with isocyanides, azides, and diazo compounds in the presence of Lewis acid catalysts represent a "ring-opening-rearrangement−cyclization" pattern.[25,26] These reactions show the most important and intriguing reactivity of NSBVs because the whole rigid-ring skeleton is involved in multisite C−C or C−N bond cleavage and formation. The use of different reagents enables efficient and selective syntheses of cage-shaped or bowl-shaped highly fused N-containing polycyclic frameworks that are structurally and chemically interesting but not readily accessible by other means. By comparison, cycloadditions of isocyanides, azides, diazo compounds, and nitroso compounds with standard aziridines are all very rare.[27,28]

The cycloaddition reactions of NSBVs with different substrates require different Lewis acid catalysts to achieve the best yields. The most efficient catalysts for cycloaddition of NSBVs with isocyanides, azides, and diazo compounds are $Zn(OTf)_2$, $La(OTf)_3$, and $Sc(OTf)_3$, respectively. The $Zn(OTf)_2$-catalyzed formal [5 + 1] cycloaddition reaction of NSBVs **2** with isocyanides at room temperature afforded 5,8-diaza-4,8-brexadienes **17** (Scheme 7a).[25] In contrast to the insertion reactions of NSBVs with DMAD and RNCO, the product of isocyanide insertion into the C−N bond was not detected. The $La(OTf)_3$-catalyzed cycloaddition of azides with NSBVs **2** afforded 2,5,9-triaza-4,8-brexadienes **18** as single diastereomers (Scheme 7b).[25] This reaction features skeletal rearrangement of **2**, loss of N_2 from the azide, cleavage of the unstrained C4−C5 bond of **2**, and C4−C8 coupling. Normal [3 + 2] cycloaddition of azide 1,3-dipole[29] or [2 + 1] cycloaddition of nitrene did not occur.[30]

The $Sc(OTf)_3$-catalyzed reaction of NSBV **2a** with a diaryl diazomethane afforded *N*-ylideneamino-2,5,9-triazabrexadiene **19** without loss of dinitrogen (Scheme 7c).[25] The diaryl diazomethane showed reactivity as a nitrene rather than a carbene, forming two C−N bonds in one cycloaddition reaction. We suggest that the α-C in the diaryl diazomethane is less nucleophilic and more sterically hindered than the γ-N.[31] This type of reactivity is rarely reported.[32]

The reaction of NSBVs **2** with nitroso compounds cleanly afforded 2,5,8-triaza-3-oxatriquinacene derivatives **20** (Scheme 7d).[26] The normal [3 + 2] cycloaddition product was not isolated. This reaction does not require a Lewis acid catalyst. The C4−C8 coupling and three-ring fused bowl-like skeleton of the product suggest a different cycloaddition mode and mechanism. Representative single-crystal X-ray structures of **17a**, **18b**, **19**, and **20a** are shown at the bottom of Scheme 7.

Scheme 7. Rearrangement−Cycloaddition Reactions of NSBVs 2 with Isocyanides, Azides, Diazo Compounds, and Nitroso Compounds



Mechanisms for the chemoselective rearrangement−cycloaddition reactions of NSBVs have been proposed (Scheme 8). First, coordination of the Lewis acid activates the aziridine ring and gives zwitterionic intermediate **21** as a result of nucleophilic ring opening. The reaction with a nitroso compound does not require the assistance of a Lewis acid. Ring opening of one pyrroline ring in **21** leads to C4−C5 cleavage and the formation of different kinds of *N*-3-pyrrolylimines **22** as key intermediates, depending on the

