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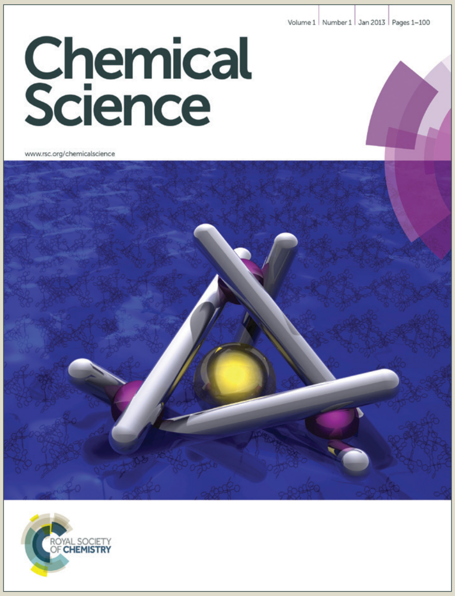

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ARTICLE TYPE

Formal Hydrogenation of Arynes with Silyl C_β–H Bonds as an Active Hydride Source†

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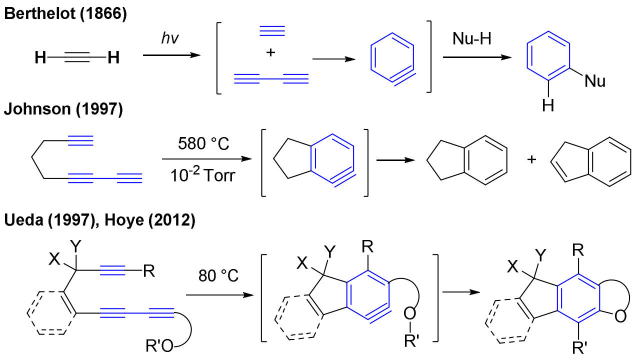
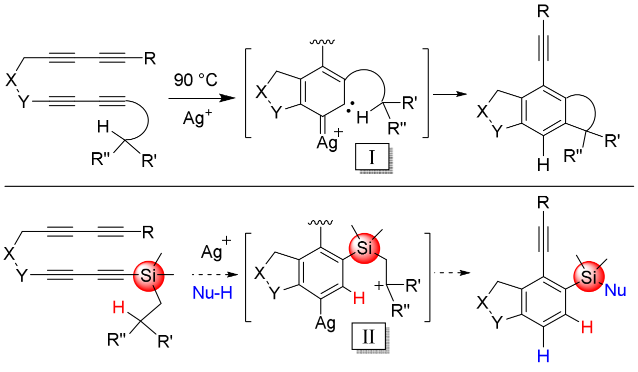
Formal hydrogenation of arynes was realized by using trialkylsilyl groups tethered to the arynes as the hydride source. In stark contrast to the effective 1°, 2°, and 3° C–H bond insertion of alkyl groups tethered to arynes, the 2° and 3° C–H bonds on the β-carbon of silyl groups show high tendency for hydride transfer rather than C–H insertion, whereas the corresponding 1° C–H bonds exclusively undergo C–H insertion. The exclusive hydride transfer and C–H insertion behavior of different C–H bonds in these two reaction pathways were rationalized by the stability of the incipient cabocationic intermediates which could be further bolstered by DFT-calculations.

The recent resurgence of aryne-mediated functional group transformations[1,2] is based on the availability of reported protocols to generate the aryne intermediate under relatively mild conditions. The fluoride-mediated elimination of arene-1,2-trialkylsilyl triflate, originally developed by Kobayashi,[3] is the most popular protocol in this regard. An alternative approach relying on the hexadehydro Diels-Alder reaction[4] (intramolecular Berthelot reaction)[4a] has emerged over time starting from the initial investigations by Ueda[4c,4f] and Johnson[4d,4e,4h] and culminated in the recent report by Hoye [4i,4j] (Scheme 1).



Scheme 1 Evolution of hexadehydro Diels-Alder reaction of a diyne and an alkyne

Similarly, Lee and coworkers reported an effective aryne formation of bis-1,3-diynes[5] followed by C–H insertion[5a] catalyzed by silver (I) complexes (Scheme 2). Although the electrophilic nature of arynes caused by the low-lying LUMO[6] readily allows the addition of heteroatom- and carbon-based nucleophiles, dienes, 1,3-dipoles, and enophiles, the corresponding addition of C−H bond promoted by silver catalyst is assumed to involve an organosilver intermediate (Scheme 2).[5,7,8] Among many possibilities,[9,10] the Ag-carbenoid I mediated concerted C–H insertion is most plausible due to greater evidential support.[5a] Yet, an alternative mechanism involving cationic intermediate II formed from an initial hydride transfer cannot be entirely excluded.



