

# Hydroarylation of Arynes Catalyzed by Silver for Biaryl Synthesis

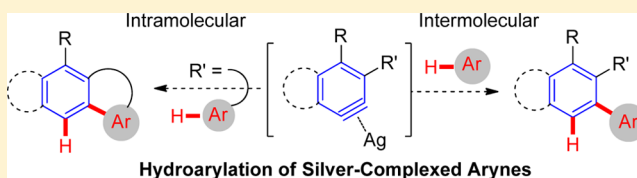
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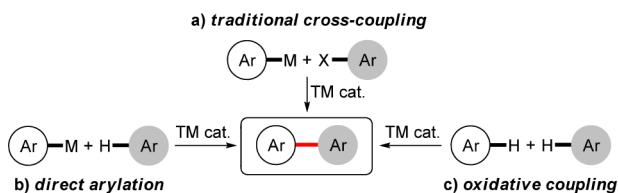
**S** Supporting Information

**ABSTRACT:** A new biaryl synthesis via silver-catalyzed hydroarylation of arynes from acyclic building blocks with unactivated arenes in intra- and intermolecular manners has been developed. The previously observed Diels–Alder reactions of arynes with arene were not observed under the current silver-catalyzed conditions. Deuterium scrambling and DFT calculations suggest a stepwise electrophilic aromatic substitution mechanism through the formation of a Wheland-type intermediate followed by a water-catalyzed proton transfer in the final step of the hydroarylation.



The biaryl motif is an important structural feature in many natural products, pharmaceuticals, and functional materials. Therefore, a variety of synthetic methods to form aryl–aryl bonds have been developed.<sup>1</sup> One common approach is the transition-metal-catalyzed cross-coupling (Negishi, Stille, Kumada, and Suzuki) (a, Scheme 1),<sup>1c,d</sup> which, despite its high

## Scheme 1. Catalytic Biaryl Formation<sup>a</sup>



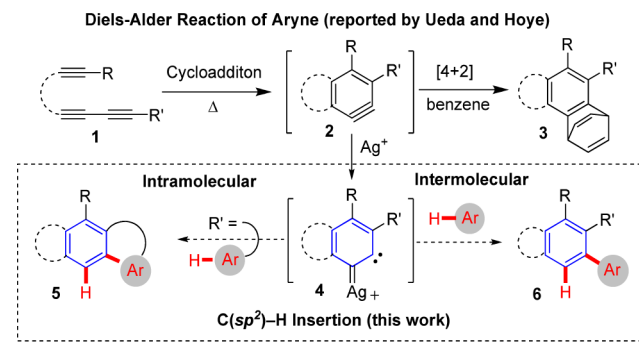
<sup>a</sup>TM = transition-metal complex, X = halides, pseudohalides, sulfonates, M = organometallic group.

efficiency and regiochemical control, requires preactivated aryl precursors such as aryl halide and aryl metal species. Recently, more atom-economical and greener alternatives such as direct C–H arylation (b, Scheme 1)<sup>1e–h</sup> and oxidative coupling of arenes (c, Scheme 1)<sup>1h</sup> have emerged. In the direct arylations, the Ar–Ar bond is formed through the activation of an aryl C–H bond by aryl-metal species (Ar–Pd, Ar–Rh, and Ar–Ru) generated from aryl halides. On the other hand, in the oxidative couplings, the aryl-metal species are generated via C–H bond activation by a catalyst in the presence of oxidants.

Different from the transition-metal-based catalytic processes, aryne<sup>2</sup>-based biaryl synthesis was first reported by Huisgen<sup>3a</sup> in 1958 and has continued to evolve through the research of several groups.<sup>3</sup> However, all of these reported methods require strongly activated aryl nucleophiles such as Grignard, lithium, and cuprate reagents. Recently, Daugulis and co-workers reported intra- and intermolecular arylation of C–H bonds in

electron-rich arenes by arynes.<sup>4</sup> On the other hand, Ueda<sup>5a</sup> and Hoye<sup>5b</sup> reported that the hexadehydro-Diels–Alder reaction of acyclic precursors **1** generate aryne intermediates **2**,<sup>6</sup> which undergo [4 + 2] cycloaddition rather than hydroarylation with arenes such as benzene to form product **3** (Scheme 2).<sup>7</sup> At this

## Scheme 2. Distinctive Reactivity of Arynes toward Arenes with and without Silver Catalyst



juncture, we hypothesized that if the [4 + 2] cycloaddition with benzene is suppressed, the electrophilic aryne species would participate in a Friedel–Crafts<sup>8</sup>-type electrophilic aromatic substitution reaction, which would then lead to an effective hydroarylation<sup>9</sup> to form various biaryls. Since the reactive aryne intermediate is generated via cycloaddition and the silver-catalyzed arynes<sup>10–12</sup> would have high enough reactivity toward arenes, neither the prefunctionalization of reacting arenes nor the use of an oxidant is necessary for this hydroarylation process.