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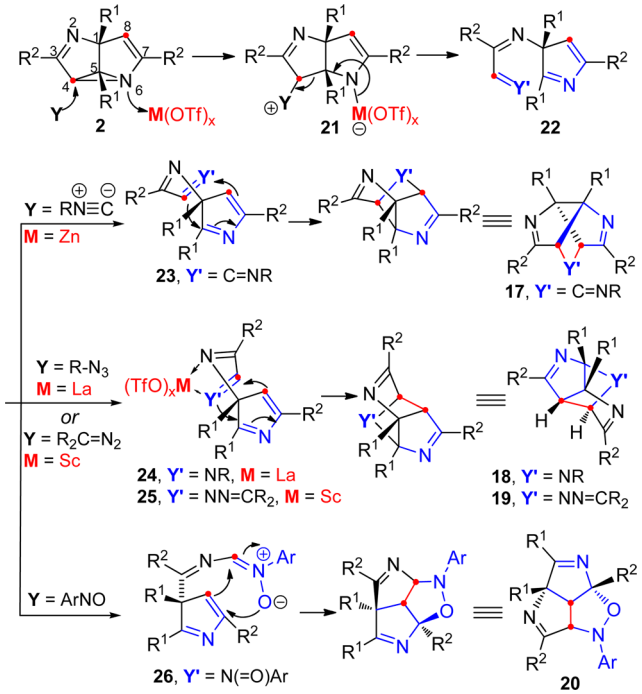
Scheme 8. Proposed Mechanisms for Cycloaddition of 2,6-Diazasemibullvalenes with Isocyanides, Azides, Diazo Compounds, and Nitroso Compounds

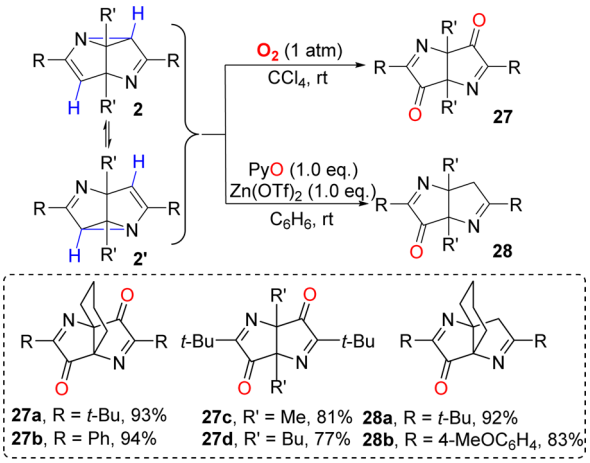


nature of the nucleophilic reagent **Y**. For the reactions with isocyanides, azides, diazo compounds, and nitroso compounds, the structures of the corresponding intermediates **22** are ketenimine **23**, diimine **24**, hydrazone **25**, and nitrone **26**. Finally, an intramolecular [4 + 2] cycloaddition of the 3*H*-pyrrole ring and C═**Y**′ moiety constructs the cyclopentanimine or pyrroline core in **17**, **18**, and **19** in a regio- and diastereospecific fashion. The [3 + 2] cycloaddition of a 1,3-dipole moiety with the C═C bond of the 3*H*-pyrrole ring in **26** leads to the formation of the isoxazolidine ring in **20**. The different nature of the C═**Y**′ moiety leads to different regiospecificity of the [4 + 2] or [3 + 2] cycloaddition. The diastereoselectivity is controlled by the substituents on the rigid ring skeletons.

These rearrangement−cycloaddition reactions have several features: (i) unique reaction patterns, (ii) site selectivity, (iii) high reactivity, (iv) involvement of the whole ring skeleton of the NSBV, and (v) useful synthons.

3.3.4. Oxidation Chemistry of NSBV. Oxidation of C−H bonds to C═O bonds by oxygen (O_2) is a very important and useful process, but it often requires additives or promoters such as bases, transition-metal complexes, or photosensitizers.[33,34] Our results showed that O_2 oxidation of NSBV at room temperature affords Δ^1-bipyrrolinones via C−N bond cleavage and C−H bond oxidation (Scheme 9).[35] C−H bonds are oxidized to C═O bonds by oxygen only, without any additives or promoters.[34] 1,5-Bridged or nonbridged NSBVs **2** bearing different alkyl or aryl substituents could all be applied in this oxidation reaction, affording Δ^1-bipyrrolinones **27**. Besides, pyrrolino[3,2-*b*]pyrrolinone derivatives **28** were efficiently generated when NSBVs were treated with *N*-oxides in the presence of Lewis acids. Δ^1-Bipyrrolinones are valuable cyclic *α*-acyl imines that could be readily transformed into other heterocyclic compounds, such as dihydropyrrolo[3,2-*b*]-

Scheme 9. Oxidation of NSBVs 2 by Oxygen or *N*-Oxides: Synthesis of Δ^1-Bipyrrolinones and Pyrrolino[3,2-*b*]pyrrolinones



pyridine-3,6-dione and tetrahydro-1,5-naphthyridine-3,7-dione.[35]

Standard aziridines cannot be oxidized by O_2 only,[36] while O_2 oxidation of SBVs was reported to give cycloaddition products.[6c,e] Thus, the oxidation chemistry of NSBVs is different from the known oxidation of either standard aziridines or SBV derivatives.

