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One-Pot Selective Syntheses of 5-Azaindoles through Zirconocene-Mediated Multicomponent Reactions with Three Different Nitrile Components and One Alkyne Component

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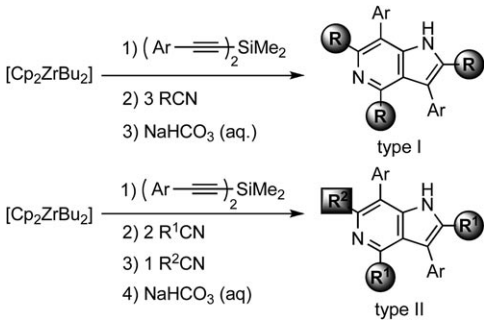
Abstract: 5-Azaindoles either with three different substituents at their 2-, 4-, and 6-positions or with two identical substituents at their 2- and 6-positions and a different one at the 4-position, were obtained in good to excellent isolated yields by a zirconocene-mediated multicomponent process. Each reaction involved four organic partners, comprising a Si-tethered diyne, one *t*BuCN component, and two (either different or identical) nitriles. All these four components were combined through the action of a Cp_2Zr^{II} species into a three-ring fused Zr/Si-containing organometallic complex in a perfectly chemo- and regioselective manner. This multicomponent reaction process consisted of three reaction steps, all of which were made clear through the isolation and characterization of their corresponding organometallic intermediates: the zirconacyclopropene-azasilacyclopentadienes **2**, the allenyl-aza-zirconacycles **3**, and the three-ring fused complexes **6**. X-ray single-crystal structural analyses of two three-ring fused Zr/Si-containing intermediates and two 5-azaindoles unambiguously showed the positions of the different substituents and the regioselectivity. Iminopyrrole derivatives could be also highly selectively prepared from a Si-tethered diyne and two different nitriles.

Keywords: 5-azaindoles · multicomponent reactions · nitriles · nitrogen heterocycles · zirconium

Introduction

The development of synthetic methods for azaindoles and pyrrole derivatives has attracted much attention because these heterocyclic compounds are of great importance in many areas.[1–8] Recently, we have developed a synthetic method for 5-azaindole derivatives.[9] As shown in Scheme 1, this method involved zirconocene-mediated intermolecular couplings of one Si-tethered diyne with three nitriles. Either three identical nitriles or two different nitriles could be used. The reactions were found to proceed in step-by-step fashion. When three identical nitriles were used, the reactions afforded 5-azaindoles with the same substituents (R) at the 2-, 4-, and 6-positions (type I). When two different nitriles were used, the first and the second substituents were the same, but the third one could be different. In these cases, the reactions generated 5-azaindoles with the same substituents (R^1) at the 2- and 4-positions and a different substituent (R^2) at the 6-position (type II).



Scheme 1. Previous work on the synthesis of 5-azaindoles of type I (the same substituents at the 2-, 4-, and 6-positions) and type II (the 2- and 4-positions with the same substituents and the 6-position with a different one). Different shapes around R^1, R^2 represent different substituents.

We have very recently disclosed a coordination-induced Zr–C/Si–C bond cleavage and reorganization reaction,[10] starting from the zirconacyclobutene-silacyclobutene ring-fused compound **1** (Scheme 2), first reported by Takahashi et al., which could readily be generated in situ in high yields through zirconocene-mediated reactions of Si-tethered diynes.[11–13] As shown in Scheme 2, *t*BuCN was found to behave both as an initiator and as a brake/release handle for initiation and control of the reaction process of **1**. The *t*BuCN-stabilized zirconacyclopropene-azasilacyclopenta-

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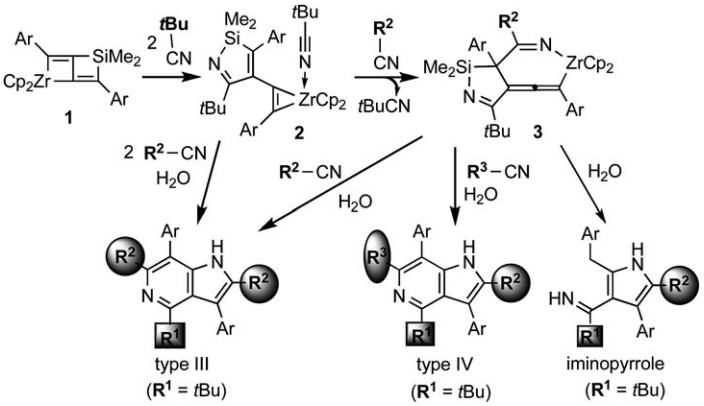
diene complexes **2** and the allenyl-aza-zirconacycles **3** were thus generated in high yields from *t*BuCN, a different nitrile RCN, a Si-tethered diyne, and the zirconocene species.[14–17] We believe that these two reactive organometallic intermediates **2** and **3** should be synthetically useful for the synthesis of heterocyclic compounds. Indeed in this work, as shown in Scheme 2, further reactions of these intermediates with nitriles were found to proceed smoothly through interesting insertions and skeletal rearrangements, providing useful synthetic methods for N-containing heterocyclic compounds. When the *t*BuCN-stabilized zirconacyclopropene-azasilacyclopentadiene complex **2** was treated with a single nitrile (2 equiv), the reaction generated a 5-azaindole with the same substituents (R^2) at the 2- and the 6-positions and a different substituent ($R^1 = t$Bu) at the 4-position (type III). The allenyl-aza-zirconacycle **3** was found to react with a third nitrile smoothly at higher temperature. A 5-azaindole of type IV, with three different substituents at the 2- (R^2), 4- (R^1), and 6-positions (R^3), was obtained in a high isolated yield upon hydrolysis of the reaction mixture.



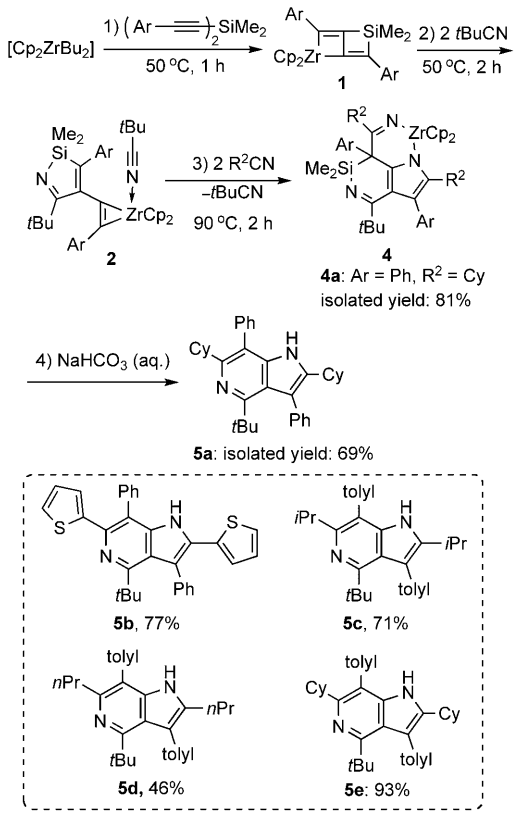
Scheme 2. This work: synthesis of 5-azaindoles of type III (the 2- and 6-positions with the same substituents and the 4-position with a different one) and type IV (2-, 4-, and 6-positions with three different substituents).

