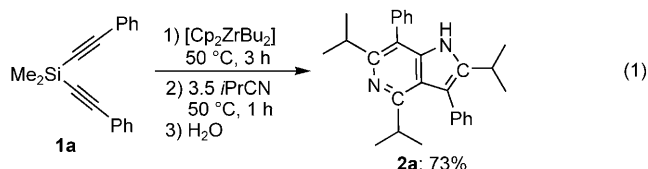


Reaction Mechanisms

Zirconium- and Silicon-Containing Intermediates with Three Fused Rings in a Zirconocene-Mediated Intermolecular Coupling Reaction**

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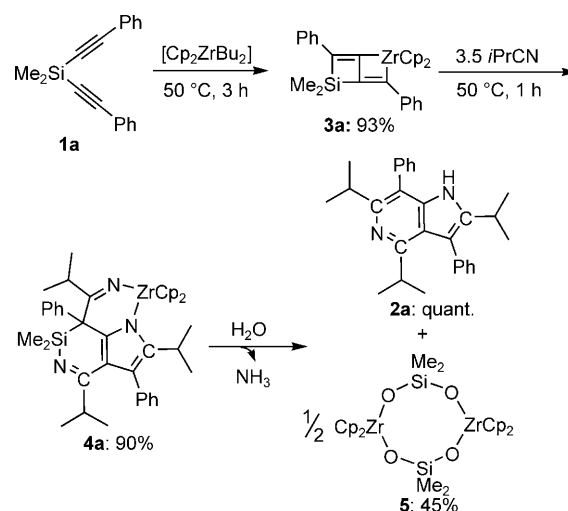
The isolation and reactivity of important intermediates in transition-metal-mediated reactions are of interest in both organometallic and synthetic organic chemistry. Studies of these intermediates not only play an important role in the in-depth understanding of seemingly complicated reaction mechanisms, but can also lead to the discovery of new synthetically useful reactions. We have reported a zirconocene-mediated intermolecular coupling reaction of one molecule of a silyl-tethered diyne with three molecules of organonitriles, which afforded pyrrolo[3,2-c]pyridine derivatives (5-azaindoles) upon hydrolysis of the reaction mixture [Eq. (1)].^[1,2]



The most interesting feature of this above one-pot reaction is that five components are involved and integrated in a perfect selective manner via an unknown pathway, which tempted us to investigate what is really going on.^[3] We anticipated that novel and important reaction patterns might be involved. Indeed, we have now finally discovered that the process that combines all the five components together is very unusual, unpredictable, and of general importance to metal-mediated reactions involving the cleavage of $\text{C}\equiv\text{N}$ triple

bonds and Si–C bonds.^[4] Complicated reactive intermediates were found to be formed by surprising mechanisms. Synthetically useful applications of these reactive intermediates were also achieved based on deep understanding of the reaction mechanism.

The first reaction step between $[\text{Cp}_2\text{ZrBu}_2]$ ^[5] and 1a, as previously reported by Takahashi and co-workers,^[6] generates a zirconacyclobutene–silacyclobutene fused complex 3a (Scheme 1).^[6,7] To investigate the reaction mechanism in a



Scheme 1. Formation of zirconocene-containing intermediate 4a and its reaction with water.

pure and controllable system, we prepared and successfully isolated the intermediate 3a in 93% yield by a modified procedure.^[8] Then, 3.5 molar equivalents of $i\text{PrCN}$ was added to a toluene solution of 3a. After the reaction mixture was stirred at 50 °C for 1 h, a red powder was isolated in 90% yield, which was confirmed to be the unexpected complex 4a (Scheme 1).

