

Communication

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# Alkane C–H Insertion by Aryne Intermediates with a Silver Catalyst

Sang Young Yun, Kung-Pern Wang, Nam-Kyu Lee, Phani Mamidipalli and Daesung Lee\*

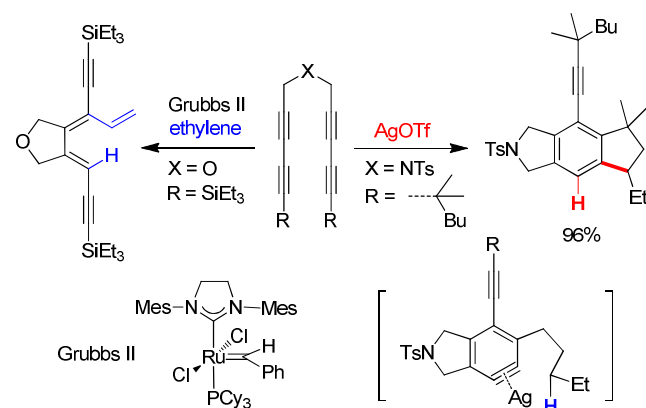
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Supporting Information

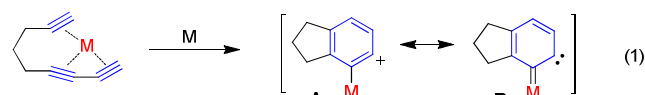
**ABSTRACT:** Arynes generated directly from alkyne building blocks in the presence of silver catalyst effectively activate primary, secondary and tertiary alkane C–H bonds. This C–H insertion requires only a catalytic amount of silver complex and modest heating compared to harsh conditions and extra promoters including directing groups, oxidants, and bases in typical transition metal-based C–H bond functionalizations. Preliminary mechanistic studies suggest that the C–H bond-breaking and new bond-forming events take place in a concerted manner, rendering a formal 1,2-addition of C–H bond across the  $\pi$ -bond of arynes.

Alkane C–H bonds exist ubiquitously in organic compounds, but due to their inert nature, they are reluctant to be engaged in chemical processes forming new bonds. The functionalization of these inert C–H bonds, although challenging and thus a long-standing research objective in academia and industry, would allow the most abundant natural saturated hydrocarbon feedstock to be processed to more valuable products.<sup>1–3</sup> From the perspective of developing environmentally benign and atom-economical methods, the direct catalytic C–H bond functionalization would have a significant merit because in principle, this technology will allow production of valuable chemical entities with the formation of a lesser amount of harmful by-products in more cost- and energy-effective manners. In recent years, a rapid evolution of directing group-assisted metal-catalyzed C–H bond functionalization processes has been witnessed.<sup>4</sup> Despite their benefits in facilitating the functionalization of inert C–H bonds in these approaches, the directing group needs to be removed after all when it is not a part of the target molecules, which is a significant limitation of this approach. In addition, the necessity of stoichiometric amounts of activators such as oxidants and bases or other additives significantly compromise the practicality of the current metal-catalyzed C–H functionalization approaches.<sup>5</sup>

## Scheme 1.



Previously we reported an unusual reactivity of multynes<sup>6</sup> with Grubbs ruthenium alkylidene complexes<sup>7</sup> under an ethylene atmosphere whereby a 1,4-hydrovinylative cyclization was effectively promoted (Scheme 1).<sup>8,9</sup> While expanding the synthetic utilities of this hydrovinylation process,<sup>10</sup> we found that in the presence of other metal complexes such as AgOTf, tetrayne **1** was converted into a tricyclic compound, which could be rationalized by the formation of an aryne intermediate<sup>11,12</sup> followed by its alkane C–H bond insertion. Even though arynes have been employed in organic synthesis for more than a century,<sup>13,14</sup> alkane C–H bond functionalization by aryne species has not been reported in the literature except for electron-rich aromatic C–H bonds.<sup>15</sup> We surmised that the effective C–H bond functionalization should be the consequence of the presence of a suitable metal catalyst that would generate an



intermediate viewed as a metal-stabilized aryl cation (A in eq 1) or a 1,2-bis-carbene-carbenoid canonical form (B in eq. 1). Different from free arynes, these metal-complexed arynes<sup>16</sup> have a subtle balance for its stability and reactivity such that even the least nucleophilic C–H bonds can be activated. Here we report a new C–H bond functionalization by arynes in the presence of silver catalyst, where unactivated 1°, 2° and 3° C–H bonds are effectively added across the  $\pi$ -bond of arynes.