Iminopyrrole derivatives with all different substituents could also be prepared highly selectively. Two of the important three-ring fused Zr/Si-containing intermediates, each composed of a Cp_2Zr^{II} species, a Si-tethered diyne, one *t*BuCN, and two (different or identical) nitrile units, were isolated in high yields and characterized by single-crystal X-ray structural analysis, which unambiguously showed the positions of the different substituents and the regioselectivity.

Results and Discussion

Formation of 5-azaindoles

i) 5-Azaindoles of type III from one Si-tethered diyne, one t*BuCN component, and two identical nitrile units*: The zirconacyclobutene-silacyclobutene fused-ring compounds **1** could readily be generated in situ in high yields through zirconocene-mediated reactions of Si-tethered diynes.[9–12] When a compound **1** was treated with *t*BuCN (2 equiv), a *t*BuCN-stabilized zirconacyclopropene-azasilacyclopentadiene complex **2** was generated in high yield, as we had previously communicated.[10] In this work, treatment of **2a** (Ar = Ph) with CyCN (2 equiv) at 90 °C in benzene for 1 h afforded the three ring-fused compound **4a** (Ar = Ph, R^2 = Cy) in 81 % isolated yield (Scheme 3). The X-ray structure



Scheme 3. Formation of 5-azaindoles with the same substituents at the 2- and 6-positions and a different substituent at the 4-position (type III).

of **4a** clearly revealed that the *t*Bu group was located on the six-membered azasilacycle, adjacent to the *N*-silyl imine moiety (Figure 1). Hydrolysis of **4a** afforded the 5-azaindole derivative **5a** in 69 % isolated yield. As well as CyCN, other nitriles such as the aromatic nitrile 2-ThCN or the aliphatic nitriles *i*PrCN and *n*PrCN could be also applied to afford good to high yields of the 5-azaindoles **5b**, **5c**, **5d**, and **5e**, with the same substituents (R^2) at the 2- and the 6-positions and a different substituent (*t*Bu) at the 4-position (type III). The mechanism of the hydrolysis of the intermediates **4** to afford the 5-azaindoles **5** can be related to that proposed in our previous communication.[9c] The single-crystal X-ray structure of **5c** (Figure 2) again confirmed the location of the *t*Bu group at the 4-position of the azaindole, and the two cyclohexyl groups at the 2- and the 6-positions.

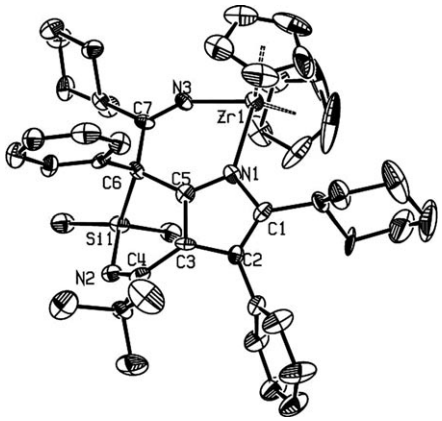


Figure 1. ORTEP drawing of **4a** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: Zr1–N1 2.262(6), Zr1–N3 1.999(6), Si1–N2 1.762(6), Si1–C6 1.967(7), C7–N3 1.231(8), C4–N2 1.283(9), C1–C2 1.374(9), C2–C3 1.422(9), C3–C5 1.415(9), C3–C4 1.497(10), C5–C6 1.575(9), C6–C7 1.546(9).

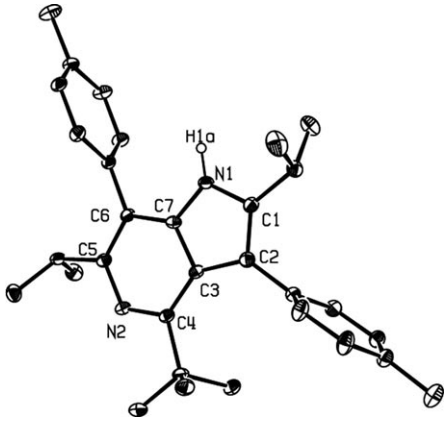
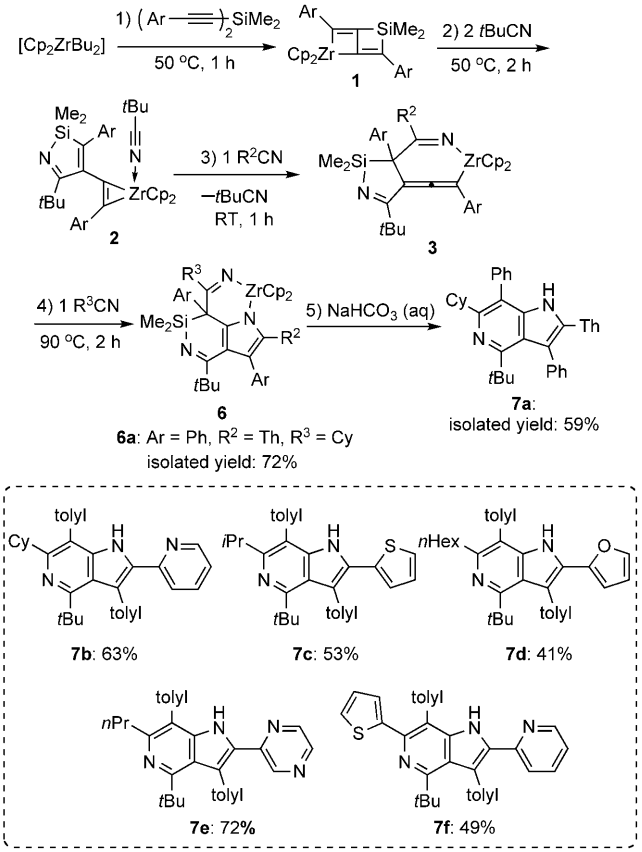


Figure 2. ORTEP drawings of **5c** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity except for the polar N–H bond. Selected bond lengths [Å]: N1–C1 1.378(3), N1–C7 1.371(3), N2–C4 1.340(3), N2–C5 1.362(3), C1–C2 1.371(3), C2–C3 1.461(3), C3–C7 1.417(3), C3–C4 1.427(3). C5–C6 1.386(3), C6–C7 1.386(3).