Single crystals of 4a suitable for X-ray analysis were grown in benzene at room temperature. X-ray analysis of 4a (Figure 1) reveals that it consists of three fused rings: one six-membered ring containing silicon and nitrogen, one five-membered pyrrolo ring, and one six-membered zirconacycle.^[9] The zirconium center is bonded to two cyclopentadienyl (Cp) rings, one imine nitrogen atom, and one nitrogen of the pyrrolo ring. The silicon atom is bonded to one quaternary carbon atom, one imine nitrogen atom, and two methyl groups. Two imine carbon atoms neighboring the silicon and zirconium atoms in 4a result in a singlet at $\delta =$

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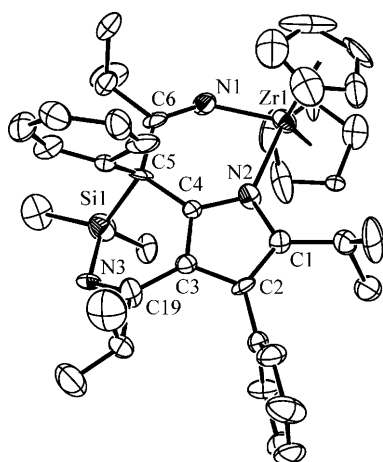


Figure 1. ORTEP of **4a** with ellipsoids set at 30% probability; hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: Zr1–N1 1.953(6), Zr1–N2 2.205(5), Si1–N3 1.752(8), Si1–C5 1.854(14), C1–C2 1.367(9), C2–C3 1.426(8), C3–C4 1.375(8), C3–C19 1.438(9), C4–C5 1.516(9), C5–C6 1.523(9), N1–C6 1.240(8), N3–C19 1.376(14).

183.9 and 188.2 ppm in the ^{13}C NMR spectrum in $[\text{D}_6]\text{benzene}$, and the quaternary carbon atom neighboring the silicon atom gives rise to a singlet at $\delta = 60.6$ ppm.

Hydrolysis of **4a**, after isolation, with 1–3 equiv of water afforded the corresponding pyrrolo[3,2-*c*]pyridine derivative **2a** in quantitative yield. Along with **2a**, formation of NH_3 in the reaction solution was detected using in-situ ^1H NMR spectra. Furthermore, the whereabouts of the $\{\text{Cp}_2\text{Zr}\}$ and the Me_2Si moieties was determined by successful isolation of the cyclic zirconasiloxane **5**, which was obtained in 45% yield of isolated product (the maximum yield is 50%). Compound **5** formed crystals suitable for X-ray structural analysis (Figure 2).^[9]

To understand the reaction mechanism, one more important question still remained. How is **4a** formed from the reaction of **3a** with *i*PrCN? To obtain intermediates in between, we decreased the amount of *i*PrCN to 1.5 equiv. We found after several trials that the tolyl substituent was better

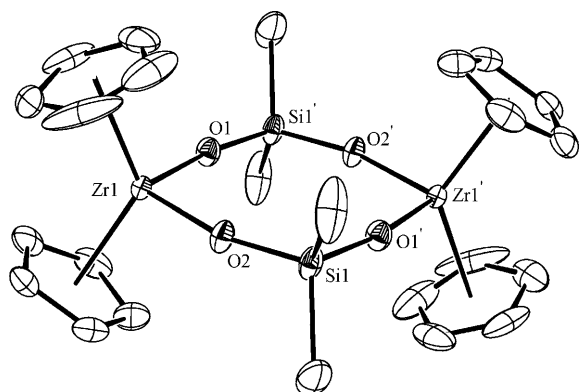
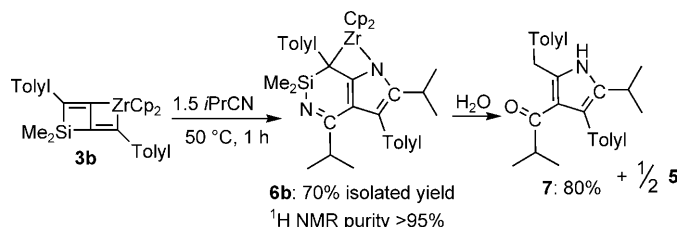


Figure 2. ORTEP of **5** with ellipsoids set at 30% probability; hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: Zr1–O1 1.9632(19), Zr1–O2 1.965(2), Si1–O2 1.612(2). Symmetry-equivalent atoms (') are given by $-x+1, -y, -z+1$.

