Indole Synthesis

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Zirconium-Catalyzed Multistep Reaction of Hydrazines with Alkynes: A Non-Fischer-Type Pathway to Indoles**

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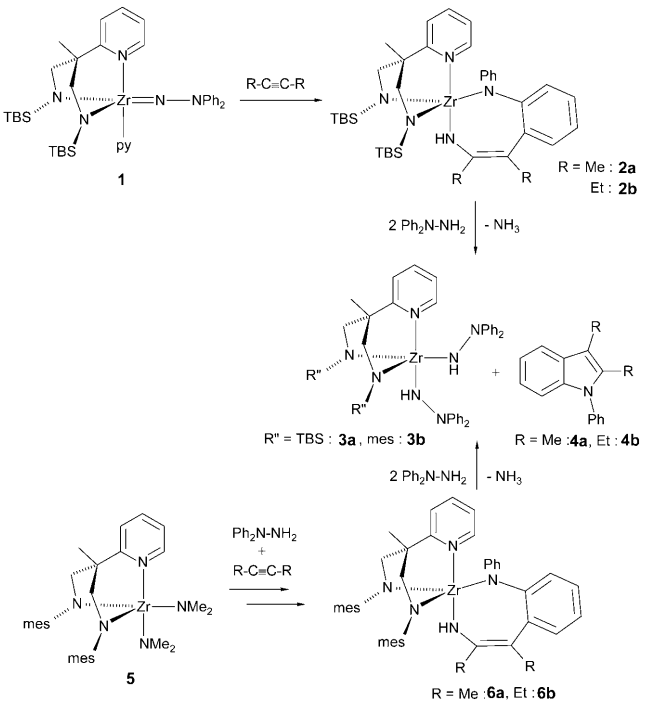
The combined formation and scission of several chemical bonds in one process, frequently referred to as a "domino reaction", is the key to the assembly of complex molecules in just a few reaction steps.[1,2] For these transformations there are relatively few examples of early-transition-metal catalysts, in particular from Group 4. Examples include the titanium-catalyzed syntheses of N-heterocycles reported by Odom, Beller, and others,[3–6] involving a catalytic hydrohydrazination of an alkyne and subsequent transformations of the resulting hydrazones, which may either occur by direct coupling with other unsaturated organic substrates[3] or a Fischer-type conversion to indoles.[5] Little is known about the reaction mechanisms of these transformations although the stoichiometric reactivity of titanium hydrazides is the subject of growing interest.[7] The reactivity of their zirconium analogues is dominated by facile N–N bond scission which appears to precede C–N and related coupling steps, as first demonstrated by Bergman and co-workers in 1991 for $[Cp_2Zr(N_2Ph_2)(dmap)]$ ($Cp = C_5H_5$, dmap = 4-dimethylaminopyridine).[8] We explored the scope of the hydrazinediidozirconium complex $[Zr(N_2{}^{TBS}N_{py})(NNPh_2)(py)]$ (**1**)[9] in stoichiometric and catalytic transformations of alkynes and other unsaturated substrates analogous to those reported for titanium. We observed strikingly different reaction pathways, characterized by the absence of a hydrohydrazination step in favor of early N–N bond cleavage. Here we report the catalytic transformation of alkynes and diarylhydrazines to indoles through a non-Fischer-type reaction cascade.

Reaction of one equivalent of $[Zr(N_2{}^{TBS}N_{py})(NNPh_2)(py)]$ (**1**)[9a] with the disubstituted alkynes R-C≡C-R (R = Me, Et) leads to the formation of seven-membered diazazirconacycles **2a**,**b** (Scheme 1), which are closely related to the Cp_2Zr-derived complexes reported by Bergman et al.[8] The zirconacycles result from a scission of the N–N bond and the coupling of the alkyne with one of the phenyl rings of the diphenylhydrazinediide, involving a formal C–H activation step. The corresponding metallacyclic complexes **6a**,**b** containing an N-arylated ancillary tripod ligand were obtained by reaction of the (bis)dimethylamido complex **5**[10] with one molar equivalent of both the alkyne and diphenylhydrazine.



Scheme 1. Reaction of the hydrazinediido complex **1** or alternatively the zirconium hydrazide, which is formed in situ from **5** and Ph_2NNH_2, with alkynes to yield the metallacyclic compounds **2a**,**b** and **6a**,**b**; these undergo hydrazinolysis to give the bis(hydrazides) **3a**,**b** and indoles **4a**,**b**. TBS = *tert*-butyldimethylsilyl, mes = mesityl.