ii) 5-Azaindoles of type IV from one Si-tethered diyne, one t*BuCN, and two different nitriles*: When the allenyl-aza-zirconacycle **3a** (Ar = Ph, R^2 = Th, generated in situ) was treated with a third nitrile—CyCN—at 90 °C in benzene for 1 h, the reaction afforded the three ring-fused Zr/Si-containing compound **6a** (Ar = Ph, R^2 = Th, R^3 = Cy) in 72% isolated yield (Scheme 4). The structure of **6a** was characterized by single-crystal X-ray structural analysis (Figure 3), which clearly showed the positions of the three different nitriles. Hydrolysis of **6a** afforded the 5-azaindole derivative **7a** in 59% isolated yield. The structure of **7a** was also confirmed by single-crystal X-ray structural analysis (Figure 4). The *t*Bu group from the first nitrile was fixed at the 4-position, the thienyl group from the second nitrile was found at the 2-position on the pyrrole ring, and the cyclohexyl group from the third nitrile was bonded at the 6-position on the pyridine ring.



Scheme 4. Formation of 5-azaindoles with three different substituents at the 2-, 4-, and 6-Positions (type IV).

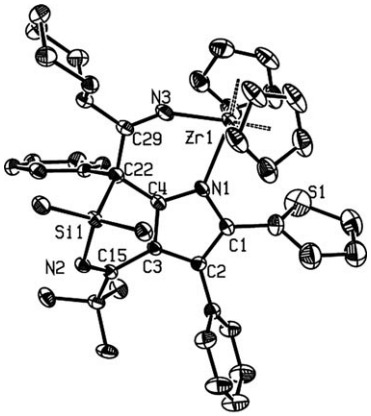


Figure 3. ORTEP drawings of **6a** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: Zr1–N1 2.250(5), Zr1–N3 1.990(5), Si1–N2 1.752(5), Si1–C22 1.941(6), C29–N3 1.251(7), C15–N2 1.284(7), C1–C2 1.392(8), C2–C3 1.416(8), C3–C15 1.490(7), C3–C4 1.409(7), C4–C22 1.531(8), C22–C29 1.523(8).

As well as CyCN, other nitriles, either aromatic or aliphatic, could also be applied as the third different nitrile to afford the 5-azaindoles **7b–f** (Scheme 4) in good to high yields upon hydrolysis of the reaction mixtures. In each of these cases only one regioisomer was obtained. These results clearly demonstrate that the 5-azaindoles are each substitut-

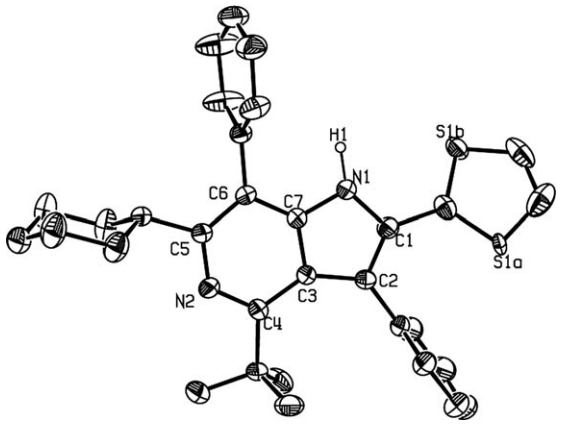
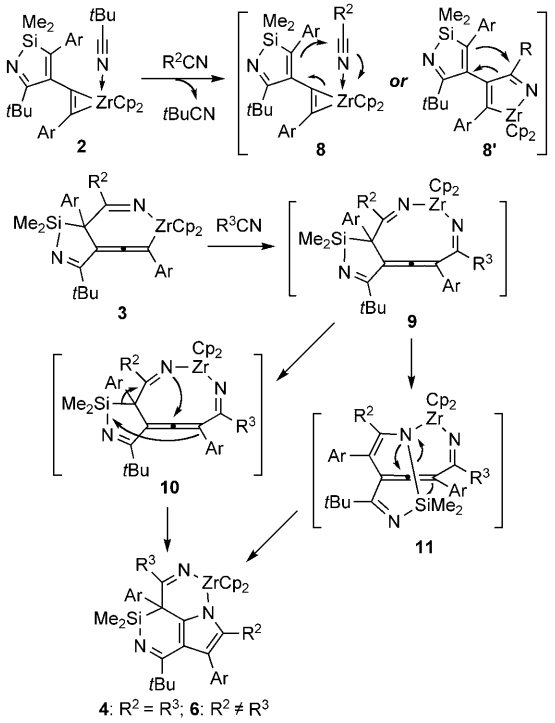


Figure 4. ORTEP drawings of **7a** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity except for the polar N–H bond. Selected bond lengths [Å]: N1–C1 1.400(5), N1–C7 1.383(5), N2–C4 1.329(4), N2–C5 1.351(4), C1–C2 1.371(5), C2–C3 1.470(5), C3–C7 1.413(5), C3–C4 1.434(5), C5–C6 1.385(5), C6–C7 1.377(5).

ed with three different substituents at the 2-, 4-, and 6-positions (type IV).

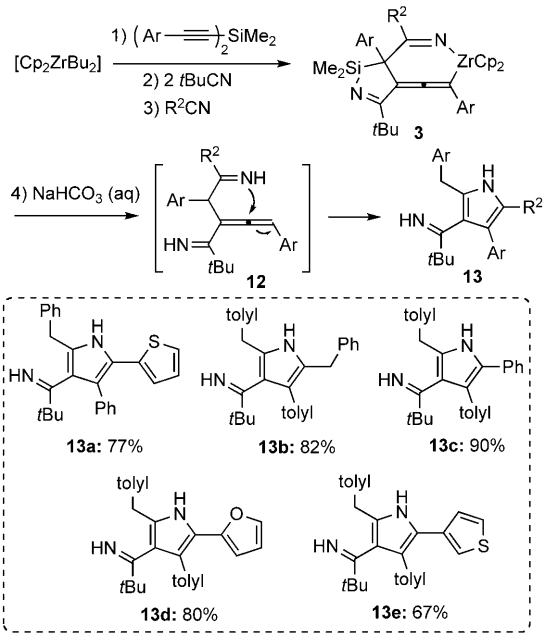
iii) Mechanistic aspects: In our previous communication,[10] we had isolated and characterized the Zr/Si-containing intermediates **2** and **3**. Here we have successfully isolated and characterized the third type of important Zr/Si-containing intermediates: **4a** and **6a**, the X-ray structures of which clearly showed the positions of the three different nitriles. A proposed possible mechanism for the formation of compounds **4** or **6** from compounds **2**, based on the above experimental evidence, is shown in Scheme 5. For the first step, it is proposed that one R^2CN unit replaces the bulky *t*BuCN and revives the reactivity of the zirconacyclopropene moiety. The coordinating R^2CN, which is generally smaller than *t*BuCN, can insert into the zirconacyclopropene moiety in **8** to form its corresponding azazirconacyclopentadiene moiety in **8′**. Skeletal rearrangement of **8** or **8′** would then generate the allenyl-aza-zirconacycle **3**. The third R^3CN unit could then insert into the Zr–C bond of the allenyl-aza-zirconacycle **3** to generate the nine-membered allenyl-aza-zirconacycle **9**. This cyclic intermediate **9** would be unstable and would undergo intramolecular nucleophilic attack or a 1,3-silyl shift to give the final three-ring fused compound **6**. When $R^2 = R^3$, this gives the corresponding compound **4**.

