

Intramolecular Ynamide–Benzyne (3+2) Cycloadditions

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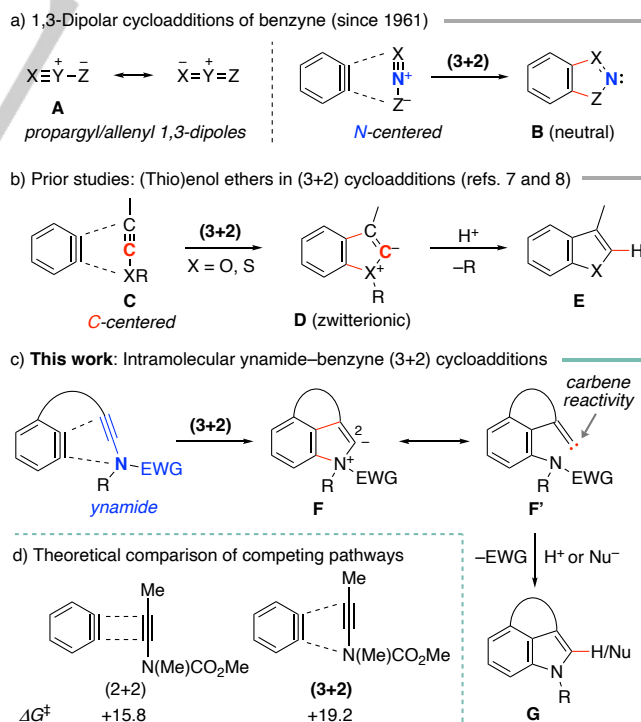
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Abstract: We report herein intramolecular (3+2) cycloaddition reactions between ynamides as three-atom components and benzyne. In these intramolecular reactions, the two-bond formation is realized by exploiting benzyne precursors that contain a chlorosilyl group as a linking functionality. This method thus highlights the ambivalent character of the intermediate indolium ylide, which exhibits both nucleophilic and electrophilic properties at its C2 atom.

In the long history of 1,3-dipolar cycloaddition reactions, which have been pioneered by Huisgen in the 1960s,¹ the (3+2) cycloaddition of 1,3-dipoles to benzyne, a highly reactive species with a distorted formal triple bond, is one of the earliest examples, and still serves as an attractive approach to forge benzo-fused five-membered heterocycles.² Among the various 1,3-dipoles that have been extensively investigated for this reaction over the past decades, the propargyl/allenyl-type 1,3-dipoles **A**, such as azides,³ diazoalkanes,⁴ nitrile oxides,⁵ and nitrile imines⁶ provide direct methods for the generation of heteroaryl frameworks without requiring post-aromatization techniques (Scheme 1a). However, such 1,3-dipoles are normally limited by their structure, i.e., the central sp-hybridized atom is typically nitrogen, as after cycloaddition, it must accommodate the newly generated lone pair of electrons of the neutral bicyclic product **B**. Heteroatom-substituted alkynes **C**, which are isoelectronic carbon-centered analogues of **A**, can also participate in this process. Even though this approach has been explored only sporadically so far, it seems feasible to expect that it is able to significantly expand the synthetic utility of this type of cycloaddition reactions (Scheme 1b). An early study by Wasserman exemplifies the use of (thio)ynol ethers in (3+2) cycloadditions,⁷ the scope of which was later widely expanded by Yoshida.⁸ In both cases, the direct cycloadduct **D** undergoes *in-situ* trapping of electrophiles at the anionic carbon center followed by dealkylation to afford neutral heteroaromatics **E**. The unique zwitterionic character of **D** promises great synthetic potential to provide diverse heterocyclic scaffolds that are inaccessible via classical 1,3-dipolar cycloadditions of benzyne. Notable along these lines is the recent related report by Gagosz, in which the reactivity of thiophenium ylides was thoroughly investigated.⁹

Herein, we document unprecedented (3+2) cycloaddition reactions of benzyne with internal ynamides, which are a subclass of nitrogen-substituted alkynes that contain *N*-electron-withdrawing group(s) (EWG), which opens a novel route to multifunctionalized indole derivatives **G** (Scheme 1c).¹⁰ Another notable finding is that, in this sequence, the C2 carbon atom in the intermediate indolium ylide **F**, whose resonance structure is the vinylidene **F'**,¹¹ exhibits ambivalent character with both nucleophilic and electrophilic properties.