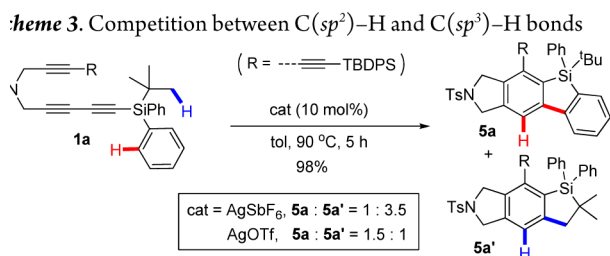
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The feasibility of this aryne-based hydroarylation was demonstrated by our recent observation where the *in situ* generated arynes from multiynes, in the presence of silver salt, resulted in an effective alkane C–H functionalization.<sup>10a</sup> This novel C–H bond activation by arynes is considered to be the consequence of the involvement of carbene-like species **4**.<sup>1a,13</sup> We surmise that the unusual reactivity of silver-complexed arynes can provide a powerful tool for hydroarylation via either direct activation of C(sp<sup>2</sup>)–H bonds or an electrophilic aromatic substitution in both intra- and intermolecular manners to deliver the final products **5** and **6**.

To exploit this catalyst-modulated aryne reactivity, we planned to test the feasibility of an intramolecular C(sp<sup>2</sup>)–H bond insertion. First, symmetrical substrate **1a** that contains potentially competing C(sp<sup>3</sup>)–H and C(sp<sup>2</sup>)–H bonds on the *tert*-butyldiphenylsilyl group was subjected to typical reaction conditions (Scheme 3). Indeed, with 10 mol % silver

### Scheme 3. Competition between C(sp<sup>2</sup>)–H and C(sp<sup>3</sup>)–H Bonds



hexafluoroantimonate (AgSbF<sub>6</sub>) as the catalyst, the insertion reactions on both the C(sp<sup>2</sup>)–H and C(sp<sup>3</sup>)–H bonds occurred, affording products **5a** and **5a'** in a 1:3.5 ratio. On the other hand, with silver triflate (AgOTf) a similar efficiency was observed but with a reversed 1.5:1 selectivity. Other silver salts containing different counterions or different transition-metal complexes also effected the insertion but in relatively low yields.<sup>14</sup>

Once the feasibility of C(sp<sup>2</sup>)–H insertion was demonstrated, we examined its generality with various substrates (Table 1). For C(sp<sup>2</sup>)–H insertion, AgOTf consistently showed superior performance compared to AgSbF<sub>6</sub>. This is the opposite in C(sp<sup>3</sup>)–H insertion where AgOTf tended to generate a triflate adduct. Similar to the beneficial effects of the *gem*-dialkyl groups on ring closure reactions,<sup>15</sup> the two alkyl or aryl groups on the silyl groups of the silyl-tethered substrate **1** confer the expected *gem*-dialkyl effect. Therefore, the efficiency of C(sp<sup>2</sup>)–H insertion with substrates **1b–1g** is generally higher than that with substrates **1h** and **1i** that contain a nitrogen or an oxygen tether.

Under optimized conditions with AgOTf (10 mol %) in toluene at 90 °C, substrates **1b** and **1c** afforded five-membered silacyclic products **5b** and **5c** in 87 and 67% yields, respectively (entries 1 and 2). It is worthwhile to note that the reaction of substrate **1c** afforded an insertion product of only a C(sp<sup>2</sup>)–H bond even though the *n*-pentyl group can still undergo insertion with its C(sp<sup>3</sup>)–H bonds. The different insertion behavior of **1c** compared to that of **1a** seems to be caused by the lack of *gem*-dimethyl effect when the *n*-pentyl moiety of **1c** is engaged in the insertion as opposed to the *gem*-dimethyl effect the *tert*-butyl group in **1a** would have. The substrates **1d–1g**, which contain a dimethylsilylmethylene tether, provided six-