Formation of iminopyrroles with all different substituents through hydrolysis of the allenyl-aza-zirconacycles 3: The development of synthetic methods for pyrrole derivatives has been an ongoing major research topic in synthetic chemistry, because pyrrole derivatives are of great importance in many areas.[6–8] The synthesis of pyrrole derivatives with functional groups and all different substituents on the ring remains a great challenge.[6,7] When the allenyl-aza-zirconacycles **3**, each generated in situ from two different nitriles and a Si-tethered diyne, were hydrolyzed with water, a wide variety of iminopyrrole derivatives—**13a**–**e**—were obtained in 67–90% yields (Scheme 6). These pyrroles **13** are



Scheme 5. Proposed reaction mechanism for the formation of the three-ring fused compounds **4** and **6**.

each functionalized with an imino group and substituted with all different substituents. It is proposed that the formation of the pyrroles **13** takes place through nucleophilic-attack-induced hydroamination cyclizations of the iminoallene species **12**.[18]



Scheme 6. Formation of iminopyrroles with all different substituents through hydrolysis of the allenyl-aza-zirconacycles **3**.

Conclusion

In summary, here we report a selective synthesis of 5-azaindoles with a diverse range of substituents through zirconocene-mediated multicomponent reactions. 5-Azaindoles of two new types—5-azaindoles with three different substituents at their 2-, 4-, and 6-positions or 5-azaindoles with two identical substituents at their 2- and 6-positions and a different one at the 4-position—are synthesized in good to excellent isolated yields by this method. This work represents a new synthetic strategy for achieving selectivity in multicomponent reactions. Single-crystal X-ray structural analyses of the important three-ring fused Zr/Si-containing intermediates, each consisting of a Cp_2Zr^{II} species, a Si-tethered diyne, one *t*BuCN, and two different nitriles, unambiguously showed the positions of the different nitriles and the high regioselectivity. In addition, iminopyrrole derivatives could be prepared in high yields from a Si-tethered diyne and two different nitriles.

Experimental Section

General methods: All reactions were conducted under a slightly positive pressure of dry nitrogen by standard Schlenk line techniques or under nitrogen in a glovebox (Mikrouna Super 1220/750). The nitrogen in the glovebox was constantly circulated through a catalyst unit (copper/molecular sieves). The oxygen and moisture concentrations in the glovebox atmosphere were monitored with an O_2/H_2O Combi-Analyzer to ensure both were always below 1 ppm. Unless otherwise noted, all starting materials were commercially available and were used without further purification. Solvents were purified with a solvent purification system (MBRAUN SPS-800) and dried over fresh Na chips in the glovebox. *n*BuLi was obtained from Acros. Organometallic samples for NMR spectroscopic measurements were prepared in the glovebox by use of valve NMR tubes (J. Young, Wilmad 528-JY). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 400 spectrometer (FT, 400 MHz for ^{1}H; 100 MHz for ^{13}C) or a JEOL-AL 300 spectrometer (FT, 300 MHz for ^{1}H; 75 MHz for ^{13}C) at room temperature, unless otherwise noted. Elemental analyses were performed with an Elemental Analyzer vario EL apparatus.

Isolation of the reactive intermediate 4a from one bis(alkynyl)silane, one *t*BuCN, and two CyCN components: A compound **2** was isolated by the method we reported previously.[10] In a 20 mL Schlenk tube, cyclohexanecarbonitrile (178 μL, 1.50 mmol) was added to a benzene (3 mL) solution of compound **2** (Ar = Ph, 318 mg, 0.50 mmol) by syringe. After the reaction mixture had been stirred at 90 °C for 1 h, it was concentrated and dried under vacuum and the residue was extracted with hexane. After filtration and concentration, the solid was dried under vacuum to provide **4a** as an orange powder (312 mg, 0.405 mmol, 81 %). Single crystals of **4a** suitable for X-ray analysis were grown in benzene/hexane at room temperature for one week. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 0.29 (s, 3H; $SiMe_2$), 1.01 (s, 9H; CMe_3), 1.02 (s, 3H; $SiMe_2$), 1.23–2.18 (m, 20H; C_6H_{11}), 2.28–2.36 (m, 1H; C_6H_{11}), 2.71–2.77 (m, 1H; C_6H_{11}), 6.11 (s, 5H; C_5H_5), 6.26 (s, 5H; C_5H_5), 7.12–7.46 (m, 6H; C_6H_5), 7.66 (d, J = 7.8 Hz, 2H; C_6H_5), 7.90 ppm (d, J = 7.5 Hz, 2H; C_6H_5); ^{13}C NMR (75.4 MHz, C_6D_6, 25 °C): δ = −3.35, 2.95, 15.54, 25.76, 26.31, 27.82, 28.16, 29.74, 31.33, 32.09, 32.22, 37.45, 41.42, 46.44, 46.86, 60.53, 111.29, 111.41, 119.54, 125.82, 126.47, 126.94, 127.50, 127.68, 130.70, 132.45, 134.66, 140.07, 141.24, 142.02, 144.23, 181.56, 194.26 ppm; elemental analysis calcd (%) for $C_{47}H_{57}N_3SiZr$: C 72.07, H 7.33, N 5.36; found: C 72.00, H 7.56, N 5.00.