than phenyl groups for this purpose. As was the case for the isolation of **3a**, we were successful in isolation and characterization of the intermediate **3b**, which forms orange crystalline solids in 95% yield of isolated product.^[8] A green solid **6b** was formed in 70% yield by the reaction of **3b** with 1.5 equiv of *i*PrCN at 50 °C for 1 h (Scheme 2). Although single crystals of

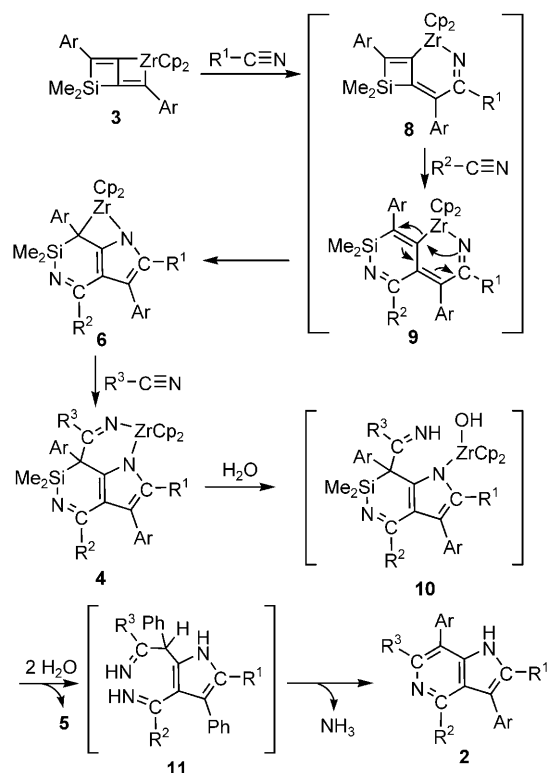


Scheme 2. Formation of **6b** and its reaction with water.

6b suitable for X-ray crystallographic analysis were not obtained, its ^1H and ^{13}C NMR data were rather informative for the elucidation of the structure. The imine carbon atoms in **6b** gave rise to a singlet at $\delta = 181.5$ ppm, and the quaternary carbon atom linked by the zirconium and the silicon atom led to a singlet at $\delta = 80.9$ ppm in the ^{13}C NMR spectrum in $[\text{D}_6]\text{benzene}$. Hydrolysis of **6b** with 1–3 equiv of H_2O gave the compound **7** in 80% yield after short-column chromatography. The cyclic zirconasiloxane **5** was also obtained in 45% yield of isolated product (the maximum yield is 50%). Formation of **7** in this hydrolysis process strongly supported a tricyclic structure of **6b** consisting of one six-membered ring containing silicon and nitrogen, one five-membered pyrrolo ring, and one four-membered zirconacycle bearing a reactive quaternary carbon center.

We propose a reaction mechanism for the formation of pyrrolo[3,2-*c*]pyridine based on all of the above experimental results (Scheme 3).^[10] Insertion of the $\text{C}\equiv\text{N}$ triple bond of the first organonitrile R^1CN into one of the $\text{Zr}-\text{C}$ bonds of **3** would afford the intermediate **8**, which might immediately undergo insertion of the $\text{C}\equiv\text{N}$ triple bond of the second organonitrile R^2CN into one of the $\text{Si}-\text{C}$ bonds to afford **9**. This intermediate **9** is thermodynamically unstable and would undergo skeletal rearrangement by a 1,2-shift of the $\{\text{Cp}_2\text{Zr}\}$ moiety in the azazirconacyclic ring to afford the key intermediate **6**, which is stable enough at room temperature and could be characterized by ^1H and ^{13}C NMR. Although the proposed intermediates **8** and **9** could not be characterized owing to the fast insertion of the $\text{C}\equiv\text{N}$ bonds to both $\text{Zr}-\text{C}$ and $\text{Si}-\text{C}$ bonds and the skeletal rearrangement, the insertion chemistry of the $\text{C}\equiv\text{N}$ triple bond of organonitriles into $\text{Zr}-\text{C}$ bonds to afford azazirconacycles^[11–16] and into $\text{Si}-\text{C}$ bonds^[17] has been documented. Insertion of the $\text{C}\equiv\text{N}$ triple bond of the third organonitrile R^3CN to the $\text{Zr}-\text{C}$ bond in **6** would lead to the formation of **4**.