Scheme 2 A possible mechanism for the C–H insertion mediated by aryne-silver complex

To further probe these mechanistic issues, we envisaged a new class of substrates where the propargylic carbon was replaced with a trialkylsilyl moiety. This subtle structural change would introduce a significant electronic bias (β-effect of silicon)[11] to the system so that a cationic mode of reaction via hydride transfer could be manifested over a direct C–H insertion. The replacement of carbon with silicon preserves the potential Thorpe-Ingold effect of the dialkyl substituents on the silicon,[12] a highly favorable factor for ring-forming reactions analogous to the typical *gem*-dialkyl effect. In addition, the mechanistic change induced by the silicon would provide a new handle in developing a novel formal hydrogenation of aryne intermediates. This would further increase the diversity of the product structures generated by aryne-based transformations.

With these potential merits in mind, we explored various silyl-substituted bis-1,3-diynes. Herein we report the general reactivity profiles of the silyl-substituted substrates toward either C–H insertion or hydride transfer pathway depending on the degree of the involved C–H bonds. Our investigation commenced with catalyst screening with silicon-substituted bis-1,3-diyne **1a**

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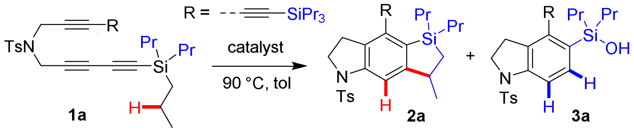
(Table 1). Without catalyst, the substrate was recovered (entry 1). Among the same set of catalysts used for all of the carbon-tether systems, except for AgOTf and $Cu(OTf)_2$ which produced low yields of the C–H insertion product **2a** and hydrogenation product **3a** mixture (entries 2 and 7), only $AgSbF_6$ provided a reasonably good yield of **3a** without the formation of **2a** (entry 3). All other metal triflates were entirely ineffective and the substrate was decomposed under those conditions (entries 4–6 and 8–12). This behavior is in stark contrast to that of the alkyl-substituted bis-1,3-diynes where most of these metal triflates provided good yields of C–H insertion products.[5a]

Table 1 Screening of catalyst for optimization of hydride transfer



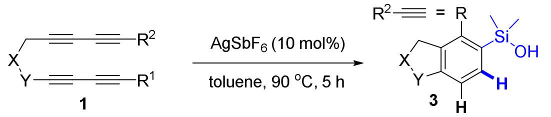
entry	catalyst	[a]yield (%) 2a/3a	entry	catalyst	[a]yield (%) 2a/3a
1	none	0/0	7	$Cu(OTf)_2$	17/22
2	AgOTf	5/11	8	$Zn(OTf)_2$	0/0
3	**$AgSbF_6$**	**0/80**	9	$Sm(OTf)_3$	0/0
4	$AgNO_3$	0/0	10	$In(OTf)_3$	0/0
5	AgOAc	0/0	11	$Sc(OTf)_3$	0/0
6	AgO	0/0	12	[b]$Ru_3(CO)_{12}$	0/0

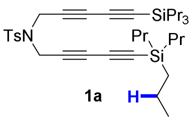
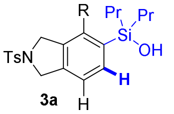
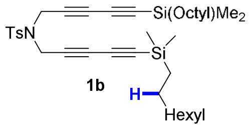
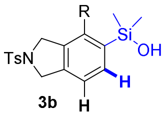
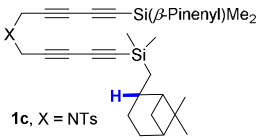
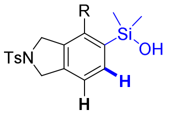
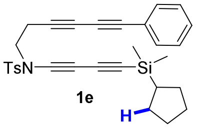
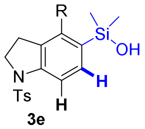
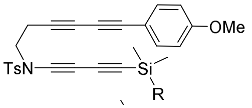
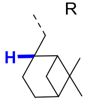
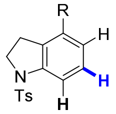
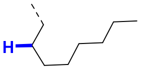
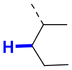
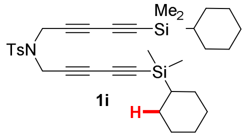
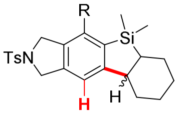
[a]Determined by ^1H NMR. [b]$HBF_4 \cdot OEt_2$ (15 mol%).