The molecular structures of the metallacyclic complexes were established by X-ray diffraction for complexes **2b** and **6a** (Figure 1).[11] The coordination geometry of the complexes is best described as distorted trigonal bipyramidal. The chelating bisamide fragment within the puckered metallacyclic unit, which is generated by the N–N cleavage and C–C coupling of the alkyne and one of the N-phenyl groups of the hydrazinediide, occupies one equatorial and one axial position at the metal; the bulky diarylamide is bonded in the equatorial position and the small primary amide in the sterically more crowded axial position. The C–C and C–N distances are consistent with the structural assignment in Scheme 1.

Reaction of compounds **2a**,**b** and **6a**,**b** with two molar equivalents of diphenylhydrazine gave the corresponding bis{hydrazido(1−)} complexes **3a**,**b** as well as one equivalent of 1-phenyl-2,3-dimethylindole (**4a**) and 1-phenyl-2,3-diethylindole (**4b**). Since bis(hydrazido) complexes such as **3a**,**b** may be employed as precursors in the generation of hydrazine-

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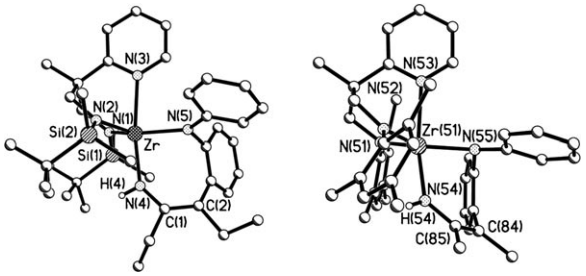


Figure 1. Molecular structures of complexes **2b** (left) and **6a** (right). The asymmetric unit of **6a** contains two independent molecules. Because of their similarity only one of the two independent molecules is shown. Bond lengths and angles of the second molecule are given in square brackets. Selected bond lengths [Å] and angles [°] for **2b**: Zr(1)–N(4) 2.0983(15), Zr(1)–N(5) 2.1304(15), C(1)–N(4) 1.3925(19), C(1)–C(2) 1.359(2); N(3)-Zr-N(4) 171.30(4), N(4)-Zr-N(5) 87.40(5), Zr-N(4)-C(1) 137.02(10), Zr-N(4)-C(1)-C(2) −44.1(2). Selected bond lengths [Å] and angles [°] for **6a**: Zr(51)–N(54) 2.106(2) [2.112(2)], Zr(51)–N(55) 2.113(9) [2.113(2)], C(85)–N(54) 1.394(3) [1.388.3], C(84)–C(85) 1.350(3) [1.348(3)]; N(53)-Zr(51)-N(54) 160.73(7) [160.73(7)], N(54)-Zr(51)-N(55) 84.72(7) [84.22(7)], Zr(51)-N(54)-C(85) 135.26(16) [135.13(15)], Zr(51)-N(54)-C(85)-C(84) −43.9(3) [−34.7(3)]. Hydrogen atoms, except those on the amido N atoms, are omitted for clarity.

diido compounds,[12] the reaction sequence leading to the indoles was thought to be potentially part of a catalytic cycle for the direct generation of substituted indoles from alkynes and hydrazines via metallacyclic intermediates such as **2a**,**b** and **6a**,**b**, thus without involving hydrazones and subsequent Fischer-type transformations. Reaction of 1.2 equivalents of diphenylhydrazine and various substituted alkynes (1 equiv) at ambient temperature in the presence of 10 mol% [Zr($N_2^{xyl}N_{py}$)(NMe_2)$_2$] (**7**), the more reactive N-xylylated analogue of **5**, gave the corresponding indole derivatives listed in Table 1. For nonsymmetrical disubstituted alkynes the indole with the bulkier substituent in the 3-position was the major product (entries 2 and 5), whilst terminal alkynes exclusively gave the indole substituted in 3-position (entries 4 and 6).

