A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2023** (ii) 202312017

Aromatic metamorphosis of an indole into 2-quinolone, dihydrobenzazasiline, and dihydrobenzazagermine

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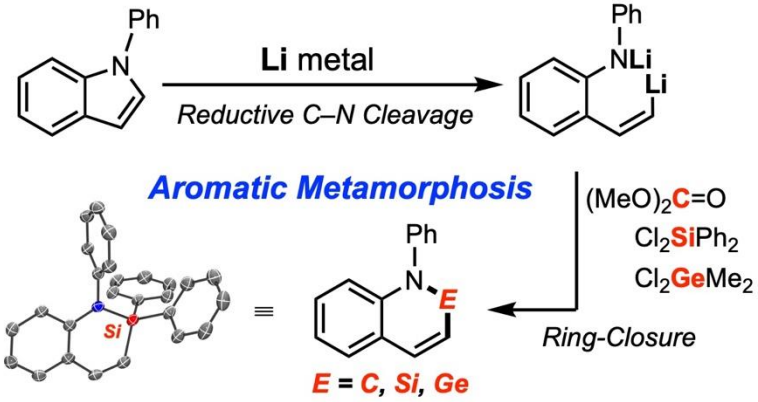
Dedicated to Professor Tien-Yau Luh

Received 05-08-2023 **Accepted Manuscript** 08-28-2023 **Published on line** 09-10-2023

Abstract

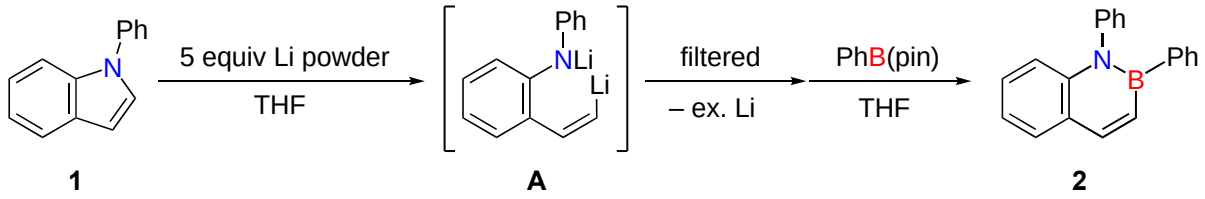
Reduction of *N*-phenylindole with self-made lithium powder has proven to be an efficient method for generating the C–N-cleaved dianionic species. Treatment of the dianionic intermediate with dimethyl carbonate, dichlorodiphenylsilane, and dichlorodimethylgermane leads to ring-expansion of the indole skeleton by insertion of the group 14 element units into the C–N bond. An X-ray diffraction study of the silicon compound displays a six-membered 1,2-azasilacyclic structure.



Keywords: Aromatic metamorphosis, ring-expansion, atom-insertion, reduction, indole, lithium

Introduction

Endocyclic transformation of aromatic compounds, which we have coined aromatic metamorphosis,[1-3] has attracted attentions as a powerful strategy to edit aromatic skeletons. Indoles can be found in various natural products and pharmaceuticals,[4-6] and ring-expansion of indoles *via* oxidative C=C cleavages has been developed.[7-14] In contrast to these well-explored oxidative strategies for transforming indoles, reductive transformation of indoles is still underdeveloped.[15-17] We have reported the sole example of the reductive aromatic metamorphosis of indoles, which provided 1,2-benzazaborins *via* reductive ring-opening by use of 5 equivalents of lithium metal. Reductive C–N bond cleavage formed dianionic intermediate **A** and treatment of **A** with group 13 boron electrophiles such as PhB(pin) resulted in the construction of the 1,2-benzazaborin skeleton (Scheme 1).[15,16]



Scheme 1. Aromatic metamorphosis of indoles into 1,2-azaborines *via* lithium-mediated reductive C–N bond cleavage followed by borylative ring-closure.

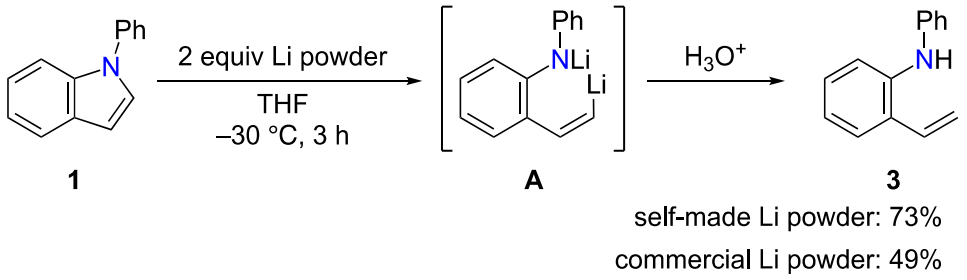
Herein, we report further exploration of the aromatic metamorphosis of *N*-phenylindole (**1**) by insertion of the group 14 elements.