Formation of the 5-azaindoles 5 (type III) from one Si-tethered diyne, one *t*BuCN, and two identical nitrile components—typical procedure for the preparation of 4-*tert*-butyl-2,6-dicyclohexyl-3,7-diphenyl-1*H*-pyrrolo-[3,2-*c*]pyridine (5a): *n*BuLi (1.6 M, 2.1 mmol, 1.32 mL) was added dropwise by syringe at −78 °C (dry ice/acetone) to a toluene (10 mL) solution of Cp_2ZrCl_2 (1.05 mmol, 307 mg) in a 20 mL Schlenk tube. After the addition was complete, the reaction mixture was stirred at −78 °C for 1 h. Bis(phenylethynyl)dimethylsilane (1 mmol) was then added, and the reaction mixture was warmed up to 50 °C and stirred at this temperature for 1 h. After trimethylacetonitrile (2.0 mmol, 166 mg, 220 μL) had been added, the reaction mixture was stirred at the same temperature for 2 h. Cyclohexanecarbonitrile (3.0 mmol, 327 mg, 356 μL) was then added and the reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted three times with diethyl ether and then washed with water and brine. The extract was dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a yellow solid, which was subjected to SiO_2 column chromatography with hexane/diethyl ether/triethylamine (100:5:1) as the eluent.

4-*tert*-Butyl-2,6-dicyclohexyl-3,7-diphenyl-1*H*-pyrrolo[3,2-*c*]pyridine (5a): Pale yellow solid, isolated yield 69 % (338 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.19–1.90 (m, 29H; CH_2, CMe_3), 2.19–2.26 (m, 1H; CH), 2.59–2.66 (m, 1H; CH), 7.34–7.54 (m, 10H; C_6H_5), 7.74 ppm (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 23.59, 24.77, 25.21, 25.79, 26.22, 27.50, 29.01, 30.30, 32.48, 32.65, 35.23, 38.87, 41.08, 112.93, 115.30, 118.64, 122.17, 126.52, 126.99, 127.09, 128.54, 129.51, 132.54, 136.01, 138.47, 139.33, 141.10, 150.39, 159.73 ppm; HRMS: *m*/*z*: calcd for $C_{35}H_{43}N_2$: 491.3426 $[M+H]^+$; found: 491.3428; elemental analysis calcd (%) for $C_{35}H_{42}N_2$: C 85.66, H 8.63, N 5.71; found: C 85.60, H 8.82, N 5.59.

4-*tert*-Butyl-3,7-diphenyl-2,6-bis(thiophen-2-yl)-1*H*-pyrrolo[3,2-*c*]pyridine (5b): White solid, isolated yield 77 % (377 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.31 (s, 9H; CMe_3), 6.40 (d, J = 3.5 Hz, 1H; C_4H_3S), 6.70–6.82 (m, 3H; C_4H_3S), 7.06 (d, J = 5.2 Hz, 1H; C_4H_3S), 7.16 (d, J = 5.2 Hz, 1H; C_4H_3S), 7.44 (s, 5H; C_6H_5), 7.50–7.60 (m, 5H; C_6H_5), 8.05 ppm (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 30.60, 39.55, 114.56, 116.05, 120.86, 124.64, 125.16, 126.17, 126.34, 126.72, 127.37, 128.20, 128.31, 128.61, 129.87, 130.04, 130.98, 133.58, 134.16, 135.52, 137.36, 138.84, 141.71, 147.21, 161.69 ppm; HRMS: *m*/*z*: calcd for $C_{31}H_{27}N_2S_2$: 491.1616 $[M+H]^+$; found: 491.1608.

4-*tert*-Butyl-2,6-diisopropyl-3,7-bis-*p*-tolyl-1*H*-pyrrolo[3,2-*c*]pyridine (5c): White solid, isolated yield 71 % (310 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.05 (d, J = 6.9 Hz, 6H; $CHMe_2$), 1.23 (d, J = 6.9 Hz, 6H; $CHMe_2$), 1.24 (s, 9H; CMe_3), 2.43 (s, 3H; CMe), 2.47 (s, 3H; CMe), 2.59–2.69 (m, 1H; $CHMe_2$), 3.00–3.08 (m, 1H; $CHMe_2$), 7.18–7.34 (m, 8H; C_6H_4), 7.72 ppm (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.33, 22.50, 23.16, 25.65, 30.75, 31.10, 39.33, 113.08, 115.54, 119.21, 128.31, 129.72, 129.80, 132.84, 133.34, 135.80, 136.48, 137.12, 139.98, 142.05, 151.40, 160.31 ppm; HRMS: *m*/*z*: calcd for $C_{31}H_{39}N_2$: 439.3108 $[M+H]^+$; found: 439.3100; elemental analysis calcd (%) for $C_{31}H_{38}N_2$: C 84.88, H 8.73, N 6.39; found: C 84.72, H 8.79, N 6.21. Single crystals of **5c** suitable for X-ray analysis were grown in hexane/diethyl ether at room temperature for one day.

4-*tert*-Butyl-2,6-dipropyl-3,7-bis-*p*-tolyl-1*H*-pyrrolo[3,2-*c*]pyridine (5d): White solid, isolated yield 46 % (201 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.77 (t, J = 6.6 Hz, 3H; CH_2CH_3), 0.86 (t, J = 7.2 Hz, 3H; CH_2CH_3), 1.24 (s, 9H; CMe_3), 1.38–1.46 (m, 2H; $CH_2CH_2CH_3$), 1.74–1.81 (m, 2H; $CH_2CH_2CH_3$), 2.25 (t, J = 7.1 Hz, 2H; $CH_2CH_2CH_3$), 2.42 (s, 3H; CMe), 2.46 (s, 3H; CMe), 2.64 (t, J = 6.8 Hz, 2H; $CH_2CH_2CH_3$), 7.16–7.33 (m, 8H; C_6H_4), 7.76 ppm (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.85, 14.19, 21.35, 22.92, 22.99, 28.44, 30.71, 36.35, 38.96, 114.58, 116.72, 119.39, 128.24, 129.67, 129.83, 132.85, 133.43, 135.72, 136.39, 137.07, 137.09, 140.31, 146.62, 160.09 ppm; HRMS: *m*/*z*: calcd for $C_{31}H_{39}N_2$: 439.3108 $[M+H]^+$; found: 439.3102.

4-*tert*-Butyl-2,6-dicyclohexyl-3,7-bis-*p*-tolyl-1*H*-pyrrolo[3,2-*c*]pyridine (5e): White solid, isolated yield 93 % (483 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.09–1.93 (m, 29H; CH_2, CMe_3), 2.19–2.27 (m, 1H; CH), 2.42 (s, 3H), 2.47 (s, 3H), 2.61–2.68 (m, 1H; CH), 7.15–7.37 (m, 8H), 7.72 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.37, 25.71, 26.24, 26.67, 30.78, 32.97, 33.12, 35.60, 39.32, 41.43,

113.24, 115.66, 119.15, 128.27, 129.72, 129.79, 132.78, 133.33, 135.71, 136.37, 136.98, 139.84, 141.55, 150.85, 160.03 ppm; HRMS: *m/z*: calcd for $C_{31}H_{39}N_2$ $[M+H]^+$: 519.3739; found: 519.3736.