Despite the recent growing interest in ynamides as easy-to-handle, versatile building blocks,¹² there is essentially no literature precedent for their use as three-atom components in (3+2) cycloaddition reactions. The recent study by Campeau and Gagosz, in which ynamides behave as three-atom components in (3+2) cycloaddition reactions to internal alkynes, is one notable exception.¹³ Moreover, related work on benzyne is limited to a single report by Krief, in which an intermolecular reaction with dialkylaminoalkynes, i.e., ynamines, afforded no (3+2) cycloadduct, with the predominant path being the (2+2) cycloaddition.¹⁴ Theoretical reference calculations on a simple ynamide model supported the (2+2) pathway ($\Delta G^\ddagger = +15.8$ kcal/mol), albeit that the obtained results also suggested that the (3+2) pathway ($\Delta G^\ddagger = +19.2$ kcal/mol) may be possible, despite a lack of experimental precedents (Scheme 1d). These results imply that precise control over the periselectivity between the (2+2) and (3+2) modes remains elusive so far.¹⁵ Thus, we became interested in applying ynamides in the context of our studies exploring novel arynophiles in intramolecular benzyne reactions (Scheme 1c).¹⁶ Specifically, our hope was that if their mutual spatial relationship could be suitably configured by



Scheme 1. (3+2) Cycloadditions between benzyne and 1,3-dipoles and heteroatom-substituted alkynes. ΔG^\ddagger values (kcal/mol) were calculated at the B3LYP/6-311++G** level (gas phase); EWG = electron-withdrawing group, Nu = nucleophile.

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tethering, ynamides would hopefully play the role of three-atom components in the cycloaddition to benzyne.

The initial feasibility study was illustrative (Table 1). The basis for our approach is the ready accessibility of cycloaddition precursors by using *o*-silylaryl triflate **1**,^{16d} which is available from 2,6-dibromophenol in four steps, as a platform to link with various ynamides via a Si–O bond. Indeed, precursors **3a–e**, which carry different *N*-EWGs, i.e., mesyl (Ms, **3a**), tosyl (Ts, **3b**), phosphoryl (**3c**), methoxycarbonyl (**3d**), and *tert*-butoxycarbonyl (Boc, **3e**) groups, were readily prepared in one step by combining **1a** with ynamides **2a–e**, which bear a hydroxy group (imidazole, CH₂Cl₂, RT). With **3a–e** in hand, the key cycloaddition was examined in order to evaluate the reactivity differences among the EWGs. A combination of Cs₂CO₃ and 18-crown-6 proved effective for the generation of a benzyne moiety while leaving the silylene tether intact.¹⁷ Upon treatment of **3a**, which contains an *N*-Ms group, with Cs₂CO₃ and 18-crown-6 (THF, RT, 22 h), the reaction smoothly afforded the desired indole **4** in 62% yield (entry 1). Thus, the initial step is the (3+2) cycloaddition of the *in-situ*-generated benzyne to the internal ynamide to give the indolium-ylide intermediate **H**, which would undergo C-protonation and selective hydrolytic removal of the Ms group rather than the benzyl group to afford **4**. Notably, no byproducts derived from potential side reactions, i.e., the (2+2) cycloaddition, were detected, demonstrating perfect (3+2) periselectivity. The other ynamides (**2b–e**; entries 2–5) were all converted into indole **4** as a major isolable product under the same conditions, whereby **2b** and **2e**, which contain Ts and Boc groups, respectively, furnished **4** in excellent yield (entries 2 and 5).

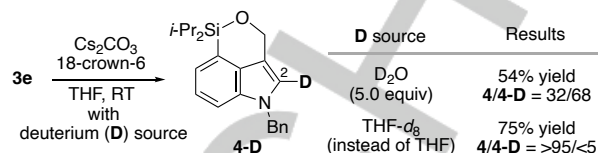
Table 1. Preparation and reaction of ynamides **3a–e**

Entry	2 (EWG)	3	Time [h]	Yield of 4 [%] ^[c]
1	2a (Ms)	3a	22	62
2	2b (Ts)	3b	18	78
3	2c [PO(OEt) ₂]	3c	19	39
4	2d (CO ₂ Me)	3d	19	63
5	2e (Boc)	3e	18	79

[a] Conditions: **1** (1.0 equiv), **2a–e** (1.1–1.2 equiv), imidazole (2.0 equiv), CH₂Cl₂, RT, 24 h. [b] Conditions: **3a–e** (1.0 equiv), 18-crown-6 (2.0 equiv), Cs₂CO₃ (2.0 equiv), THF, RT. [c] Isolated yield. Tf = trifluoromethanesulfonyl, Bn = benzyl, Ms = methanesulfonyl (mesyl), Ts = *p*-toluenesulfonyl (tosyl), Boc = *tert*-butoxycarbonyl.