Results and Discussion

For further investigation of the reductive aromatic metamorphosis of indoles, we had encountered unavailability of lithium powder due to the discontinued production of the commercial lithium powder.[18] We had recently prepared a lithium powder by dispersion of molten lithium in mineral oil following a slightly modified procedure reported by Yus,[19] and this self-made lithium powder with the particle size of 120–250 μm worked very well for desulfurative dilithiation of thiophenes[20] and other reductive carbon–heteroatom bond cleavages.[21,22] Therefore, the reactivity of the self-made lithium powder for the reductive ring-opening of indoles was also examined herein. As shown in Scheme 2, the reductive ring-opening of *N*-phenylindole (**1**) was performed with 2 equivalents of lithium powder in THF at –30 °C followed by protonation of the dianionic intermediate **A** to yield protonation product **3**. In contrast to the commercial lithium powder (49% yield),[15] the use of the freshly prepared lithium powder resulted in a higher conversion of **1** into **3** in 73% yield. A reaction time as long as 5 h was not so effective (77% yield).

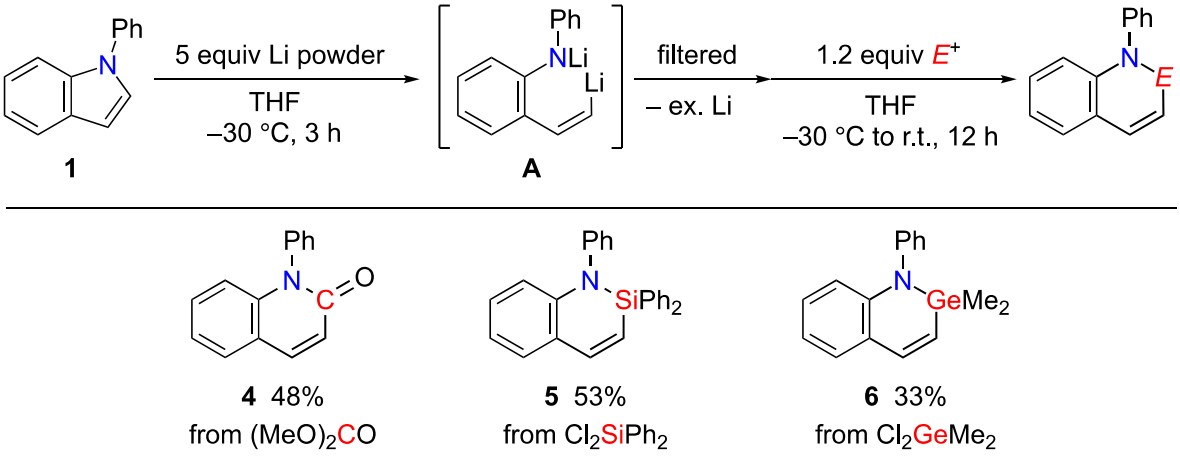
We disclosed in the previous report[15] that the remaining excessive lithium powder, theoretically 3 equivalents, had a detrimental effect on the yield of 1,2-benzazaborine **2** after treatment with PhB(pin) and that the filtration to remove the unreacted lithium powder was required. Given the higher conversion of **1** by only 2 equivalents, the theoretically stoichiometric amount, of the self-made lithium powder, we expected that we can skip the filtration step because the remaining lithium powder may be negligible in this case. However, an addition of PhB(pin) into the unfiltered reaction mixture containing **A** prepared from **1** with 2

equivalents of the self-made lithium powder afforded 1,2-benzazaborine **2** in only 5% yield. Thus, we decided to keep using an excessive amount of lithium powder and then remove the unreacted lithium powder prior to adding electrophiles.



Scheme 2. Comparison of lithium powders by yields of **3** *via* reductive ring-opening of **1**.