Isolation of the reactive intermediate 6a from one bis(alkynyl)silane, one *t*BuCN, one thiophene-2-carbonitrile and one CyCN component: Thiophene-2-carbonitrile (47 μL, 0.50 mmol) was added by syringe to a benzene (3 mL) solution of compound **2** (Ar = Ph, 318 mg, 0.50 mmol) in a 20 mL Schlenk tube. After the reaction mixture had been stirred at room temperature for 1 h, cyclohexanecarbonitrile (118 μL, 1.0 mmol) was added and the reaction mixture was stirred at 90 °C for 1 h; it was then concentrated and dried under vacuum and the residue was extracted with hexane. After filtration and concentration, the solid was dried under vacuum to provide **6a** as an orange powder (277 mg, 0.36 mmol, 72 %). Single crystals of **6a** suitable for X-ray analysis were grown in hexane at room temperature for one week. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 0.20 (s, 3H; $SiMe_2$), 0.88 (s, 3H; $SiMe_2$), 1.04 (s, 9H; CMe_3), 1.21–1.91 (m, 10H; C_6H_{11}), 2.73–2.81 (m, 1H; C_6H_{11}), 5.62 (s, 5H; C_5H_5), 6.20 (s, 5H; C_5H_5), 6.77–7.44 (m, 11H; C_6H_5, C_4H_3S), 7.74 ppm (d, J = 8.1 Hz, 2H; C_6H_5); ^{13}C NMR (75.4 MHz, C_6D_6, 25 °C): δ = −3.8, 3.0, 26.32, 30.28, 31.21, 32.16, 42.00, 46.33, 59.91, 108.41, 110.41, 111.62, 111.98, 125.62, 126.01, 126.15, 126.69, 127.80, 129.18, 130.36, 130.82, 132.81, 132.84, 140.12, 141.65, 143.20, 145.50, 179.71, 195.99 ppm; elemental analysis calcd (%) for $C_{45}H_{49}N_3SSiZr$: C 69.00, H 6.31, N 5.36; found: C 68.92, H 6.41, N 5.18.

Formation of the 5-azaindoles 7 (type IV) from one Si-tethered diyne, one *t*BuCN, and two different nitrile components—typical procedure for the preparation of 4-*tert*-butyl-6-cyclohexyl-3,7-diphenyl-2-(thiophen-2-yl)-1*H*-pyrrolo[3,2-*c*]pyridine (7a): *n*BuLi (1.6 M, 2.1 mmol, 1.32 mL) was added dropwise by syringe at −78 °C (dry ice/acetone) to a toluene (10 mL) solution of Cp_2ZrCl_2 (1.05 mmol, 307 mg) in a 20 mL Schlenk tube. After the addition was complete, the reaction mixture was stirred at −78 °C for 1 h. Bis(phenylethynyl)dimethylsilane (1 mmol) was then added, and the reaction mixture was warmed up to 50 °C and stirred at this temperature for 1 h. After trimethylacetonitrile (2.0 mmol, 166 mg, 220 μL) had been added, the reaction mixture was stirred at the same temperature for 2 h. Thiophene-2-carbonitrile (0.9 mmol, 98 mg, 84 μL) was then added and the reaction mixture was stirred at room temperature for 1 h. Cyclohexanecarbonitrile (2.0 mmol, 218 mg, 238 μL) was then added, and the reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The resulting mixture was extracted three times with diethyl ether and then washed with water and brine. The extract was dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a yellow solid, which was subjected to SiO_2 column chromatography with hexane/diethyl ether/triethylamine (100:5:1) as the eluent.

4-*tert*-Butyl-6-cyclohexyl-3,7-diphenyl-2-(thiophen-2-yl)-1*H*-pyrrolo[3,2-*c*]pyridine (7a): White solid, isolated yield: 59 % (289 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.16–1.30 (m, 2H; CH_2), 1.25 (s, 9H; CMe_3), 1.62–1.96 (m, 8H; CH_2), 2.63–2.71 (m, 1H; CH), 6.67 (d, J = 2.1 Hz, 1H; C_4H_3S), 6.80 (t, J = 5.4 Hz, 1H; C_4H_3S), 7.03 (d, J = 5.4 Hz, 1H; C_4H_3S), 7.42–7.57 (m, 10H; C_6H_5), 8.02 ppm (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 26.20, 26.61, 30.81, 32.98, 39.49, 41.65, 115.59, 115.81, 119.97, 124.32, 125.76, 126.63, 127.72, 127.97, 128.21, 129.11, 129.78, 129.93, 133.61, 134.63, 135.95, 137.91, 140.82, 152.09, 161.17 ppm; HRMS: *m/z*: calcd for $C_{33}H_{35}N_2S$: 491.2521 $[M+H]^+$; found: 491.2516; elemental analysis calcd (%) for $C_{33}H_{34}N_2S$: C 80.77, H 6.98, N 5.71; found: C 80.54, H 7.03, N 5.55.

4-*tert*-Butyl-6-cyclohexyl-2-(pyridin-2-yl)-3,7-bis-*p*-tolyl-1*H*-pyrrolo[3,2-*c*]pyridine (7b): White solid, isolated yield: 63 % (323 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.19–1.31 (m, 2H; CH_2), 1.26 (s, 9H; CMe_3), 1.63–1.95 (m, 8H; CH_2), 2.49 (s, 3H; CMe), 2.50 (s, 3H; CMe), 2.69–2.75 (m, 1H; CH), 6.32 (d, J = 8.2 Hz, 1H; C_5H_4N), 6.94–6.97 (m, 9H; C_6H_4, C_5H_4N), 8.40–8.41 (m, 1H; C_5H_4N), 9.54 ppm (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.38, 21.46, 26.27, 26.64, 30.96, 33.00, 39.54, 41.56, 116.11, 116.88, 120.76, 121.36, 129.24, 129.69, 129.85, 132.67, 133.05, 133.07, 135.63, 135.88, 137.02, 137.48, 140.35, 148.69, 150.13, 152.25, 161.76 ppm; HRMS: *m/z*: calcd for $C_{36}H_{40}N_3$: 514.3217 $[M+H]^+$; found: 514.3216; elemental analysis calcd (%) for $C_{36}H_{39}N_3$: C 84.17, H 7.65, N 8.18; found: C 84.12, H 7.77, N 8.10.