A non-Fischer reaction pathway to the indoles, which does not involve hydrazone intermediates, raised the question of the mechanism of the transformation of the hydrazinediide **1** to metallacycles of the type represented by **2a**,**b** in Scheme 1. The reaction of the perdeuterated diphenylhydrazinediide, which was also ^{15}N-labeled in the N_α position, with EtC≡CEt cleanly gave the corresponding metallacycle with the enamido N atom fully ^{15}N-labeled and completely deuterated, thus clarifying the origin of the NH group (see the Supporting Information). Since exchange with solvent hydrogen or deuterium atoms was not observed, this rearrangement is assumed to be intramolecular.

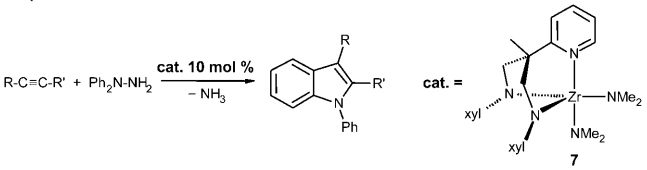
A detailed kinetic study of the reaction of **1** with EtC≡CEt revealed the pyridine dissociation pre-equilibrium:

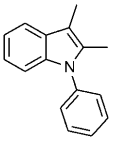
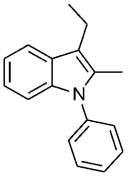
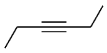
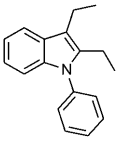
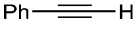
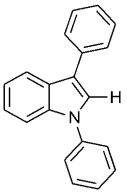
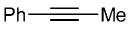
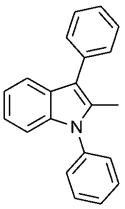
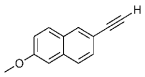
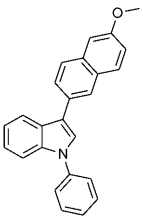
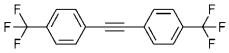
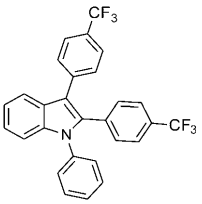
$$[Zr(N_2^{TBS}N_{py})(NNPh_2)(py)] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Zr(N_2^{TBS}N_{py})(NNPh_2)] + [py]$$

$$[Zr(N_2^{TBS}N_{py})(NNPh_2)] + [hexyne] \xrightarrow{k_2}$$

$$[Zr(N_2^{TBS}N_{py})\{\kappa^2N\text{-}(Ph)N\text{-}C_6H_4\text{-}C(Et)=C(Et)NH\}]$$

Table 1: Catalytic indole syntheses of diphenylhydrazine with various alkynes.[a]



Entry	Alkyne	Indole	r.r.[b]	Yield [%][c]
1			–	84
2			2:1[d]	59
3			–	36
4			>9:1[d]	74
5			2:1[d]	56
6			>9:1[d]	56
7			–	11

[a] Reaction conditions: alkyne (1.2 mmol), diphenylhydrazine (1.44 mmol), 10 mol% [Zr($N_2^{xyl}N_{py}$)(NMe_2)$_2$], 24 h in 2 mL of toluene at ambient temperature. [b] r.r. = Ratio of regioisomers determined by ^{1}H NMR spectroscopy. [c] Yields of isolated products determined after chromatographic workup. [d] Major isomer shown.

and a subsequent rate-determining step, which is represented by the following rate law:

$$\frac{-d[Zr(N_2^{TBS}N_{py})(NNPh_2)(py)]}{dt} = \frac{k_1 k_2 [Zr(N_2^{TBS}N_{py})(NNPh_2)(py)][hexyne]}{k_{-1}[py] + k_2[hexyne]}$$

The observation of saturation phenomena kinetics for high concentrations of alkyne (see the Supporting Information) confirms the existence of the pre-equilibrium whilst the activation parameters of the rate-determining step were determined to be $\Delta H^{\neq} = (11.5 \pm 0.7)$ kcal mol^{-1} and $\Delta S^{\neq} = (-45 \pm 10)$ cal mol^{-1} K^{-1} and thus a free enthalpy of activation for the rate-determining step of $\Delta G_{275}{}^{\neq} = (24 \pm 2)$ kcal mol^{-1}. Reaction of a derivative of complex **1**, in which one of the two phenyl rings at N_β was perdeuterated, with 0.5 equivalents of 3-hexyne gave a reaction product with an NH/ND distribution of 1:1, indicating $k_H/k_D = 1$ and thus the absence of a kinetic isotope effect. This implied that neither the C–H bond cleavage nor the H-atom rearrangement with formation of the N–H bond are involved in the rate-determining step.