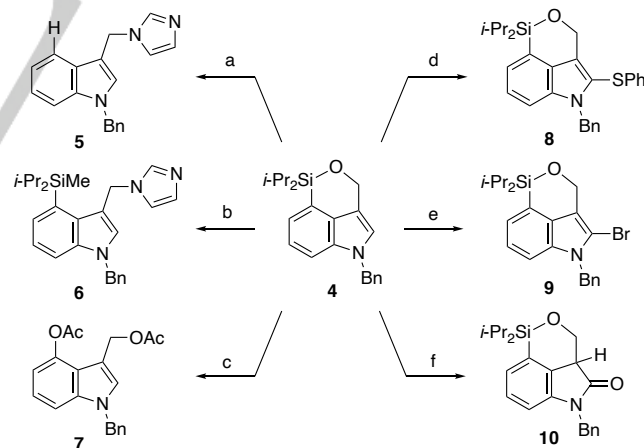
It is important to note here that the reaction was run deliberately without the addition of an obvious proton source. An analysis of the origin of the proton using deuteration experiments with D₂O or THF-*d*₈ showed that the reaction outcome depends on the deuterium source (Scheme 2). Using D₂O as an additive, the yield of product **4-D** slightly decreased, with 68%

deuteration at the C2 position, while no deuterated product was observed with THF-*d*₈ as the reaction medium. This result led us to conclude that the residual H₂O introduced with hygroscopic Cs₂CO₃ and/or 18-crown-6 is the potential origin of the *in-situ* protonation.¹⁸



Scheme 2. Deuteration experiments.

Product **4** can be regarded as the protected form of a 3-hydroxymethylindole derivative, which constitutes a versatile handle for further transformations, as highlighted in Scheme 3. Protodesilylation of indole **4** (TBAF, MS 4A, THF, reflux, 2 h) gave the corresponding primary alcohol, which underwent facile substitution reaction with imidazole [1,1-carbodiimidazole (CDI), THF, 50 °C, 1 h] to afford 3-(imidazol-1-ylmethyl)indole (**5**), a potent inhibitor against P450 aromatase¹⁹ and thromboxane synthetase,²⁰ in 87% yield (over 2 steps). In a similar fashion, 4-silyl derivative **6** was accessible via a selective cleavage of the silicon–oxygen bond with methyl lithium (THF, RT) prior to the reaction with CDI. A Tamao–Fleming oxidation of the silicon–carbon bond in the silylene tether gave the corresponding decomposition-prone 4-hydroxyindole, which was quickly subjected to acetylation conditions to give diacetate **7** in 34% yield (over 2 steps). Furthermore, indole **4** efficiently underwent various oxidative functionalizations at C2, such as sulfenylation,²¹ bromination,²² and oxindole formation²³ to give 2-oxidized products **8**, **9**, and **10**, respectively.



Scheme 3. Transformations of indole **4**. Reagents and conditions: a) TBAF (10 equiv), MS4A, THF, reflux, 2 h; CDI (5.0 equiv), THF, 50 °C, 1 h, 87% (over 2 steps). b) MeLi (2.0 equiv), THF, RT, 40 min; CDI (3.0 equiv), THF, 50 °C, 1 h, 84% (over 2 steps). c) NaH (10 equiv), TBHP (20 equiv), TBAF (2.0 equiv), MS4A, DMF, RT, 30 min; Ac₂O (10 equiv), DMAP (10 mol%), pyridine, 0 °C, 30 min, 34% (over 2 steps). d) PhSSPh (0.55 equiv), CuI (10 mol%), DMSO, 110 °C, 20 h, 84%. e) CuBr₂ (2.0 equiv), TBAB (10 mol%), (CH₂Cl)₂, H₂O, RT, 1 h, 54%. f) Oxone® (1.2 equiv), KBr (10 mol%), THF, H₂O, RT, 1.5 h, 56%. TBAF = tetrabutylammonium fluoride, CDI = 1,1'-carbonyldiimidazole, TBHP = *tert*-butyl hydroperoxide, DMAP = *N,N*-dimethyl-4-aminopyridine, TBAB = tetrabutylammonium bromide.