With the self-made lithium powder in hand, the ring-expanding aromatic metamorphosis of **1** for installation of the group 14 element units was explored (Scheme 3). After generation of **A** and removal of the excessive lithium powder, the solution of **A** was treated with dimethyl carbonate, dichlorodiphenylsilane, and dichlorodimethylgermane. The reaction of dimethyl carbonate proceeded smoothly to afford 1-phenyl-2-quinolone (**4**) in 48% yield. Dichlorodiphenylsilane and dichlorodimethylgermane also reacted with **A** to form 1,2-azasilacycle **5** (53% yield) and 1,2-azagermacycle **6** (33% yield), respectively. Synthesis of six-membered 1,2-azasilacyclic and 1,2-azagermacyclic compounds has been achieved mainly by degradation of β-diketiminate silicon[23,24] and germanium[25] complexes or cyclometallation of silylene species.[26,27] Straightforward methods to construct such 1,2-azasilacycles and 1,2-azagermacycles are still scant.[28]



Scheme 3. Ring-expansion of **1** to azacycles **4**, **5**, and **6**.

To clarify the molecular structure of the ring-expanded products, X-ray diffraction data on a single crystal of **5** grown from a concentrated hexane solution were collected. As shown in Figure 1, the solid-state structure of **5** displayed a benzo-fused 1,2-azasilacyclohexadiene skeleton. Akin to the reported 1,2-azasilacyclohexadiene compounds,[23,24,26-28] the six-membered 1,2-azasilacycle of **5** still maintains a flat skeleton even with long Si1–N1 and Si1–C1 distances (1.7521(15) Å and 1.8296(19) Å, respectively). The ^{29}Si NMR spectrum of **5** corroborates the installed silicon center at –22.6 ppm, which is slightly downfield shifted compared to that of the dibromosilane azacyclic compound at –31.2 ppm.[23]

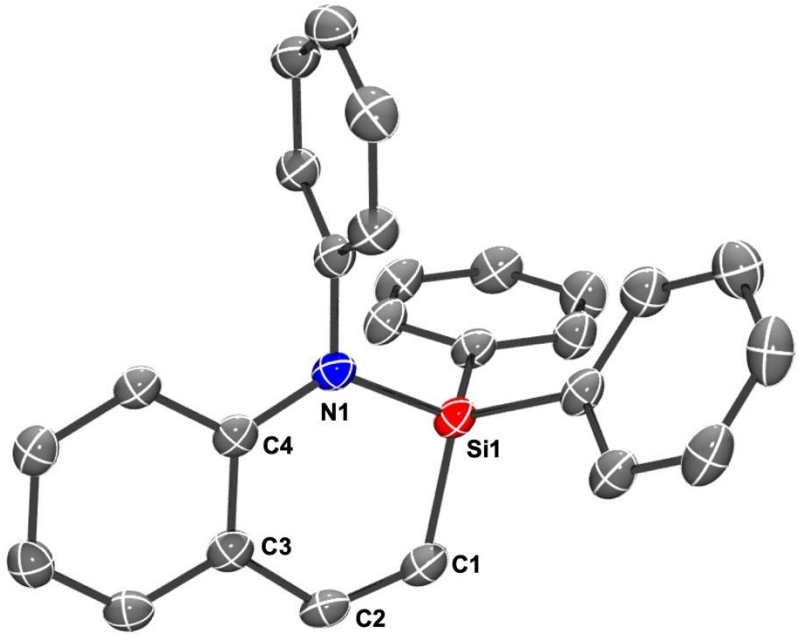


Figure 1. Solid-state structure of **5** with thermal ellipsoids at the 50% probability level. Hydrogen atoms have been omitted for clarity. Selected bond distances; Si1–N1: 1.7521(15) Å, Si1–C1: 1.8296(19) Å, C1–C2: 1.338(3) Å, C2–C3: 1.462(3) Å, C3–C4: 1.421(2) Å, C4–N1: 1.406(2) Å.

Conclusions

The self-made lithium powder has been prepared to overcome the unavailability of lithium powder from commercial sources and its high reactivity has been confirmed by the reductive ring-opening of *N*-phenylindole (**1**). We have developed ring-expansion of **1** *via* insertion of the group 14 element units by treatment of the ring-opened dianionic intermediate **A** with dimethyl carbonate, dichlorodiphenylsilane, and dichlorodimethylgermane. The X-ray diffraction study of the resulting azasilacycle shows a rare example of structurally characterized six-membered 1,2-azasilacyclic compounds. The approach based on aromatic metamorphosis represents an innovative entry to construct 1,2-azasilacyclic and 1,2-azagermacyclic skeletons.