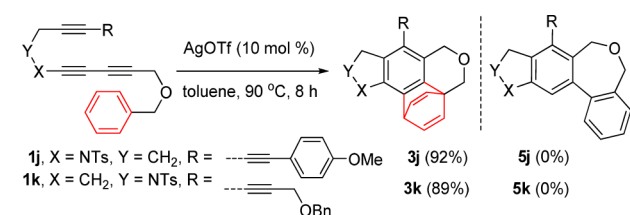
**Table 1. Intermolecular Hydroarylation of Silver Complexed Arynes**

entry	bis-1,3-diynes	product	yield (%) <sup>[a]</sup>
1	<b>1b</b>	<b>5b</b>	87%
2	<b>1c</b>	<b>5c</b>	67%
3	<b>1d</b>	<b>5d</b>	92%
4	<b>1e</b>	<b>5e</b>	92%
5	<b>1f</b>	<b>5f</b>	96%
6	<b>1g</b>	<b>5g</b>	94% <sup>[b]</sup>
7	<b>1h</b>	<b>5h</b>	49%
8	<b>1i</b>	<b>5i</b>	50%
Desilylation with TBAF (one-pot)			
9	<b>1b</b>	<b>6d</b> (89%)	
	<b>1c</b>	<b>6e</b> (88%)	
	<b>1f</b>	<b>6f</b> (93%)	

<sup>a</sup>Isolated yield. <sup>b</sup>Si–C(sp<sup>2</sup>) bond was hydrolyzed during silica gel column chromatography.

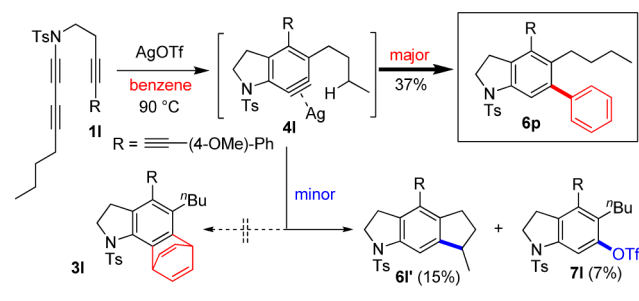
membered ring silacyclic products **5d–g** in 92–96% yields (entries 3–6). The bromide-containing aryl isoindoline derivative **5f** was also generated in excellent yield (96%). However, nitrogen- and oxygen-tethered substrates **1h** and **1i** afforded six-membered fused cycles **5h** and **5i** in only 49 and 50% yield, respectively (entries 7 and 8). Desilylation of the resulting silacyclic compounds **5d–5f** with TBAF (entry 9) efficiently afforded isoindoline derivatives containing biaryl moiety with toluene (**6d**), *p*-xylene (**6e**), and 2-bromotoluene (**6f**).

Although effective, the intramolecular C(sp<sup>2</sup>)–H insertion is limited to form only five- and six-membered rings. As shown in Scheme 4, longer tether-containing systems **1j** and **1k**

Scheme 4. Diels–Alder Reaction Rather Than C(sp<sup>2</sup>)–H Insertion

participated in only an intramolecular Diels–Alder reaction<sup>5b</sup> to generate **3j** and **3k** rather than undergoing C(sp<sup>2</sup>)–H insertion to produce seven-membered ring-containing hydroarylation products **5j** and **5k**.

To overcome this ring-size dependency in intramolecular hydroarylation, we turned our attention to intermolecular counterparts. Because we noticed that the C(sp<sup>3</sup>)–H insertion was relatively ineffective without the *gem*-dialkyl substituent at the propargylic site of the substrates,<sup>12</sup> we have chosen ynamide<sup>16</sup> derived unsymmetrical bis-1,3-diyne **1l** as a testing substrate for intermolecular hydroarylation (Scheme 5).

Scheme 5. Initial Attempt for Intermolecular C(sp<sup>2</sup>)–H Bond Insertion

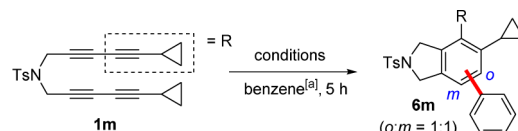
Gratifyingly, when **1l** was treated with AgOTf in benzene at 95 °C, biaryl compound **6p** was obtained predominantly along with only a trace amount of C–H insertion product **6l'** and trifluoromethanesulfonate adduct **7l**. As expected, Diels–Alder reaction product **3l** was not observed indicating the reactivity difference of aryl with and without a silver catalyst.