**Table 1.** Screening of Catalysts and Reaction Conditions

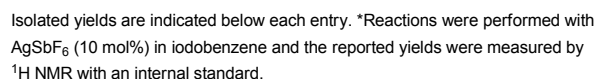
entry	catalyst	yield (%) <sup>a</sup>	entry	catalyst	yield (%) <sup>a</sup>
1	AgOTf	91 <sup>b</sup>	8	Sm(OTf) <sub>3</sub>	62
2	AgSbF <sub>6</sub>	88	9	In(OTf) <sub>3</sub>	78
3	AgNO <sub>3</sub>	82	10	Sc(OTf) <sub>3</sub>	63
4	AgOAc	85	11	Ru <sub>3</sub> (CO) <sub>12</sub>	53 <sup>c,d</sup>
5	AgO	23	12	PPh <sub>3</sub> AuCl	0
6	Cu(OTf) <sub>2</sub>	86	13	PtCl <sub>2</sub>	0
7	Zn(OTf) <sub>2</sub>	73	14	none	0

<sup>a</sup>Determined by <sup>1</sup>H NMR. <sup>b</sup>No conversion at 60 °C.

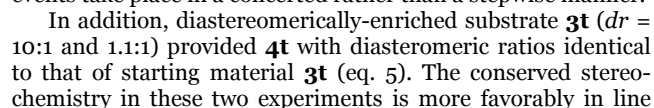
<sup>c</sup>HBF<sub>4</sub>·OEt<sub>2</sub> (15 mol%) was used. <sup>d</sup>No conversion without HBF<sub>4</sub>·OEt<sub>2</sub>

First we examined the effectiveness of various catalysts for C–H bond activation with bis-1,3-diyne substrate **1** containing ynamide tether (Table 1).<sup>17</sup> When a catalytic amount (10 mol%) of silver trifluoromethanesulfonate (AgOTf) was employed in toluene at 90 °C, complete conversion was observed within 5 h of reaction time, and the isolated product was unambiguously identified as the expected C–H insertion product **2** (entry 1). Various silver salts including AgSbF<sub>6</sub>, AgNO<sub>3</sub>, AgOAc exhibited similar level of catalytic activity, affording 82–88% yields of **2** but AgO gave only 23% yield of the product (entries 2 to 5). Other metal triflates such as Cu(OTf)<sub>2</sub>, Zn(OTf)<sub>2</sub>, Sm(OTf)<sub>3</sub>, In(OTf)<sub>3</sub>, and Sc(OTf)<sub>3</sub> were found to promote the C–H activa-

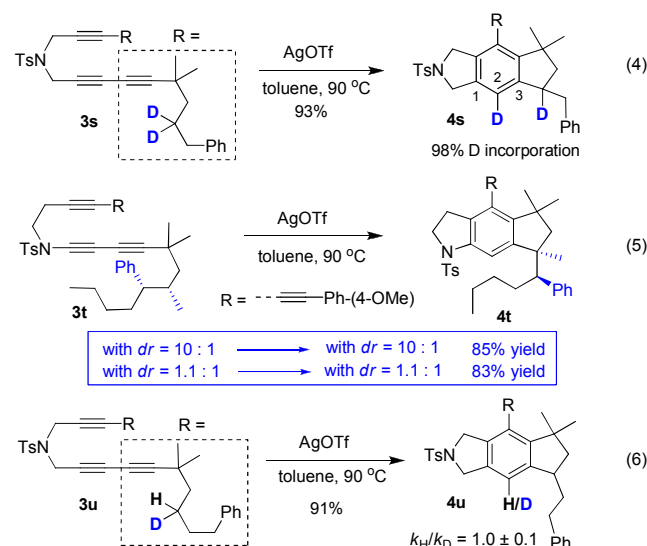
**Table 2.** Reaction Scope of Primary, Secondary and Tertiary C–H Bond Insertion