4-*tert*-Butyl-6-isopropyl-2-(thiophen-2-yl)-3,7-bis-*p*-tolyl-1*H*-pyrrolo[3,2-*c*]pyridine (7c): White solid, isolated yield: 53 % (253 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.24 (d, J = 7.2 Hz, 6H; $CHMe_2$), 1.26 (s, 9H; CMe_3), 2.45 (s, 3H; CMe), 2.47 (s, 3H; CMe), 3.03–3.12 (m, 1H; $CHMe_2$), 6.67 (d, J = 3.6 Hz, 1H; C_4H_3S), 6.79–6.82 (m, 1H; C_4H_3S), 7.03 (d, J = 5.1 Hz, 1H; C_4H_3S), 7.21–7.35 (m, 8H; C_6H_4), 8.02 ppm (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.33, 21.49, 23.05, 30.81, 31.22, 39.49, 115.55, 120.12, 124.09, 125.64, 126.57, 128.97, 129.78, 129.81, 132.86, 133.36, 134.64, 134.79, 137.39, 137.65, 140.89, 152.58, 161.28 ppm; HRMS: *m/z*: calcd for $C_{32}H_{35}N_2S$: 479.2521 $[M+H]^+$; found: 479.2518; elemental analysis calcd (%) for $C_{32}H_{34}N_2S$: C 80.29, H 7.16, N 5.85; found: C 80.31, H 7.08, N 5.95.

4-*tert*-Butyl-2-(furan-2-yl)-6-hexyl-3,7-bis-*p*-tolyl-1*H*-pyrrolo[3,2-*c*]pyridine (7d): Yellow solid, isolated yield: 41 % (206 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.84 (t, J = 6.5 Hz, 3H; CH_3), 1.20–1.27 (m, 4H; CH_2), 1.29 (s, 9H; CMe_3), 1.73–1.76 (m, 2H; CH_2), 2.34–2.42 (m, 2H; CH_2), 2.47 (s, 3H; CMe), 2.48 (s, 3H; CMe), 2.69 (t, J = 7.6 Hz, 2H; CH_2), 5.02 (d, J = 3.4 Hz, 1H; C_4H_3O), 6.16–6.17 (m, 1H; C_4H_3O), 7.27 (d, J = 4.1 Hz, 1H; C_4H_3O), 7.28 (s, 4H; C_6H_4), 7.31 (s, 4H; C_6H_4), 8.43 ppm (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.10, 21.33, 21.43, 22.60, 29.13, 29.55, 30.79, 31.78, 34.28, 39.06, 106.86, 111.89, 114.27, 117.06, 119.83, 127.10, 128.94, 129.22, 129.75, 129.84, 132.52, 133.04, 135.29, 137.27, 137.38, 140.72, 140.85, 146.87, 148.07, 161.14 ppm; HRMS: *m/z*: calcd for $C_{35}H_{41}N_2O$: 505.3213; found: 505.3210.

4-*tert*-Butyl-6-propyl-2-(pyrazin-2-yl)-3,7-bis-*p*-tolyl-1*H*-pyrrolo[3,2-*c*]pyridine (7e): White solid, isolated yield: 72 % (341 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.86 (t, J = 7.2 Hz, 3H; CH_2CH_3), 1.27 (s, 9H; CMe_3), 1.77–1.83 (m, 2H; $CH_3CH_2CH_2$), 2.48 (s, 3H; CMe), 2.49 (s, 3H; CMe), 2.69 (t, J = 7.6 Hz, 2H; $CH_3CH_2CH_2$), 7.29–7.35 (m, 4H; C_6H_4), 7.37 (s, 4H; C_6H_4), 7.51 (d, J = 1.6 Hz, 1H; $C_4H_3N_2$), 8.21 (d, J = 2.5 Hz, 1H; $C_4H_3N_2$), 8.35–8.36 (m, 1H; $C_4H_3N_2$), 9.35 ppm (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.14, 21.36, 21.46, 22.74, 30.88, 36.46, 39.25, 117.34, 118.75, 120.72, 129.62, 129.78, 129.81, 130.92, 132.33, 132.88, 134.80, 137.30, 138.22, 141.24, 141.55, 142.48, 143.15, 146.28, 148.84, 162.51 ppm; HRMS: *m/z*: calcd for $C_{32}H_{35}N_4$: 475.2862 $[M+H]^+$; found: 475.2858; elemental analysis calcd (%) for $C_{32}H_{34}N_4$: C 80.98, H 7.22, N 11.80; found: C 80.90, H 7.36, N 11.54.

4-*tert*-Butyl-2-(pyridin-2-yl)-6-(thiophen-2-yl)-3,7-bis-*p*-tolyl-1*H*-pyrrolo-[3,2-*c*]pyridine (7f): White solid, isolated yield: 49 % (251 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.31 (s, 9H; CMe_3), 2.50 (s, 3H; CMe), 2.53 (s, 3H; CMe), 6.34 (d, J = 8.3 Hz, 1H; C_5H_4N), 6.45 (d, J = 3.2 Hz, 1H; C_4H_3S), 6.79–6.81 (m, 1H; C_4H_3S), 7.18–7.42 (m, 9H; C_5H_4N, C_6H_4), 8.43 (d, J = 4.8 Hz, 1H; C_5H_4N), 9.57 ppm (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.47, 21.52, 30.74, 39.62, 115.05, 117.36, 120.91, 121.59, 121.66, 125.25, 126.19, 127.37, 129.33, 129.91, 130.47, 132.60, 132.65, 134.18, 135.07, 136.01, 137.75, 138.08, 139.04, 141.25, 148.77, 149.74, 162.35 ppm; HRMS: *m/z*: calcd for $C_{34}H_{32}N_3S$: 514.2311; found: 514.2305.

Formation of the iminopyrroles 13 with all different substituents by hydrolysis of the allenyl-aza-zirconacycles 3—general procedure for the preparation of 1-[2-benzyl-4-phenyl-5-(thiophen-2-yl)-1*H*-pyrrol-3-yl]-2,2-dimethylpropan-1-ylimine (13a): *n*BuLi (2.1 mmol, 1.6 M, 1.32 mL) was added dropwise by syringe at −78 °C (dry ice/acetone) to a toluene (10 mL) solution of Cp_2ZrCl_2 (1.05 mmol, 307 mg) in a 20 mL Schlenk tube. After the addition was complete, the reaction mixture was stirred at −78 °C for 1 h. Bis(phenylethynyl)dimethylsilane (1 mmol) was then added, and the reaction mixture was warmed up to 50 °C and stirred at this temperature for 1 h. After trimethylacetonitrile (2.0 mmol, 166 mg, 220 μL) had been added, the reaction mixture was stirred at the same temperature for 2 h. Thiophene-2-carbonitrile (0.9 mmol, 98 mg, 84 μL) was then added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The resulting mixture was extracted three times with diethyl ether and then washed with water and brine. The extract was dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a yellow

solid, which was subjected to SiO_2 column chromatography with hexane/ethyl acetate/triethylamine (100:40:1) as the eluent.