With these encouraging preliminary results in hand, we further examined an intermolecular hydroarylation employing cyclopropyl-substituted bis-1,3-diyne **1m** and benzene as the trapping agent (Table 2). When AgSbF<sub>6</sub> (10 mol %, 90 °C) was employed, complete conversion was observed within 5 h, and the isolated product was identified as the expected biaryl product **6m** (72%) with a 1:1 ratio of isomers (entry 1). AgOTf, which tends to give a triflate adduct, exhibited a similar reaction profile, but the yield was slightly lower (63%). Other metal triflates such as Cu(OTf)<sub>2</sub> and In(OTf)<sub>3</sub> were found to be inefficient (entries 3 and 4). A reaction temperature as high as 90 °C seems to be necessary because at lower temperatures either low conversion or no reaction was observed (entries 5 and 6).

When nonaromatic solvents were used together with 300 mol % benzene, no desired product was formed (entries 7–9), but in chlorobenzene, benzene adduct **6m** was obtained in 70% yield without contamination by a chlorobenzene adduct (entry 10).<sup>17</sup>

Next, we explored the prowess of the intermolecular hydroarylation employing both symmetrical and unsymmetrical

Table 2. Optimization of the Reaction Conditions



entry	catalyst (10 mol %)	solvent	temperature (°C)	yield (%) <sup>b</sup>
1	AgSbF <sub>6</sub>	benzene	90	72
2	AgOTf	benzene <sup>90</sup>	90	63
3	Cu(OTf) <sub>2</sub>	benzene	90	10
4	In(OTf) <sub>3</sub>	benzene	90	10
5	AgSbF <sub>6</sub>	benzene	50	5
6	AgSbF <sub>6</sub>	benzene	25	0
7	AgSbF <sub>6</sub>	CH <sub>3</sub> CN	90	0
8	AgSbF <sub>6</sub>	<i>c</i> -hexane	90	0
9	AgSbF <sub>6</sub>	CH <sub>2</sub> Cl <sub>2</sub>	40	trace
10	AgSbF <sub>6</sub>	PhCl	90	70

<sup>a</sup>3 Equivalent was used when the solvent is not benzene. <sup>b</sup>Isolated yield.

bis-1,3-diyne and triynes (Table 3). The formation of single isomeric products **6na**–**6nd** as well as **6o** was observed by reacting nonsymmetrical bis-1,5-diyne **1n** and **1o** containing a terminal alkynyl moiety with benzene, *p*-xylene, mesitylene, iodobenzene, and 2-bromo-1,3-dimethylbenzene. The high regioselectivity of these reactions can be rationalized by the selectivity trend that Garg<sup>18a</sup> and Houk<sup>18b</sup> identified for indolynes. It is worth noting that the known ene reaction of xylene and mesitylene with aryne<sup>7d</sup> was not observed in the current system. Among the halobenzenes (chlorobenzene, bromobenzene and iodobenzene) examined in the reaction with **1o**, only iodobenzene showed marginal reactivity and afforded **6o** as a single isomer (entry 5). The reaction of **1n** with 2-bromo-1,3-dimethylbenzene, however, afforded **6nd** efficiently (61%), which indicates that the electronic factor in the arene is crucial for successful hydroarylation. A butyl group-containing bis-1,3-diyne **1p** also afforded single isomer *ortho*-**6p** (entry 6). Triynes containing an amide or ester tether (**1q**–**1s**) also afforded single isomeric biaryl products (**6q**–**6s**) after a longer reaction time of 8 h rather than the typical 5 h for other substrates (entries 7–10). Substrate **1s**, containing a conjugated triyne moiety, showed similar reactivity and regioselectivity and afforded **6s** in 63% yield (entry 10). A set of arenes (entry 11) that is seemingly reactive enough in hydroarylation either afforded low yield or showed no reactivity in the reaction with substrate **1n**.