Experimental Section

General. All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware. Dehydrated and stabilizer-free THF was purchased from Kanto Chemical Co., Inc. *N*-Phenylindole (**1**) was prepared according to the reported procedure.[17] All other reagents were commercially available and used without further purification unless otherwise noted. ^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz), and ^{29}Si NMR (119 MHz) spectra were recorded on a JEOL ECZ-600 spectrometer. Chemical shifts in ^{1}H NMR spectra were recorded in delta (δ) units, parts per million (ppm) relative to residual $CHCl_3$ (δ = 7.26 ppm). Chemical shifts in ^{13}C NMR spectra were recorded in delta (δ) units, parts per million (ppm) relative to $CDCl_3$ (δ = 77.16 ppm). The ^{29}Si NMR spectrum of **5** was measured by ^{29}Si{^{1}H} DEPT method with tetramethylsilane (δ = 0.00 ppm) as

an external standard. High resolution mass spectra (HRMS) were obtained on a Bruker micrOTOF II-KR spectrometer by Atmospheric Pressure Chemical Ionization (APCI) method using "LC/MS tuning mix, for APCI, low concentration" (Agilent Technologies, Inc.) as the internal standard.

Preparation of lithium powder. Lithium powder was prepared according to the reported procedure by Yus[19] with a slight modification. A 2000-mL three neck flask equipped with a mechanical stirrer was charged with mineral oil (Aldrich, #330779, 300 mL). The flask was evacuated under vacuum for 1 h and then refilled with argon to degas the mineral oil. Lithium lumps (Kanto Chemical Co., Inc., #24243-35, 25 g) and oleic acid (ca. 0.5 mL) were added to the flask and the mechanical stirrer was set to 300 rpm. The flask was heated by an oil bath until the lithium lumps started melting. After the molten lithium portions were observed, the stirring rate of the mechanical stirrer was set to 3000 rpm. After vigorous stirring for 15 min, the mechanical stirrer was turned off and the flask was quickly moved into another oil bath (room temperature). After cooling the flask to room temperature without stirring, the lithium dispersion in mineral oil was filtered through a glass frit under argon. The lithium powder on the glass frit was washed with dry and degassed hexane (200 mL x 3) thoroughly to remove the remaining mineral oil and then dried under vacuum. The obtained lithium powder was collected into a vial and stored under argon. The particle size of the lithium powder was confirmed as 120–250 μm by measurement of SEM images (HITACHI, Miniscope TM3030Plus).[20]

Synthesis of 1-phenyl-2-quinolone (4). A 20-mL Schlenk tube was charged with lithium powder (34.7 mg, 5.00 mmol) and THF (2 mL) and then cooled in a mixture of *o*-xylene and dry ice around –30 °C. *N*-Phenylindole (**1**) (194 mg, 1.00 mmol) in THF (2 mL) was added to the reaction mixture, resulting in a gradual color change to greenish brown. After stirring for 3 h, the reaction mixture was filtered through a glass frit under argon and the filtrate containing intermediate **A** was added into a solution of dimethyl carbonate (108 mg, 1.20 mmol) in THF (6 mL). The mixture was warmed up to room temperature and changed in color to pale yellow. After stirring for 12 h, saturated aqueous NH_4Cl (ca. 8 mL) was added to the tube and the resulting biphasic solution was extracted with EtOAc (10 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with an eluent (hexane/EtOAc = 2/1, R_f = 0.18) to provide **4** (107 mg, 0.484 mmol, 48% yield) as a white solid. Melting point: 138.7–140.2 °C. While the melting point of **4** was reported to be 138–140 °C,[29] the solid of **4** gradually darkened in color during our measurement above 100 °C and was likely to start to decompose. It then started to melt at 138.7 °C. ^{1}H NMR ($CDCl_3$): δ 7.80 (d, *J* = 10 Hz, 1H), 7.61 (t, *J* = 8 Hz, 1H), 7.60 (d, *J* = 8 Hz, 2H), 7.53 (t, *J* = 8 Hz, 1H), 7.34 (t, *J* = 8 Hz, 1H), 7.29 (d, *J* = 8 Hz, 2H), 7.21 (t, *J* = 8 Hz, 1H), 6.82 (d, *J* = 10 Hz, 1H), 6.66 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 162.4, 141.2, 139.9, 137.7, 130.29, 130.28, 129.0, 128.9, 128.4, 122.4, 122.3, 120.4, 116.0. All the resonances in the ^{1}H and ^{13}C NMR spectra are consistent with the reported values.[29]