methyl group at the propargylic carbon afforded **4b** in markedly improved yield (92%) even under standard conditions (AgOTf, toluene), probably due to the known beneficial effect of the geminal dialkyl group on ring closure reactions.<sup>20</sup> The reactions of **3c** and **3d** were also performed with AgSbF<sub>6</sub> in iodobenzene, providing 2° C–H bond insertion products **4c** and **4d** in 78% and 75% yields, respectively. Nearly quantitative yields of 2° and 3° C–H bond insertion products **4e** and **4f** were obtained from substrates **3e** and **3f**. While the C–H insertion onto a pendant cyclopentyl moiety provided a single diastereomer **4g** in 72% yield, substrates containing the corresponding cyclohexyl and cycloheptyl moieties generated diastereomeric mixtures of **4h** and **4i**.<sup>21</sup> Interestingly, bridged bicycle frameworks, such as bicyclo[2,2,1]heptanes **4j** and **4k** as well as bicyclo[3,2,1]octane **4l**, were created in high yields via the insertion into a remote C–H bond on the pendant cycloalkyl groups. Substrates **4m–o** containing a silyl ether moiety, alkene and alkyne functionalities were tolerant if these functional groups are not directly attached to the carbon center where the C–H insertion occurs.<sup>22</sup> The existing stereogenic center like in (*S*)-citronellyl substituted *bis*-1,3-diyne **3p** did not impose any stereochemical bias for the diastereotopic C–H insertion events, affording **4p** as a 1:1 diastereomeric mixture in 85% yield. Next, we briefly examined the chemoselectivity of the insertion using substrates **3q** and **3r** that possess two different kinds of available C–H bonds for insertion environment of which is biased by both electronic and steric factors. It was found that the 2° C–H bond in substrate **3q** was significantly more reactive than its 1° C–H bond, affording a mixture of **4q** and **4q'** in 80% yield with a 13:1 ratio (eq. 2). The C–H insertion in substrate **3r** occurred at the indicated cyclic secondary C–H bond with significant preference over the primary C–H bond, generating a 10:1 mixture of **4r** and **4r'** in 88% yield (eq. 3).

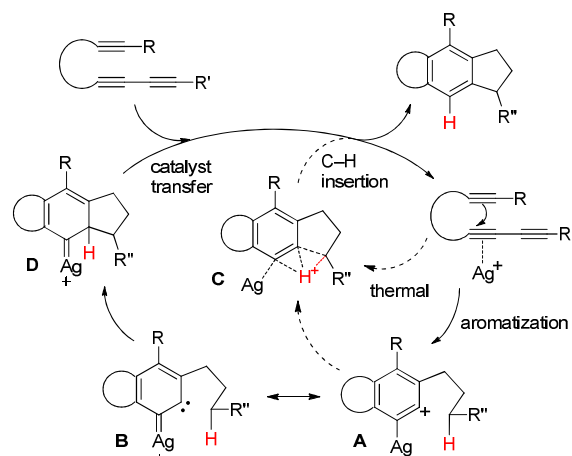


with a concerted mechanism for the C–H activation step more than a stepwise process via radical or cationic intermediate.



Finally, the transformation of mono-deuterated substrate **3u** to the insertion product **4u** showed a negligible magnitude of deuterium kinetic isotope effect<sup>23</sup> ( $k_H/k_D = 1.0 \pm 0.1$ ), which suggests that the rate-limiting step involves the aryne formation not the C–H bond cleavage (eq. 6). Although a complete picture of the mechanism for the current C–H insertion remains to be established, a tentative mechanism is proposed (Scheme 2). In this mechanistic scenario, a sequence of bond-forming events would lead to a key silver-complexed aryne intermediate **A** or its resonance form **B**,<sup>24</sup> which then undergoes C–H insertion through **C** to generate the final product or another intermediate **D**, respectively. Once, **D** is formed, a [1,2]-H shift would provide the same product with a concomitant catalyst transfer.

**Scheme 2.** Possible Mechanism for C–H Insertion



In conclusion, we have developed a new catalytic alkane C–H insertion to form carbon–carbon bonds mediated by arynes generated directly from alkyne building blocks. The simplicity of operation, broad substrate scope, and excellent site-selectivity of this unprecedented C–H activation method would inspire the synthesis of various molecular structures in green and atom-economical manners.

## 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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