For the reaction of symmetrical bis-1,3-diyne **1m**, **1t**, and **1u**, the regioselectivity depends on the nature of the substituent on the 1,3-diyne moiety (Table 4). Ethyl-containing substrate **1t** afforded **6t** with slight preference of the phenyl incorporation at the *ortho*-position relative to the ethyl group (*m:o* = 2:1) (entry 1). By increasing the steric bulkiness to secondary alkyl such as the cyclopropyl group in **1m** and to SiMe<sub>3</sub> in **1u**, the ratio of isomers of **6m** and **6u** progressively changed and ultimately favored the phenyl incorporation at the *meta*-position with slight preference in **6u** (entries 2 and 3).

To gain insight into the mechanism of this hydroarylation, we carried out a competition experiment with benzene and benzene-*d*<sub>6</sub>, the product of which was analyzed by <sup>1</sup>H NMR and high-resolution mass spectrometry. This proved the existence of isotopomers **I**–**IV** in a 1:0.3:0.5:0.8 ratio (Scheme 6). The observed 1:1 ratio of products derived from benzene (**I**

Table 3. Intermolecular Hydroarylation of Silver Complexed Arynes

entry	substrate	R	arene	product	yield (%) <sup>[a]</sup>
1		Bu	benzene		60%
2			<i>p</i> -xylene		61%
3			mesitylene		59%
4			2-bromo-1,3-dimethylbenzene		61% <sup>[b]</sup>
5		Hex	iodobenzene		52% <sup>[c]</sup>
6			benzene		65%
7		X = NPh	benzene		42% <sup>[d]</sup>
8		X = O	benzene		55% <sup>[d]</sup>
9		X = O	<i>p</i> -xylene		68% <sup>[d]</sup>
10			benzene		63% <sup>[d]</sup>
11		X = vinyl, ~30% Br, ~20% Cl, ~10% OMe, ~10% SiMe <sub>3</sub> , ~0%			~0%

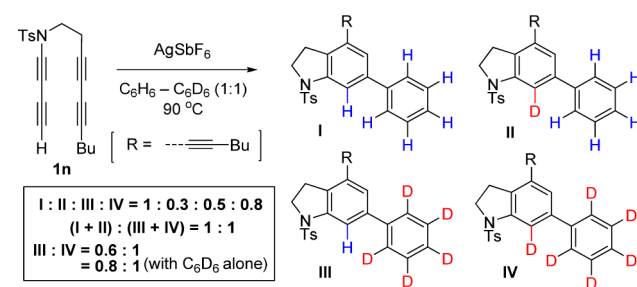
<sup>a</sup>Isolated yield. <sup>b</sup>Plus 20% regioisomer (*para* to bromide). <sup>c</sup>Plus 12% regioisomer (*para* to iodine). <sup>d</sup>5 h of reaction time instead of 5 h.

Table 4. Regioselectivity in Symmetrical bis-1,3-Dynes

entry	substrate	R	product	ratio ( <i>o</i> : <i>m</i> )	yield (%) <sup>a</sup>
1	<b>1t</b>	Et	<b>6t</b>	2:1	76%
2	<b>1m</b>	cyclopropyl	<b>6m</b>	1:1	72%
3	<b>1u</b>	SiMe <sub>3</sub>	<b>6u</b>	2:3	53% <sup>b</sup>

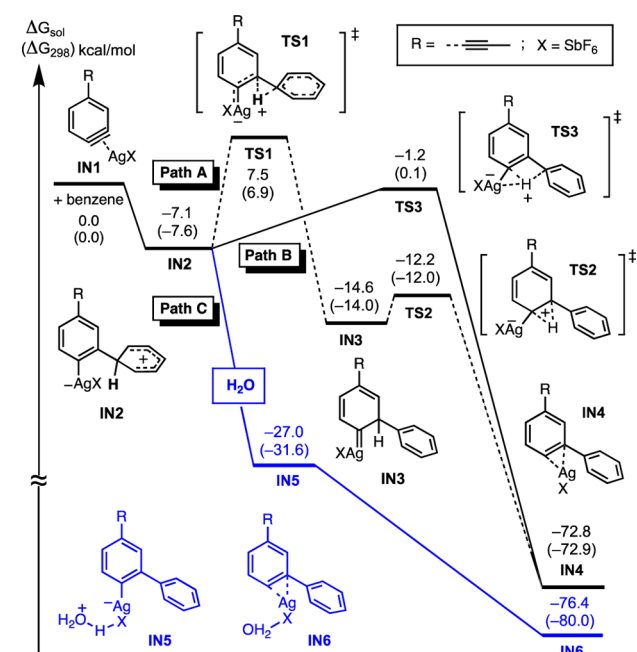
<sup>a</sup>Isolated yield as an inseparable mixture of isomers. <sup>b</sup>Plus 10% fluorinated product.