Having demonstrated the synthetic potential of this (3+2) cycloaddition, we started to explore the scope with respect to the

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electronic character of the substituents (R^1 and R^2) in the aryne precursor moieties (Table 2, entries 1–9). Precursors **11a** and **11b**, which contain electron-donating groups at the *meta*-position relative to the tether group, afforded the expected indole products **12a** (71% yield) and **12b** (72%) (entries 1 and 2). Other precursors with electron-withdrawing substituents at the same position also proved applicable (entries 3–6). The reactions of fluoro- (**11c**) and chloro-substituted (**11d**) derivatives proceeded cleanly (entries 3 and 4), while those of the trifluoromethyl- (**11e**) and cyano-substituted (**11f**) derivatives gave cycloadducts **12e** and **12f** in merely moderate yield (entries 5 and 6). As shown in the reaction of **11g**, acetal moieties are tolerated, furnishing indole **12g** in 79% yield (entry 7). In terms of the substituents (R^2) at the *ortho*-position relative to the tether group, methoxy (**11h**) and fluoro (**11i**) groups were tested (entries 8 and 9), which afforded indoles **12h** and **12i** in moderate yield. This methodology thus offers facile access to indoles that bear different *N*-substituents such as methyl (**12j**), phenyl (**12k**), and allyl (**12l**) by simply changing the *N*-substituent on the ynamide part (**11j–l**) (entries 10–12). Entries 13–17 are examples of branched ynamides that contain various substituents, i.e., methyl (**11m**), benzyloxymethyl (**11n**), vinyl (**11o**), and aryl (**11p** and

11q), at the propargylic position. Despite the increased steric demand around the reaction site, they smoothly furnished the corresponding indoles (**12m–q**). Ynamide **11r**, which carries an indolyl group, afforded indole **12r** in diminished yield, presumably due to a competing attack of the internal indole moiety to benzyne (entry 18). Next, we tested the effect of the length of the tether via the reactions of precursors **11s** and **11t**, whose tethers are by one or two carbons longer, respectively. While **11s** underwent cycloaddition to give indole **12s** in 33% yield (entry 19), the reaction of **11t** generated a complex mixture and only a trace amount of indole **12t** was observed (entry 20).²⁴ Furthermore, we found that this type of cycloaddition could be extended to ynol ether **11u** and thioynol ether **11v** to afford benzofuran **12u** (51% yield) and benzothiophene **12v** (55% yield), respectively (entries 21 and 22). It should also be noted here that we applied a nonafllyl (Nf) group²⁵ instead of a triflyl (Tf) group in the latter case in order to avoid hydrolytic loss of the sulfonyl group.²⁶

To further explore the mechanism of the (3+2) cycloaddition, we performed density functional theory (DFT) calculations starting from an aryne intermediate **IM1** generated from silylaryl triflate **3e** (Figure 1a). Two possible pathways, which were found

Table 2. Substrate scope [a]

Reaction scheme showing the conversion of ynamide **11a–s** to indole **12a–s** using 18-crown-6 (2.0 equiv.) and Cs_2CO_3 (2.0 equiv.) in THF at room temperature for 15–24 h.

Entry	Substrate 11	Cycloadduct 12	Yield [%] ^[b]	Entry	Substrate 11	Cycloadduct 12	Yield [%] ^[b]
1			71	13			83
2			72	14			84
3			67	15			64
4			62	16			72 ^[c]
5			52	17			73
6			46	18			31
7			79	19			33
8			47	20			trace
9			25	21			51
10			76	22			55 ^[d]
11			63				
12			44				

[a] Unless otherwise indicated, reactions were performed with ynamide **11** (1.0 equiv.), Cs_2CO_3 (2.0 equiv.), and 18-crown-6 (2.0 equiv.) in THF (0.06 M) at RT for 15–24 h. [b] Isolated yield. [c] The structure was confirmed by single-crystal X-ray diffraction analysis. [d] When the Tf group was used instead of the Nf group, **12v** was obtained in 45% yield. Ph = phenyl, Nf = nonafllyl ($\text{SO}_2\text{C}_4\text{F}_9$).