In order to obtain deeper insight into the reaction cascade leading to the key metallacycles **2a**,**b** and **6a**,**b**, and taking the experimental evidence outlined above into account, we modeled the mechanism by DFT (B3PW91) in detail,[13] exploring the potential reaction pathways of the reaction of the zirconium complex $[Zr(N_2^{TBS}N_{py})(NNPh_2)(py)]$ (**1**) with 2-butyne.

First, the [2+2] cycloaddition of 2-butyne to the {Zr=N} unit, a reaction step that has been studied in detail for Ti hydrazides,[7e] was modeled (Figure 2: **I**→**IV**). This conversion was found to occur without prohibitive energetic barriers, giving rise to the metallacyclic intermediate **IV**. In a subsequent rate-determining step the N–N bond is broken and the "azaallyl" species **V** is formed; in this step the calculated activation barrier of $\Delta G^{\neq} = 21$ kcal mol^{-1} for the reaction with 2-butyne is close to the experimental value of (24 ± 2) kcal mol^{-1} observed for the sterically more demanding 3-hexyne. No pathways from intermediate **V** to the reaction products with a low activation barrier were found in a systematic search of the active conformational and configurational space. However, the rearrangement of **V** to the energetically only slightly (by $\Delta G = 2.6$ kcal mol^{-1}) disfavored constitutional isomer, the dimethylazirinido complex **VI** (Figure 3), allows the subsequent transformation without prohibitive activation barriers.

We note that a species such as **VI** has been postulated by Mindiola to explain the insertion of alkynes into the N–N bonds of titanium hydrazinediides.[14] Whilst this was not confirmed in computational studies on the titanium systems,[7e] it clearly represents a key intermediate for the reaction sequence involving the zirconium complex reported in this work. Intermediate **VI** is converted into the seven-membered metallacyclic complex **VIII** (Figure 4) by nucleophilic attack of a carbon atom in the *ortho* position of a phenyl ring of the NPh_2 fragment at one of the (electrophilic) carbon atoms of the metalated azirine ring to form intermediate **VII** ($\Delta G = -20.7$ kcal mol^{-1}) via transition-state **TS(VI–VII)**, which has a relatively low activation barrier ($\Delta G^{\neq} = 19.8$ kcal mol^{-1}).

The notion of an electrophilic attack at the N-phenyl ring is supported by the observation that the analogous reaction of 2-butyne with a diphenylhydrazine derivative, in which one of the phenyl rings is *para*-fluoro-substituted [Eq. (1)], exclusively leads to the metallacyclic product **6c**, which results from the coupling of the more-electron-rich unsubstituted aryl ring.

Finally, the exergonic 1,4 proton shift ($\Delta G = -59.2$ kcal mol^{-1}) via a low-lying transition state gives the metallacyclic complex **VIII** (=**2a**). The pathway as represented in Figures 2–4 is consistent with the experimentally observed rate law, the absence of a kinetic H/D isotope effect, the magnitude of the activation barrier, and the established

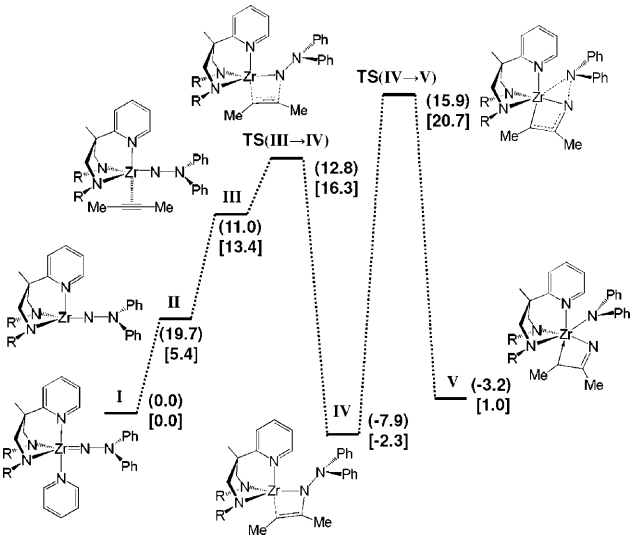


Figure 2. Reaction profile (DFT, B3PW91) of the cycloaddition of 2-butyne to the hydrazinediido unit in **1** (**I**→**IV**) and the subsequent (rate-determining) N–N bond scission to give the diphenylamido-(azaallyl) intermediate **V** (R = TBS). Energies are given in parentheses, free energies in square brackets.