With the optimized conditions in hand we next examined the reaction profile of bis-1,3-diyne substrates **1a–i** containing silyl groups with 2° or 3° C–H bonds at the carbon where hydride transfer can occur (Table 2). The reactions of *NTs*-, or *O*-substituted symmetrical substrates **1a–d** containing 2° or 3° C–H bonds provided the hydrogenated products **3a–d** in 80, 80, 66, and 91% yields respectively without the formation of C–H insertion products (entries 1–4). In a similar manner, the unsymmetrical substrate **1e** with 2° C–H bond on a cyclopentyl group produced the expected product **3e** in 64% yield (entry 5). On the other hand, unsymmetrical substrate **1f–h** containing 3° or 2° C–H bonds in their alkyl substituents of the silyl groups led to the formation of common product **3f** where the silyloxy group was lost (entries 6–8). This is most likely the consequence of the 4-methoxyphenylethynyl substituent (R in **3f**) that makes the newly formed aromatic ring relatively more electron-rich compared to **3c–e** such that adventitious proton-catalyzed protodesilylation occurred readily under the conditions[13]. Interestingly, the reaction of a dimethylcyclohexylsilyl group-containing bis-1,3-diyne **1i** produced the C–H insertion product **2i** rather than the expected formal hydrogenation product (entry 9). The different reactivity of **1i** compared to other substrates containing 2° C–H bonds (e.g., **1e** in entry 5), should be the consequence of a relatively unfavorable nature of the developing sp^2-hybridization on the cyclohexyl moiety during the hydride transfer. The contrasting reactivity of **1i** compared to the rest of 2° or 3° C–H bond-containing substrates suggests that the subtle conformational and electronic factors can change the reaction course.

To confirm this, we employed substrates **1j–q** that contained silyl groups having only 1° C–H bonds, which invariably provided C–H insertion products **2j–q** in excellent yields without any hydride transfer product (Table 3). Under the re-optimized conditions (10 mol % AgOTf, toluene, 90 °C, 5 h), a sulfonamide (*NTs*)-tethered symmetrical bis-1,3-diynes containing $SiEt_3$, TIPS, and TBS groups produced only C–H insertion products **2j–l** in excellent yields.

Table 2 Formal hydrogenation of arynes with silyl-substituted alkyl groups containing 2° or 3° C–H bonds at β-carbons



entry	substrate	product	yield (%)
1	 **1a**	 **3a**	80
2	 **1b**	 **3b**	80
3	 **1c**, X = NTs	 **3c**	66
4	**1d**, X =O	**3d**	91
5	 **1e**	 **3e**	64
6	 **1f**, R = 	 **3f**	75
7	**1g**, R = 	**3g = 3f**	68
8	**1h**, R = 	**3h = 3f**	56
9	 **1i**	 **2i**[a]	94

[a]Mixture of diastereomers in a 10:1 ratio.

Similarly, oxygen-tethered substrate produced product **2m** in 95% yield. Also, an ynamide-tethered[14] unsymmetrical bis-1,3-diynes bearing a TBS and 4–methoxyphenyl group participated only in the predicted C–H insertion, producing indoline-based structures **2n** and **2o** in 87 and 85% yield, respectively. Both $SiEt_3$- containing unsymmetrical bis-1,3-diynes provided C–H insertion products **2p** and **2q** in 81% yield, respectively. Although the reason for the formation of **2q** is not clear at this point, it can be easily inferred that this is a secondary product formed via an adventitious proton-catalyzed protodesilylation of the initially formed C–H insertion product. The functionalization flexibility of these C–H insertion products was demonstrated with