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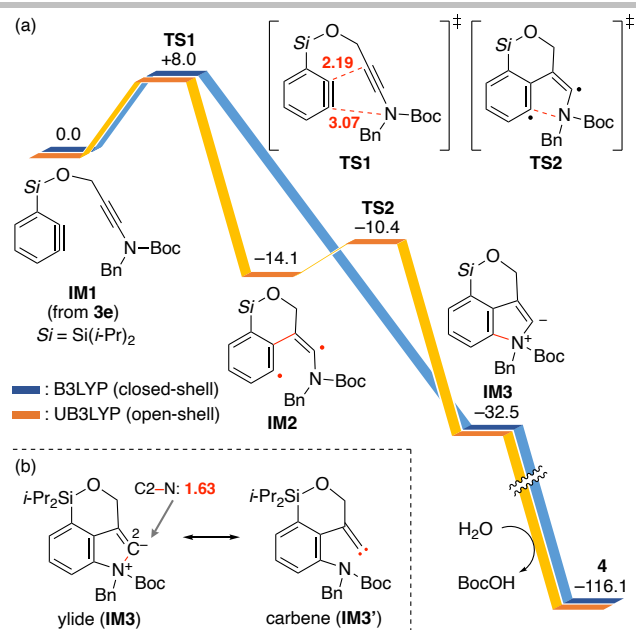


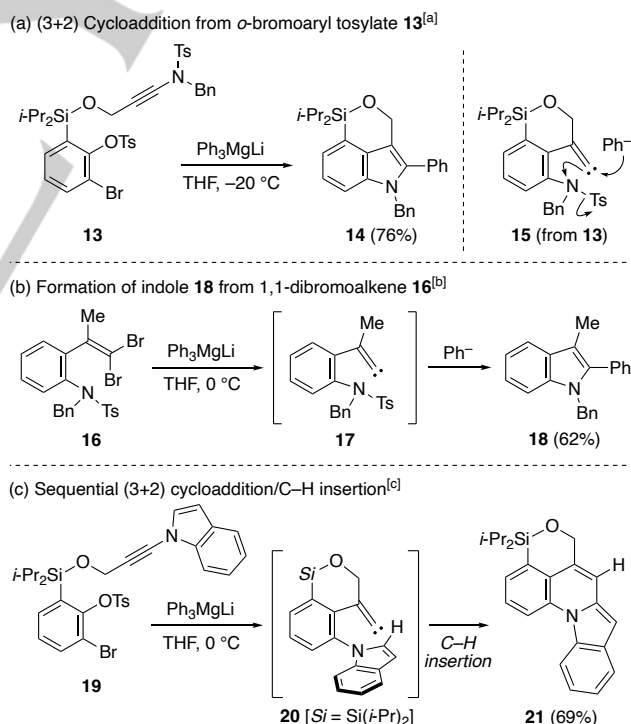
Figure 1. (a) DFT calculations for the (3+2) cycloaddition step and (b) the resonance form of ylide **IM3**. Free-energy changes at the CPCM(THF)/B3LYP/6-311++G** and CPCM(THF)/UB3LYP/6-311++G** level are shown in kcal·mol⁻¹. The bold values in red denote the bond lengths in ångströms [Å].

for the cycloaddition step in restricted and unrestricted B3LYP calculations, can be considered viable. The first is the direct formation of indolium ylide **IM3**, a feasible intermediate with a relative energy of -32.5 kcal·mol⁻¹, via transition state **TS1**. A concerted asynchronous process in terms of the formation of the C–C and C–N bonds was calculated at the B3LYP/6-311++G** level. The predicted barrier of 8.0 kcal/mol is consistent with a reaction that proceeds at ambient temperature. The second stepwise pathway was found via a UB3LYP calculation employing the 6-311++G** basis set to afford diradical intermediate **IM2**,²⁷ leading to **IM3** via cyclization through **TS2**. It is noteworthy that both pathways share the common closed-shell transition state **TS1**, which does not exhibit diradical character. To probe the possibility of an open-shell process and the involvement of a diradical species, the reaction of model substrate **3e** was performed in the presence of TEMPO; however, no radical species could be trapped, i.e., so far we were unable to experimentally confirm **IM2**.²⁸ The last process from **IM3** is protonation and hydrolytic removal of the Boc group en route to the final product **4** with a large energy gain of -83.6 kcal/mol. Considering the resonance structure of ylide **IM3** (Figure 1b), whose C2–N bond is the longest (1.63 Å) among all the C–N bonds connected to the cationic nitrogen atom, one might expect a possible contribution from free carbene **IM3'**, which was indeed experimentally observed (*vide infra*).