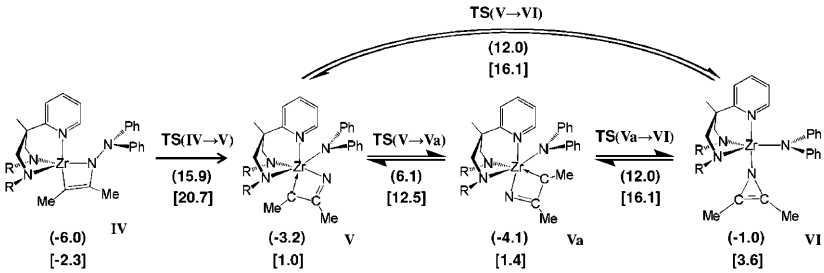


Figure 3. Reaction profile (DFT, B3PW91) of the transformation of the [2+2] cycloaddition product **IV** to the isomeric azaallyl intermediates **V** and **Va** and to the key 2,3-dimethyl-azirinido species **VI** (R = TBS). Energies are given in parentheses, free energies in square brackets.

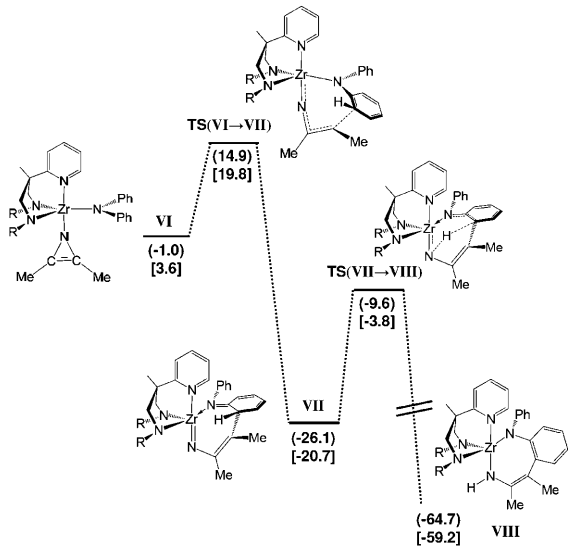
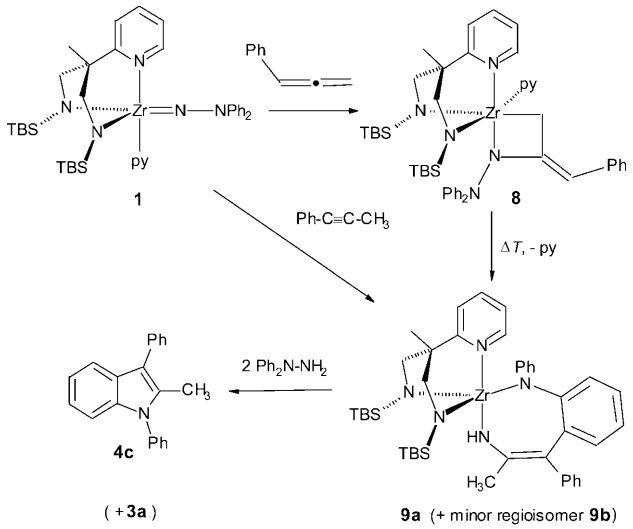
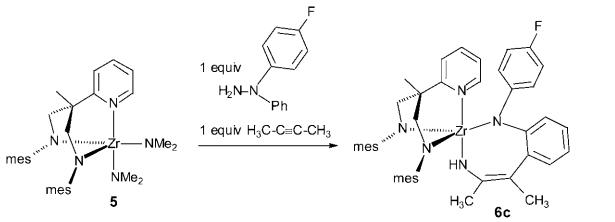


Figure 4. Reaction profile (DFT, B3PW91) of the transformation of the 2,3-dimethylazirinido species **VI** to the metallacycle **VIII** (R = TBS). Energies are given in parentheses, free energies in square brackets.



Scheme 2. Reaction of complex **1** with phenylallene to yield the [2+2] cycloaddition product **8** and its thermal rearrangement to the metallacyclic compound **9a** (+**9b** as a minor regioisomer).