Synthesis of 1,2,2-triphenyl-1,2-dihydrobenzo[*e*][1,2]azasiline (5). According to the procedure above, the filtrate containing **A** was obtained. The filtrate was added into a solution of dichlorodiphenylsilane (304 mg, 1.20 mmol) in THF (6 mL). The mixture was warmed up to room temperature and changed in color to pale orange. After stirring for 12 h, similar extractive workup followed by chromatographic purification on silica gel with an eluent (hexane/CH_2Cl_2 = 10/1, R_f = 0.35) provided **5** (199 mg, 0.53 mmol, 53% yield) as a white solid. Melting point: 138.8–142.2 °C. The solid of **5** also behaved like that of **4** as described above. ^{1}H NMR ($CDCl_3$): δ 7.69 (d, *J* = 14 Hz, 1H), 7.46 (d, *J* = 7 Hz, 4H), 7.38 (t, *J* = 7 Hz, 2H), 7.31 (t, *J* = 7 Hz, 4H), 7.67 (dd, *J* = 2 Hz, 8 Hz, 1H), 7.22–7.15 (m, 3H), 7.02 (t, *J* = 5 Hz, 1H), 6.90 (d, *J* = 8 Hz, 2H), 6.81 (t, *J* = 8 Hz, 1H), 6.40 (d, *J* = 8 Hz, 1H), 6.17 (d, *J* = 14 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 148.2, 147.4, 143.0, 135.7, 135.3, 132.0, 130.9, 130.0, 129.6, 129.2, 127.8, 126.4, 123.5, 118.5, 118.2, 116.3; ^{29}Si NMR ($CDCl_3$): δ –22.6; HRMS (APCI-MS, positive): *m/z* $[M+H]^+$ Calcd for $C_{26}H_{22}NSi$ 376.1516; Found 376.1513.

Synthesis of 1,2,2-trimethyl-1,2-dihydrobenzo[*e*][1,2]azagermine (6). According to the procedure above, the filtrate containing **A** was obtained. The filtrate was added into a solution of dichlorodimethylgermane (209 mg, 1.20 mmol) in THF (6 mL). The mixture was warmed up to room temperature and changed in color to yellow. After stirring for 12 h, all volatile materials were removed under vacuum. The brown residue was suspended in hexane (15 mL) and centrifuged to remove insoluble materials. The collected yellow supernatant was concentrated under reduced pressure. The residue was triturated in pentane (10 mL) to form a brown oil and a yellow supernatant. The supernatant was collected into a vial and stored at –20 °C to provide **6** (93.6 mg, 0.326 mmol, 33% yield) as a yellowish brown wax. Further purification of **6** to obtain an analytically pure sample resulted in failure due to instability of **6** on silica gel. ^{1}H NMR ($CDCl_3$): δ 7.41 (t, J = 8 Hz, 2H), 7.31 (d, J = 13 Hz, 1H), 7.24 (t, J = 8 Hz, 1H), 7.13 (d, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 1H), 6.92 (t, J = 8 Hz, 1H), 6.62 (t, J = 8 Hz, 1H), 6.36 (d, J = 8 Hz, 1H), 6.00 (d, J = 13 Hz, 1H), 0.39 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 149.3, 145.8, 145.3, 132.8, 130.0, 129.5, 129.0, 125.6, 122.7, 119.9, 116.4, 116.0, 2.5; HRMS (APCI-MS, positive): *m/z* $[M]^+$ Calcd for $C_{16}H_{17}N^{74}Ge$ 297.0570; Found 297.0568.

X-ray crystallographic study. Crystallographic data of **5** are summarized in Tables S1. A suitable crystal of **5** for X-ray analysis was placed on the end of a micro-mount coated with NVH oil. The X-ray intensity data collection was carried out on a Rigaku XTALAB P200 with a photon-counting detector at –180 °C using Cu-Kα radiation (λ = 1.5418 Å). Equivalent reflections were merged and the collected images were processed by a Rigaku CrysAlisPro program. The initial structure was determined by SHELXS.[30] The further structure determination was performed by Fourier transform method and refined by least squares method on SHELXL.[30] All reflections were used during refinement with the exception of some abnormal reflections. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using riding models. The generated CIF file was checked by the IUCR's CheckCIF routine.

Acknowledgements

This work was supported by JST CREST Grant Number JPMJCR19R4 as well as JSPS KAKENHI Grant Number JP19H00895. We thank Mr. Shun Tsuchiya and Dr. Hayate Saito for their initial efforts on this work. We also thank Prof. Makoto Yamashita, Dr. Satoshi Kurumada, and Mr. Yoshiki Sugano (Nagoya University) for helping the preparation of the lithium powder.

Supplementary Material

Crystallographic data of **5** and NMR spectra of **4**, **5**, and **6** can be found in the supplementary material file.

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