A proposed hydrolysis process of **4** that rationalizes the formation of NH_3 , **2**, and **5** is also shown in Scheme 3 (see Supporting Information for more details). Intermediate **10** might be formed by cleavage of the $\text{Zr}-\text{N}$ (imine) bond in **4** by the first molecule of water. Intermediate **10** can then undergo

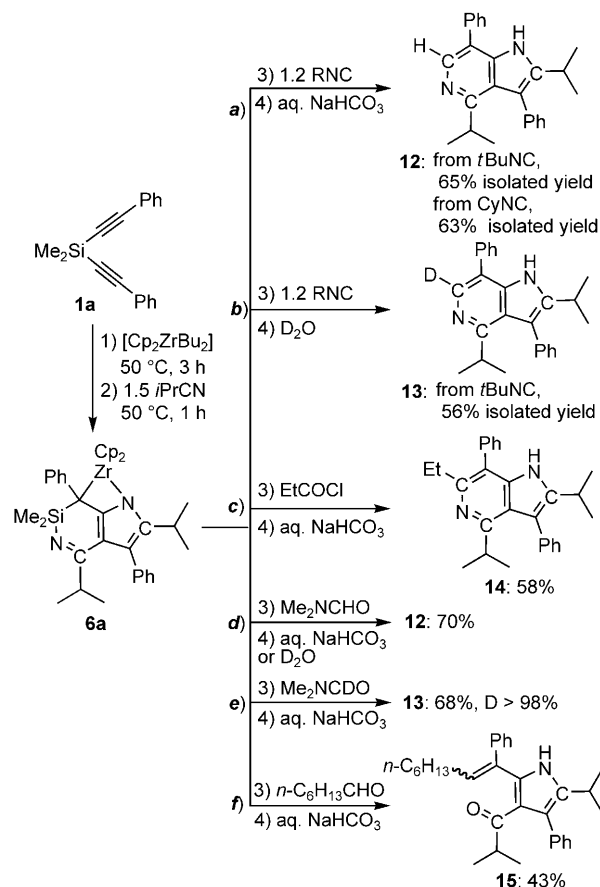


Scheme 3. A proposed reaction mechanism involving one silicon-atom-tethered diyne and three organonitriles.

further hydrolysis with two molecules of water to afford the diimine **11** along with loss of **5**, which is formed through coupling of Me_2SiOH and Cp_2ZrOH molecules. The final product **2** was generated by the cyclization of the diimine **11** along with loss of NH_3 . Such a diimine cyclization producing a pyridine ring has been reported.^[11]

From the proposed reaction mechanism, we expected that the intermediate **6** could be reacted further. Therefore, a wide variety of substrates, such as isocyanides, formamides, acid chlorides, aldehydes, carbon monoxide, and alkynes, were used in place of R^3CN in a one-pot process. Although carbon monoxide and alkynes (including diphenylacetylene, DMAD, and 4-octyne) do not show useful reactivity, many other substrates, such as isocyanides, formamides, acid chlorides, and aldehydes, did undergo interesting reactions and resulted in synthetically useful methods for more diversified structures of *N*-containing compounds. Representative applications of intermediate **6a** are summarized in Scheme 4.