Scheme 6. Competition with Benzene and Deuterated Benzene



+ **II**) and benzene-*d*<sub>6</sub> (**III** + **IV**) indicates that there is no deuterium kinetic isotope effect. Furthermore, the formation of a significant amount of crossover products **II** (12%) and **III** (21%) implies that the reaction proceeded through a stepwise mechanism rather than a concerted C–H insertion process.

To further clarify this suggestive mechanistic data, we carried out DFT calculations<sup>19</sup> for the reaction of a simplified model substrate with benzene (Scheme 7).

Scheme 7. Energy Profiles for the Hydroarylation Calculated at the PCM-M06/6-31G\*/LanL2DZ Level<sup>19</sup>

In the calculation, Ag-complexed aryne **IN1**<sup>20</sup> interacted strongly with benzene to form Wheland-type intermediate **IN2**. Starting from this intermediate, three different reaction pathways were calculated including 1,2- (Path A) and 1,3-proton shift (Path B), and water-catalyzed proton transfer (Path C).<sup>19</sup> In path A, 1,2-proton shift through **TS1** led to carbenoid intermediate **IN3**, which ultimately provided silver-coordinated hydroarylation product **IN4** through **TS2**. The 1,3-proton transfer in Path B has a significantly lower activation barrier (5.9 kcal/mol) to reach transition state **TS3**, which collapses to the same product **IN4**. Considering the formation of crossover product **II** and **III** in Scheme 5, we surmise that the proton transfer is either mediated by an adventitious water molecule or by a bimolecular process. When a water molecule was placed around the H to be removed (O–H = 3.2 Å), no H-

bonded complex was located, and the simultaneous formation of intermediate **IN5** occurred. In the following step, however, no transition state for protodemetalation involving proton donation from the hydronium ion was found. Instead, a slight displacement of the hydronium ion toward the Ag–C bond rendered the direct formation of product complex **IN6**. Similar reaction profiles were found when calculated with a cationic silver species without the ligand ( $\text{SbF}_6^-$ ), although the water-catalyzed path had a sizable activation barrier (10.6 kcal/mol) for the proton transfer.<sup>19</sup> Based on these calculated energy profiles and the observed deuterium scrambling results, the most probable mechanism for the current hydroarylation involves the conversion of aryne-silver complex **IN1** to Wheland-type intermediate **IN2** followed by a water-catalyzed proton transfer.<sup>21,22</sup>

In summary, we have explored silver-catalyzed intra- and intermolecular hydroarylations of arynes that render an effective new biaryl synthesis from acyclic building blocks. Under the current silver-catalyzed conditions, the previously observed intermolecular Diels–Alder reaction of arynes with arene was not observed. The regioselectivity of C–H insertion in intermolecular reactions depends on both steric and electronic factors in the aryne intermediates. For the corresponding intramolecular insertion reactions, however, due to geometrical constraint of the short tether between the aryne and arene moieties, uniform regioselectivity was observed. Through this hydroarylation of arynes, various indoline, isoindoline, isoindolinone, and dihydroisobenzofuran derivatives containing a biaryl moiety were synthesized. The deuterium scrambling experiments and DFT calculations suggest that the hydroarylation occurs via a stepwise electrophilic aromatic substitution mechanism involving the formation of a Wheland-type intermediate followed by a water-catalyzed proton transfer in the final step instead of the direct insertion into the  $\text{C}(\text{sp}^2)$ –H bond of arenes by silver-activated arynes.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Experimental details, characterization data, NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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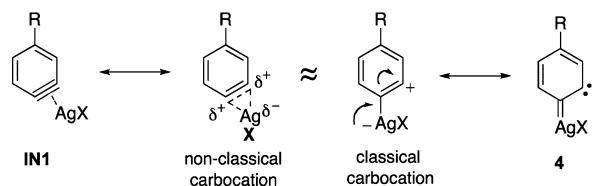
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(20) Carbene-type structure **4** is one of many possible heuristic representations of Ag-aryne complex. The structure used in the DFT calculation starts with another representation **IN1**. The relationship between these structures can be shown as follows.



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