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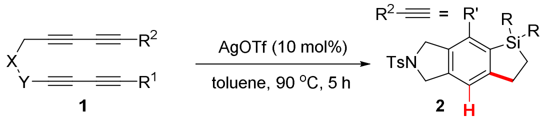
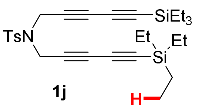
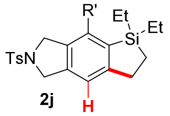
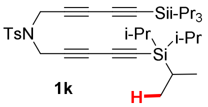
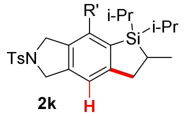
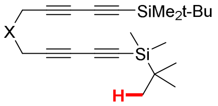
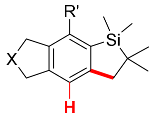
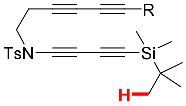
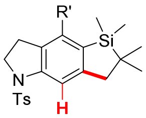
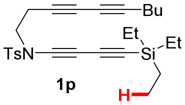
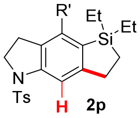
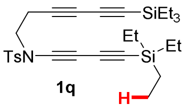
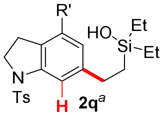
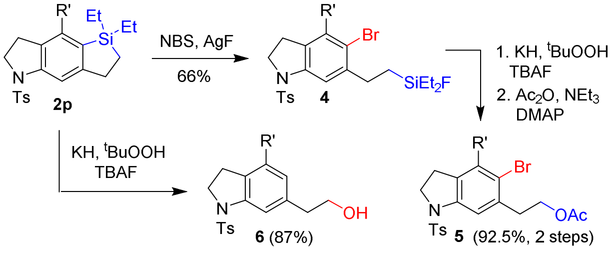
2p, which can be converted to either **5** via bromide intermediate **4** or primary alcohol **6** via direct Tamao-Fleming oxidation.[15,16]

Table 3 C–H insertion of arynes with various silicon-tethered alkyl groups containing only 1° C–H bonds at β-carbons

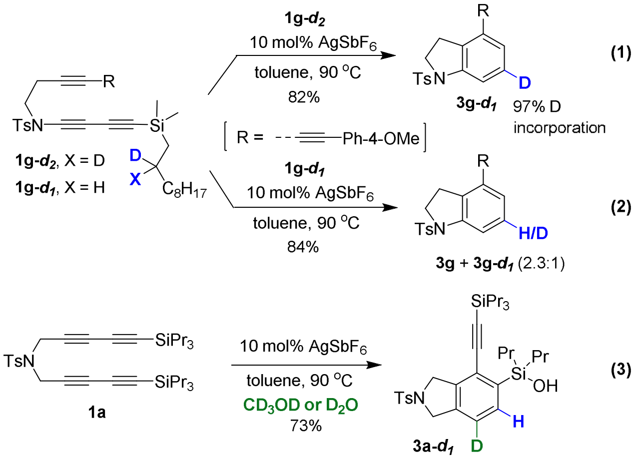


entry	substrate	product	yield (%)
1	 **1j**	 **2j**	95
2	 **1k**	 **2k**	92
3	 **1i**, X = NTs	 **2i**	89
4	**1m**, X =O	**2m**	95
5	 **1n**, R = SiMe$_2$t-Bu	 **2n**	87
6	**1o**, R = 4-Methoxyphenyl	**2o**	85
7	 **1p**	 **2p**	81
8	 **1q**	 **2q**[a]	81



[a] Si-C(sp^2) bond was hydrolysed during silica gel column chromatography.

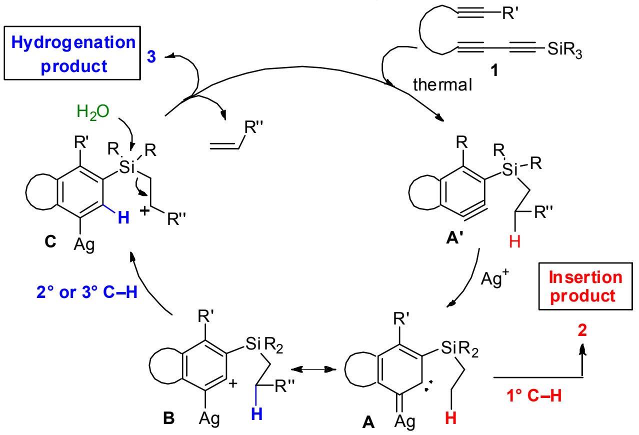
To gain more insights into this mechanistic dichotomy, bis- and mono-deuterated substrates **1g-d_2** and **1g-d_1** were prepared and their products were analyzed (Scheme 3). When bis-deuterium-labeled substrate **1g-d_2** was treated under the typical reaction conditions, nearly complete mono deuterium-incorporated product **3g-d_1** was isolated in 82% yield with 97% deuterium label only at the indicated position (eq 1), and the reaction of mono-deuterium-labeled substrate **1g-d_1** showed large deuterium kinetic isotope effect[17] (k_H/k_D = 2.3) to generate **3g** and **3g-d_1** in a 2.3:1 ratio (eq 2).