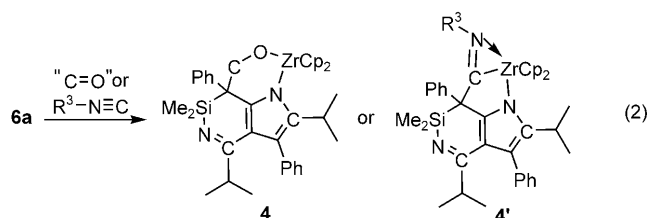
A new type of pyrrolo[3,2-*c*]pyridine derivative **12** having a hydrogen at position 6 was obtained upon hydrolysis with saturated aqueous NaHCO_3 (Scheme 4a). It is noteworthy that only one carbon atom from $\text{C}\equiv\text{N}-\text{R}$ was integrated into the newly formed carbon–hydrogen bond. The hydrogen atom originated from the hydrolysis process, because deuteration of the reaction mixture with D_2O could afford the deuterium-labeled product **13** (Scheme 4b). Reaction of the acid chloride EtCOCl with **6a** generated in situ provided its corresponding azaindole **14** in 58% yield of isolated product (Scheme 4c). When a formamide Me_2NCHO was used in the



Scheme 4. Further applications of intermediate **6a**.

above one-pot process (Scheme 4d), azaindole **12** was surprisingly obtained in 70% yield upon hydrolysis with saturated aqueous NaHCO_3 . When hydrolyzed with D_2O instead of saturated aqueous NaHCO_3 , **12** was again obtained in a similar yield; the deuterium-labeled product **13** was not formed. We then used Me_2NCDO instead of Me_2NCHO ; hydrolysis of the reaction mixture with aqueous NaHCO_3 afforded the deuterated product **13** in 68% yield with $\text{D} > 98\%$ (Scheme 4e). These results indicate that the CH or CD moiety of the carbonyl groups in formamides ($-\text{NHCHO}/-\text{NHCDO}$) is incorporated into the product. Other moieties in formamides were absent. When **6a** was treated with heptanal, formation of a new type of pyrrole derivative **15** was observed as a mixture of two isomers (Scheme 4f).

For all those above successful applications of intermediate **6a**, insertion of the unsaturated substrates into the $\text{Zr}-\text{C}$ bond in **6a** leading to the formation of **4** (in the case of isocyanide, 1,1-insertion would lead to **4'**) is most likely [Eq. (2)], and has been demonstrated in the reaction of **6a** with formamide Me_2NCHO . The key intermediate **4b** thus formed (yield of isolated product 86% as brown crystals) was characterized by X-ray single crystal structural analysis (See Supporting Information),^[9] which clearly shows the $\text{C}=\text{O}$ double bond of the formamide being inserted into the $\text{Zr}-\text{C}$ bond of **6a**. Hydrolysis of **4b** with aqueous NaHCO_3 gave azaindole **12** in a quantitative yield.



In summary, the isolation and structural information of three key Zr/Si-containing intermediates **4a**, **4b**, and **6b** were achieved in the zirconocene-mediated intermolecular coupling reaction. The fate of Me₂Si and Cp₂Zr moieties and the cleaved nitrogen of organonitrile was determined by characterization of zirconasiloxane **5** and ammonia, respectively. Furthermore, the reactivity of the intermediate **6** with a variety of unsaturated substrates, such as isocyanide, formamide, acid chloride, and aldehyde, are disclosed to provide synthetically useful methodology for diversified structures of *N*-containing compounds. This work demonstrates that the isolation and reactivity investigation of reactive organometallic intermediates are not only of importance and interest for the in-depth understanding of seemingly complicated reaction mechanisms, but can also lead to the discovery of new synthetic methods.

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- [8] This complex **3a** was prepared by a modified procedure using the reaction of the silicon-atom-tethered diyne with [Cp₂ZrBu₂] in toluene, and characterized by ¹H and ¹³C NMR spectroscopy and elemental analysis. Two sp² carbons attached to the zirconium center in **3a** resulted in singlets at δ = 202.8 and 248.8 ppm in the ¹³C NMR spectrum in [D₆]benzene. Complex **3b** was obtained for the first time in a manner analogous to that described for the synthesis of **3a**.
- [9] CCDC 652444 (**4a**), CCDC 733672 (**4b**·THF), and CCDC 656017 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For crystal data of **4a**, **4b**, and **5**, see the Supporting Information.
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