We initially assumed that the C2 carbon center in the intermediate indolium ylide (e.g., **IM3**; Figure 1) would exhibit only nucleophilic character given the reactivity of reported congeners such as a thiophenium ylide⁹ and a pyrrolium ylide.¹³ However, the reaction of *o*-bromoaryl tosylate **13**, which bears a pendant *N*-tosylamide moiety, demonstrated that it could also act as an electrophile (Scheme 4a). Upon generation of the corresponding benzyne by treatment of **13** with Ph₃MgLi (THF, -20 °C), 2-phenylindole **14** was isolated and identified as the

major product.²⁹ This unexpected result suggests that after the cycloaddition, intermediate vinylidene **15**, i.e., the resonance structure of the corresponding indolium ylide (*vide supra*), undergoes nucleophilic addition at C2 by a phenyl anion, i.e., Ph₃MgLi and/or Ph₂Mg, followed by intramolecular S_N2 displacement on the nitrogen atom to liberate a sulfinate ion.³⁰ This notion is supported by two intriguing observations that reflect the key carbene reactivity.³¹ The first is that vinylidene **17**, which is generated from dibromostyrene **16** via Br–Li exchange with Ph₃MgLi followed by α -elimination, is able to form 2-phenylindole **18** in the same manner (Scheme 4b). The second is the results of the reaction of benzyne with an internal *N*-alkynylindole moiety, which is a congener of ynamides (Scheme 4c). Upon treatment of bromoaryl tosylate **19** with Ph₃MgLi (THF, 0 °C, 30 min), the (3+2) cycloaddition afforded the corresponding vinylidene intermediate **20**, which underwent facile intramolecular C–H insertion reaction at C2 to give pentacyclic product **21** in 69% yield.³²

In summary, we have demonstrated an unprecedented intramolecular benzyne–ynamide cycloaddition with a broad substrate scope, thus expanding the synthetic utility of ynamides as three-atom components. The present study revealed that the key (3+2) cycloadduct, i.e., the indolium ylide, exhibits an unprecedented carbene-like reactivity, which highlights their synthetic potential in the realm of heterocyclic chemistry. Further investigations along these lines are currently in progress in our laboratories.



Scheme 4. Control experiments. [a] **13** (1.0 equiv), Ph₃MgLi [3.3 equiv., dropwise (0.82 equiv/h)], THF, -20 °C, 4 h. [b] **16** (1.0 equiv), Ph₃MgLi (3.3 equiv), THF, 0 °C, 30 min. [c] **19** (1.0 equiv), Ph₃MgLi (2.2 equiv), THF, 0 °C, 30 min.

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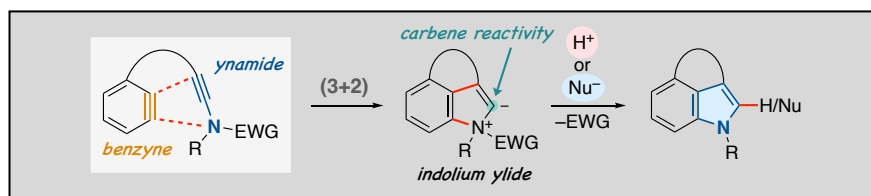
Keywords: benzyne · nynamides · heterocycles · cycloaddition · ylides

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- [29] The corresponding phenyl adduct **S38** (11%) and 2-tosylindole **S37** (7%) resulting from 1,2-migration of the *N*-tosyl group were identified as other byproducts. For details including other substrates in this context, see the Supporting Information.
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The intramolecular (3+2) cycloaddition reactions involving benzyne and ynamides as three-atom components have been accomplished through the utilization of benzyne precursors furnished with a linking functionality. The ambivalent nature of the intermediate indolium ylide, which exhibits both nucleophilic and electrophilic properties at its C2 atom, is thus brought to light via this approach.

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