3.3.5. Nucleophilic Ring-Opening Reactions. Aziridines have shown rich reaction patterns and synthetic applications in organic and pharmaceutical chemistry.[17−19] Since the aziridine ring of NSBV is highly fused and has specific substituents with steric effects, enhanced reactivity and selectivity toward nucleophiles are expected.[19] Ring-opening reactions of NSBVs **2** with alcohols, phenols, thiols, carboxylic acids, and amines as O-, S-, and N-nucleophiles all proceeded smoothly at room temperature, giving unsymmetrical, functionalized Δ^1-bipyrrolines **29** (Scheme 10).[37] In the presence of Lewis acid catalysts, cyclohexanone as an enol nucleophile and *N*-methylindole as a C-nucleophile could also be applied to the nucleophilic ring-opening reaction of NSBV **2a**. In contrast, Lewis acid-catalyzed reactions of standard aziridines with ketones or activated indoles give [3 + 2] cycloaddition products.[38,39] Various types of anionic nucleophiles were also used in the ring-opening reactions of NSBVs **2**, such as Et_2Zn (Scheme 10).

^{1}H NMR spectra of compounds **29a−e** as well as the X-ray structures of **29b** and **29e** revealed that all of the products are single exo diastereoisomers, probably because bulky substitutents at the 3- and 7-positions on NSBVs **2** prevented nucleophilic attack at the endo face. Exo-face selectivity was also observed for the nucleophilic ring opening of SBV.[40]

Nucleophilic ring opening of NSBV **2a** with sulfoxonium ylide gave methylidene Δ^1-bipyrroline **33** (Scheme 11). Ring expansion of the aziridine core in the NSBV with sulfoxonium ylides did not occur. This result is in obvious contrast with the reactivity of aziridines with sulfoxonium ylide, which was reported to give four-membered azetidines.[41]

4. SUMMARY AND OUTLOOK

In this Account, we have described our recent achievements in both the experimental and theoretical chemistry of SBV and NSBV. After the prediction of interesting properties of NSBV

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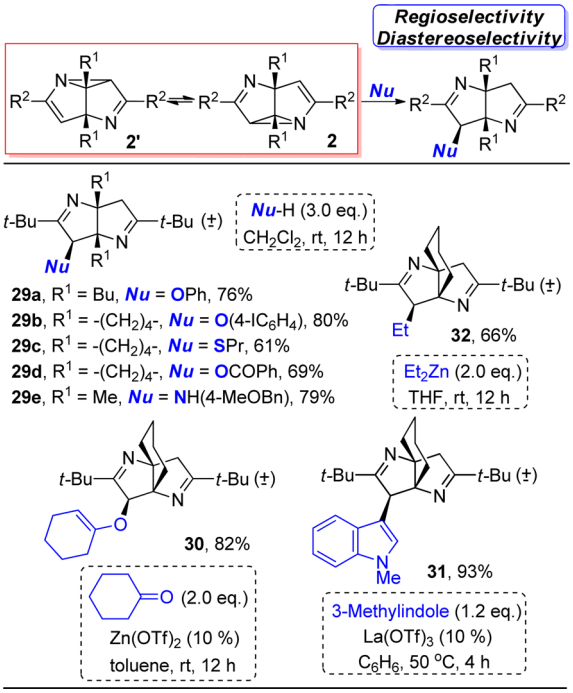
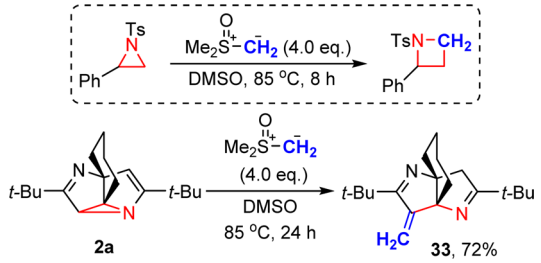
Scheme 10. Nucleophilic Ring Opening of NSBVs: Diastereoselective Synthesis of Functionalized Δ^1-Bipyrrolines[a]



[a]Reaction conditions are given in the dashed boxes.