1-[2-Benzyl-4-phenyl-5-(thiophen-2-yl)-1*H*-pyrrol-3-yl]-2,2-dimethylpropan-1-imine (13a): Yellow solid, isolated yield: 77% (306 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.89$ (s, 9H; CMe_3), 3.92 (s, 2H; CH_2), 6.76–6.86 (m, 2H; C_4H_3S), 7.02–7.05 (m, 1H; C_4H_3S), 7.26–7.34 (m, 10H; C_6H_5), 8.22 ppm (brs, 1H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C, TMS): $\delta = 28.51$, 32.60, 40.68, 120.75, 121.66, 123.77, 126.56, 126.78, 127.05, 128.08, 128.63, 128.88, 130.55, 134.68, 135.84, 138.57, 187.77 ppm; HRMS: m/z: calcd for $C_{26}H_{27}N_2S$: 399.1895 $[M+H]^+$; found: 399.1892; elemental analysis calcd (%) for $C_{26}H_{26}N_2S$: C 78.35, H 6.58, N 7.03; found: C 78.25, H 6.66, N 7.08.

1-[5-Benzyl-2-(4-methylbenzyl)-4-*p*-tolyl-1*H*-pyrrol-3-yl]-2,2-dimethylpropan-1-imine (13b): Yellow solid, isolated yield: 82% (355 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.93$ (s, 9H; CMe_3), 2.31 (s, 3H; CMe), 2.33 (s, 3H; CMe), 3.80 (s, 2H; CH_2), 3.92 (s, 2H; CH_2), 7.01–7.29 (m, 13H; C_6H_4, C_6H_5), 7.46 ppm (brs, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta = 21.00$, 21.16, 28.70, 29.70, 31.85, 31.94, 40.74, 120.29, 122.83, 125.13, 125.86, 126.30, 128.27, 128.36, 128.59, 128.90, 129.25, 129.35, 133.80, 135.34, 136.04, 139.84, 188.67 ppm; HRMS: m/z: calcd for $C_{31}H_{35}N_2$: 435.2795 $[M+H]^+$; found: 435.2793; elemental analysis calcd (%) for $C_{31}H_{34}N_2$: C 85.67, H 7.89, N 6.45; found: C 85.54, H 7.66, N 6.58.

2,2-Dimethyl-1-[2-(4-methylbenzyl)-5-phenyl-4-*p*-tolyl-1*H*-pyrrol-3-yl]-propan-1-imine (13c): White solid, isolated yield: 90% (378 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.93$ (s, 9H; CMe_3), 2.32 (s, 3H; CMe), 2.34 (s, 3H; CMe), 3.90 (s, 2H; CH_2), 7.01–7.25 (m, 13H; C_6H_4, C_6H_5), 7.73 ppm (brs, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta = 21.04$, 21.20, 28.59, 32.37, 40.85, 126.28, 126.95, 127.00, 128.41, 128.67, 128.91, 129.60, 130.04, 132.92, 133.47, 135.46, 135.61, 136.39, 188.33 ppm; HRMS: m/z: calcd for $C_{30}H_{33}N_2$: 421.2638 $[M+H]^+$; found: 421.2635.

1-[5-(Furan-2-yl)-2-(4-methylbenzyl)-4-*p*-tolyl-1*H*-pyrrol-3-yl]-2,2-dimethylpropan-1-imine (13d): Yellow solid, isolated yield: 80% (328 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.91$ (s, 9H; CMe_3), 2.34 (s, 3H; CMe), 2.35 (s, 3H; CMe), 3.88 (s, 2H; CH_2), 5.98 (d, $J = 3.3$ Hz, 1H; C_4H_3O), 6.22–6.23 (m, 1H; C_4H_3O), 7.12–7.22 (m, 9H; C_6H_4, C_4H_3O), 8.23 ppm (brs, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 21.00, 21.21, 28.59, 32.26, 40.59, 103.44, 111.34, 119.05, 119.66, 124.67, 127.24, 128.54, 128.87, 129.53, 130.06, 132.88, 135.42, 136.27, 136.31, 139.89, 147.21, 187.68 ppm; HRMS: m/z: calcd for $C_{28}H_{31}N_2O$: 411.2431 $[M+H]^+$; found: 411.2408.

2,2-Dimethyl-1-[2-(4-methylbenzyl)-5-(thiophen-3-yl)-4-*p*-tolyl-1*H*-pyrrol-3-yl]propan-1-imine (13e): Yellow solid, isolated yield: 67% (285 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.93$ (s, 9H; CMe_3), 2.29 (s, 3H; CMe), 2.30 (s, 3H; CMe), 3.89 (s, 2H; CH_2), 6.78–6.79 (m, 1H; C_4H_3S), 6.93–6.94 (m, 1H; C_4H_3S), 7.06–7.15 (m, 9H; C_6H_4, C_4H_3S), 7.82 ppm (brs, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 21.01$, 21.19, 28.60, 32.31, 40.73, 119.21, 123.18, 125.30, 126.56, 128.53, 128.61, 128.74, 128.83, 129.41, 129.45, 129.56, 130.11, 133.39, 133.58, 135.51, 135.82, 136.35, 188.12 ppm; HRMS: m/z: calcd for $C_{28}H_{31}N_2S$: 427.2202 $[M+H]^+$; found: 427.2205.

X-ray crystallographic studies: Single crystals of **4a**, **5c**, **6a**, and **7a** suitable for X-ray analysis were grown as described above. The crystals of **4a** and **6a** were manipulated under nitrogen and were sealed in thin-walled glass capillaries. Data collection for **4a** was performed at 20°C, for **7a** at 25°C, and for **5c** at −150°C with use of a Rigaku RAXIS RAPID IP diffractometer and graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda =$ 0.71073 Å). Data collection for **6a** was performed at −100°C with use of a RIGAKU CCD SATURN 724 diffractometer and graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The determination of crystal class and unit cell parameters was carried out with the Rapid-AUTO (Rigaku 2000) program package for **4a**, **5c**, and **7a** or with CrystalClear (Rigaku Inc., 2007) for **6a**. The raw frame data were processed with the aid of Crystal Structure (Rigaku/MSC 2000) for **4a**, **5c**, and **7a** or of CrystalClear (Rigaku Inc., 2007) for **6a** to yield the reflection data file. The structures of **4a**, **5c**, **6a**, and **7a** were solved by use of the SHELXTL program.[19] Refinement was performed on F2 anisotropically for all the non-hydrogen atoms by the full-matrix, least-squares method. The hydrogen atoms were placed at the calculated positions and were included in the structure calculation without further refinement of the parameters. Crystal data, data collection, and processing parameters for compounds **4a**, **5c**, **6a**, and **7a** are summarized in the Supporting Information.

CCDC-797061 (**4a**), CCDC-797062 (**5c**), CCDC-797063 (**6a**), and CCDC-797064 (**7a**) 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.

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