Scheme 3 Deuterium labeling studies

To confirm that one of the incorporated hydrogens is not from the alkyl group but from adventitious water molecules, substrate **1a** reacted separately with deuterium oxide and then with deuterated methanol. As expected, one deuterium in product **3a-d_1** was incorporated at only the indicated position (eq 3).

On the basis of these observed reactivity profiles, we propose a plausible reaction mechanism for the current formal hydrogenation and C–H insertion (Scheme 4). In this mechanistic scenario, we surmise that the concerted thermal hexadehydro-Diels–Alder reaction followed by silver complexation generates the silver-complexed aryne intermediates **A** and **B**.One of the most salient features of this mechanism is the dual reaction path that ultimately depends on the nature of the C–H bonds at the β-carbon of the silyl group in aryne intermediates **A** and **B**. The silver-complexed aryne[7,8] represented in form **A** containing only 1° C–H bonds at the β-carbon, undergoes a direct C–H insertion to generate the observed product **2**. On the other hand, more substituted intermediate represented in **B** containing 2° or 3° C–H bonds at the β-carbon preferentially undergoes hydride transfer to form a silicon-stabilized carbocation **C**, which then evolves to the



Scheme 4 Possible mechanisms for C–H insertion and hydride transfer with an aryne intermediate

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final product **3** through the traping of adventious water. The only exception to this general trend is the formation of the C–H insertion product **1i** from substrate **2i** containing a cyclohexyl group.

To provide a more detailed mechanistic picture on these proposed reaction pathways, we carried out DFT calculations[18] at the M06/6-31G*/LANL2DZ level of theory[19] on two model systems that represent the formation of C–H insertion product **2**, and hydrogenation product **3**, respectively. As shown in Figure 1, when **A-IN1** was used as a model intermediate containing 1° C–H bonds at β-carbon, the C2–H bond is activated by C1 of the aryne moiety with the C2–H and C1–H distances at 1.107 and 2.301 Å, respectively (Detailed geometric structures are given in the Supporting Information). From this intermediate, the C–H cleavage could be readily accessed with an activation barrier of 6.0 kcal/mol via transition state **A-TS1**, which adopts a fused tricyclic ring geometry (C1–H = 1.243, C2–H = 1.280, and C1–C2 = 2.220 Å) and leads smoothly to the C–H insertion intermediate **A-IN2**. In the next step, a 1,2–H shift via transition state **A-TS2** requires a barrier of about 3 kcal/mol to form the Ag-complexed intermediate **A-IN3**, which then leads to the formation of final product **3** after silver decomplexation. Although it is possible that **A-IN2** can undergo an ethyl group elimination to form a hypothetical intermediate **A-IN4** via **A-TS3**, the associated high activation barrier (24.3 kcal/mol) compared to that of its conversion to **A-IN3** (3.1 kcal/mol) will make this pathway highly unlikely. This is consistent with the observed experimental results and probably because the generated intermediate **A-IN4** is thermodynamically unfavorable.

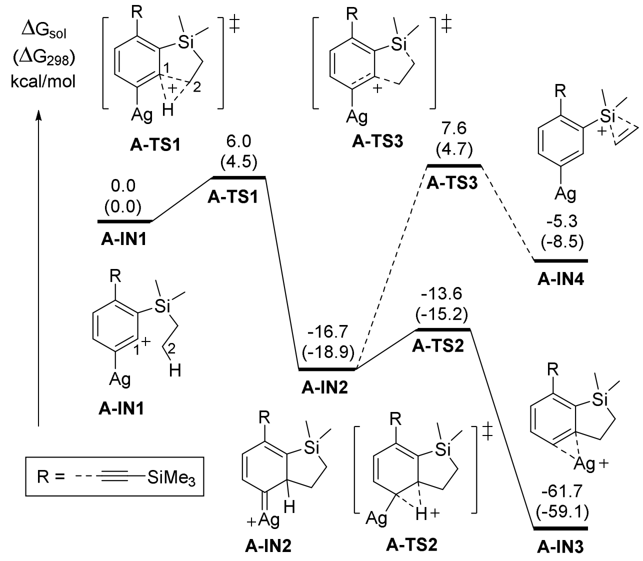

Figure 1 DFT-calculated reaction profile of intermediate **A-IN1** containing 1° C–H bonds at the β-carbon of the silicon[17]