Scheme 11. Nucleophilic Ring Opening of NSBV 2a with Sulfoxonium Ylides

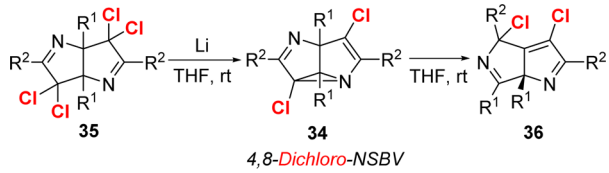


in 1971 and the first in situ synthesis in 1982, we made significant progress on the efficient synthesis and isolation of NSBVs via reactions of 1,4-dithio-1,3-butadiene reagents, making further structural studies and reaction chemistry possible. For the first time, the single-crystal structure of one NSBV derivative and the activation barrier for its aza-Cope rearrangement were determined. NSBVs have proved to be synthetically useful. Unique reaction patterns, high activity, and remarkably different chemo- and diastereoselectivity from standard aziridines were achieved. The polycyclic skeleton of NSBVs as either a whole or a part could be involved in the reaction. On the basis of extensive investigations on structural characterization, we have concluded that the unique strained ring systems are the key for both the rapid degenerate aza-Cope rearrangement and the diversified reaction patterns of NSBVs.

Homoaromaticity has long been one of the ultimate questions in SBV and NSBV chemistry. Our computational results showed that the localized NSBV **2a** is the predominant form and that the homoaromatic **2a**^{deloc} exists as a minor component in the equilibrium. Our work has provided solid results and answers on this controversial topic and filled in the blank of NSBV chemistry in the past few decades.

We are currently developing new synthetic methods toward different types of SBVs and NSBVs, especially those having nitrogen atoms at different positions. New substitution patterns are expected to have a significant impact on the bonding structure, the rate of the (aza-)Cope rearrangement, and the reactivity. For example, we very recently developed the synthetic method for 4,8-dichloro-2,6-diazasemibullvalenes **34** via reduction of $\alpha,\alpha,\alpha',\alpha'$-tetrachloro-$\Delta^1$-bipyrrolines **35** with lithium metal (Scheme 12).[42] Other than the thermal

Scheme 12. New Types of NSBVs: Synthesis of 4,8-Dichloro-2,6-diazasemibuvallenes and Their Skeletal Rearrangement



rearrangement to give 1,5-diazocines **12**, dichloro-NSBVs **34** underwent a new type of skeletal rearrangement to give **36**. This different rearrangement shows that the substitution pattern of NSBVs has a significant impact on their reaction chemistry. We expect interesting new structures and useful reaction chemistry from such new SBV and NSBV compounds.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Wen-Xiong Zhang received his B.Sc. degree from Hunan Normal University in 1996, his M.Sc. degree from Guangxi Normal University in 1999, and his Ph.D. degree from Nankai University with Professor Li-Cheng Song in 2003. He carried out postdoctoral research at Peking University with Professor Zhenfeng Xi in 2002 and at RIKEN in Japan with Chief Scientist Zhaomin Hou in 2004. In 2007 he joined the College of Chemistry at Peking University, where he is now an associate professor. His research focuses on characterization and

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application of organometallic intermediates in metal-mediated organic synthesis and small-molecule activation using rare-earth metal compounds.

Zhenfeng Xi received his B.S. degree from Xiamen University in 1983, his M.S. degree from Nanjing University, Zhengzhou University, and the Henan Institute of Chemistry in 1989, and his Ph.D. degree from the Institute for Molecular Sciences (IMS), Japan, in 1996 with Prof. Tamotsu Takahashi. He took an assistant professor position at Hokkaido University in 1997. In 1998 he joined the College of Chemistry at Peking University, where he is now a professor. His research interests include the development of organometallic reagents, studies of mechanisms of reactions involving reactive organometallic intermediates, and the synthesis of functional structures.

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