(1)

intramolecular migration of a hydrogen atom from a phenyl ring of the hydrazine to the NH unit in metallacycles **2a**,**b** and **6a**,**b**.

A notable variation of the reaction scheme is observed upon reaction of **1** with phenylallene giving the [2+2] cycloaddition product **8** (Scheme 2). Its molecular structure, determined by X-ray diffraction, is depicted in Figure 5. Complex **8** is the first structurally characterized example of a [2+2] cycloaddition product to a hydrazinediidozirconium unit; similar cycloaddition products have been obtained previously with titanium hydrazides.[7]

Heating complex **8** for 5 h to 80 °C yielded the seven-membered zirconacycle **9a**,**b** as a mixture of regioisomers (also accessible by reaction of **1** with 1-phenylpropyne) which could also be converted to the corresponding indole **4c** by reaction with diphenylhydrazine. That the conversion of **8** to **9a**,**b** occurs intramolecularly and not through cycloreversion was established by a crossover experiment in which the thermal transformation was carried out in the presence of a 100-fold excess of $PhC{\equiv}CCD_3$; no deuterium was found in the resulting metallacycle. The reaction of phenylallene with diphenylhydrazine to give **4c** could also be carried out catalytically using 10 mol% $[Zr(N_2^{xyl}N_{py})(NMe_2)_2]$ (**7**). The observation of the same intermediate **9a** and product **4c** upon when **1** was reacted with either 1-phenylpropyne or phenylallene suggests that the common reaction intermediate **VIa** leads to the metallacyclic product **9a** (Scheme 3). Complex **VIa** is the analogue of the zirconated azirine **VI** in Figures 3

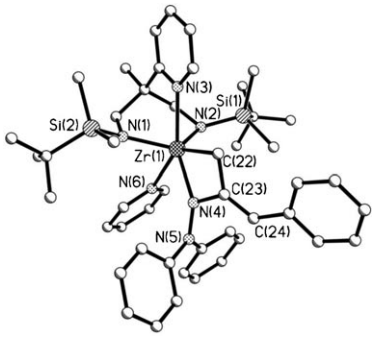
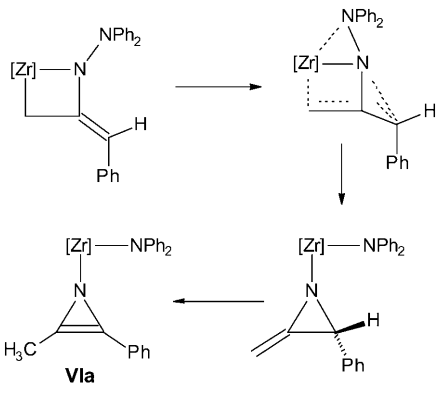


Figure 5. Molecular structure of complex **8**. Selected bond lengths [Å] and angles [°]: Zr(1)–N(4) 2.1830(12), Zr(1)–C(22) 2.3341(14), N(4)–N(5) 1.4150(15), C(22)–C(23) 1.4946(18), C(23)–N(4) 1.3950(16), C(23)–(C24) 1.3608(18); Zr(1)-C(22)-C(23) 56.0(6), Zr(1)-N(4)-N(5) 139.55(8), C(24)-C(23)-N(4) 124.5(11), N(3)-Zr(1)-N(6) 140.93(4). Hydrogen atoms are omitted for clarity.



Scheme 3. Proposed pathway for the rearrangement of **8** to the 2-methyl-3-phenylazirinido species **VIa**, the key intermediate in the transformation to the metallacyclic compound **9a**.

and 4. A preliminary computational study has revealed that the rearrangement of the primary [2+2] cycloaddition product **8** to a **VI**-type species is viable.

In the few examples of zirconium-catalyzed domino reactions in the literature[15] the metal appears to act primarily as a Lewis acid, though mechanistic details have not been established. The reaction of hydrazines with alkynes reported herein proceeds along a complex pathway in which the metal stabilizes a range of reactive intermediates distinct from those found for titanium-catalyzed hydrohydrazinations. This capability merits the development of further applications of the heavier Group 4 metals in the synthesis of N-heterocycles.[16]

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Keywords: C–N coupling · homogeneous catalysis · indoles · reaction mechanism · zirconium

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