For the formation of the formal hydrogenation product **3**, a simplified model system **B-IN1** was used to represent the tripropylsilyl-containing intermediate containing 2° C–H bonds at the β-carbon to silicon (Figure 2). As compared with that in **A-IN1**, the C2–H bond in **B-IN1** is more activated with much closer C1–H interaction (2.184 Å). As a consequence, the hydride transfer is favorably realized via a very low activation barrier (1.1 kcal/mol) transition state **B-TS1**, which is more flexible than **A-TS1** with longer C1–H (1.674 Å) and C1–C2 (2.652 Å) and shorter C2–H (1.144 Å) distances and leads directly to the propene-stabilized silylium ion **B-IN4**, which ultimately traps water to form the observed product **3**.

Although the formation of a hypothetical bicyclic intermediate **B-IN2** from the C–H insertion reaction of **B-IN1** is quite possible, the corresponding transition state could not be found. As the formation of **B-IN4** is almost a barrierless process, the reaction pathway involving **B-IN2** and its transition to the C-H insertion product is discredited, which is also consistent with

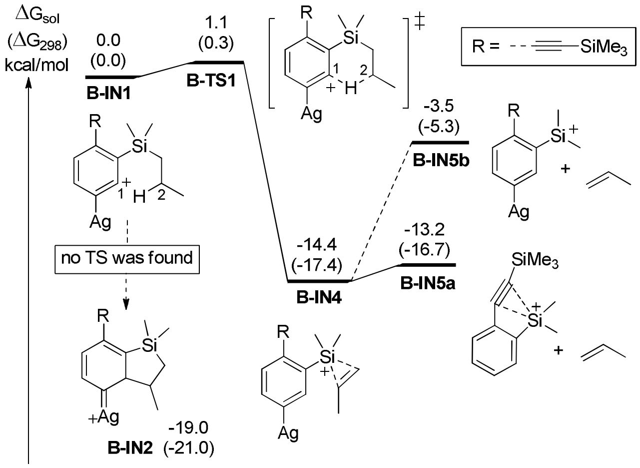

Figure 2 DFT-calculated reaction profile of intermediate **B-IN1** containing 2° C–H bonds at the β-carbon of the silicon[17]

the experimental results. Only the transition structure **B-TS1** evolved from **B-IN1** in the calculations, which indicates that the C–H insertion and hydride transfer steps become significantly more favorable than the competing direct C–H insertion that leads to **B-IN2**. This is the consequence of a subtle change in electronic and steric factors in the 2° C–H bonds relative to the 1° C–H bonds in **A-IN1**. In addition, the stronger stabilization effect of propene (in **B-IN4**) over ethylene (in **A-IN4**) on the silylium ion is shown by the larger exergonicity for the generation of **B-IN4**, indicating that the hydride transfer reaction becomes more thermodynamically favorable when 2° C–H bonds are involved. Calculations indicated that the decomplexation of the olefin from **B-IN4** should be facile, as the formation of **B-IN5a** is almost an energetically neutral process. In this latter intermediate the cationic silicon center could be stabilized by the π-electrons of the *ortho*-alkynyl group. As a comparison, the non-alkyne-complexed variant **B-IN5b**, in which the silyl cation is in conjugation with the phenyl ring, is found to be much higher in energy.

In conclusion, we have developed an efficient formal aryne hydrogenation relying on the 1,5-hydride transfer from the β-carbon of the silyl group in the aryne intermediates. Two contrasting reactivities of aryne intermediates have been observed and are dependent on the nature of the C–H bonds participating in the reaction, where 2° and 3° C–H bonds were exclusively subject to a hydride transfer to generate formal hydrogenation products and the corresponding 1° C–H bonds participated in only a direct C–H insertion process. This subtle electronic effect of the C–H bonds at the β-carbon of silyl groups ultimately results in completely different end products. The DFT

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calculations provide good mechanistic rationales for the respective C–H insertion with 1° C–H and hydride transfer of 2° and 3° C–H bonds. This novel control of aryne reactivity and the utility of the products from the C–H insertion and the formal hydrogenation will be further investigated in the future.

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Notes and references

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