Alkane C−H Insertion by Aryne Intermediates with a Silver Catalyst

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S *Supporting Information*

ABSTRACT: Arynes generated directly from alkyne building blocks in the presence of silver catalysts 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 π-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 into more valuable products.[1−3] 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 byproducts 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.[4] Despite their benefits in facilitating the functionalization of inert C−H bonds in these approaches, the directing groups must be subsequently removed when they are not part of the target molecules, which is a significant limitation of this approach. In addition, the need for stoichiometric amounts of activators such as oxidants and bases or other additives significantly compromises the practicality of the current metal-catalyzed C−H functionalization approaches.[5]

Previously we reported an unusual reactivity of multiynes[6] with Grubbs ruthenium alkylidene complex[7] under an ethylene atmosphere whereby a 1,4-hydrovinylative cyclization was effectively promoted (Scheme 1).[8,9] While expanding the synthetic utilities of this hydrovinylation process,[10] we found that, in the presence of other metal complexes such as AgOTf, tetrayne was converted into a tricyclic compound, which could be rationalized by the formation of an aryne intermediate[11,12] followed by its alkane C−H bond insertion. Even though arynes have been employed in organic synthesis for more than a century,[13,14] alkane C−H bond functionalization by aryne

Scheme 1
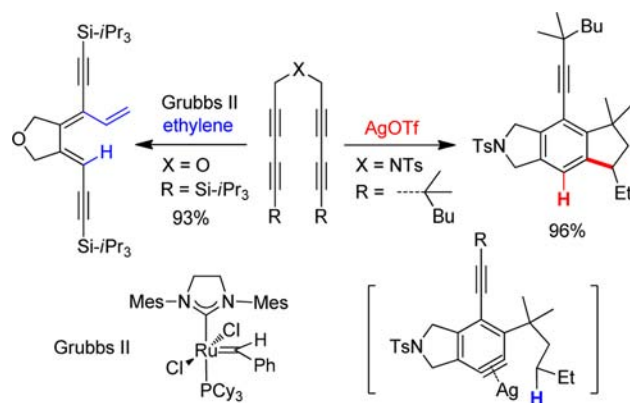
species has not been reported in the literature except for electron-rich aromatic C−H bonds.[15] We surmised that the effective C−H bond functionalization should be the consequence of the presence of a suitable metal catalyst that would generate an intermediate viewed as a metal-stabilized aryl cation (**A** in eq 1) or a 1,2-bis-carbene-carbenoid canonical form (**B** in
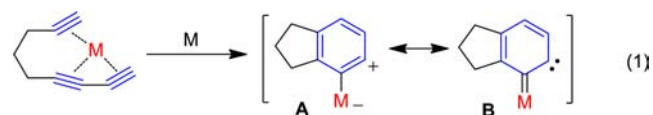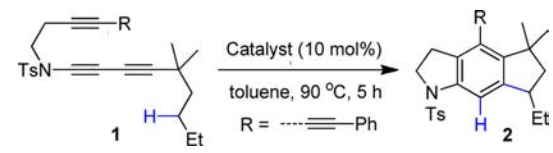

eq 1). Unlike free arynes, these metal-complexed arynes[16] have a subtle balance of stability and reactivity such that even the least nucleophilic C−H bonds can be activated. Here we report a new C−H bond functionalization by arynes in the presence of silver catalyst, where unactivated primary, secondary, and tertiary C−H bonds are effectively added across the π-bond of arynes.

First we examined the effectiveness of various catalysts for C−H bond activation with bis-1,3-diyne substrate **1** containing an ynamide tether (Table 1).[17] 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$_6$, AgNO$_3$, and AgOAc, exhibited similar levels of catalytic activity, affording 82−88% yields of **2**, but AgO gave only 23% yield of the product (entries 2−5). Other metal triflates such as Cu(OTf)$_2$, Zn(OTf)$_2$, Sm(OTf)$_3$, In(OTf)$_3$, and Sc(OTf)$_3$

Table 1. Screening of Catalysts and Reaction Conditions
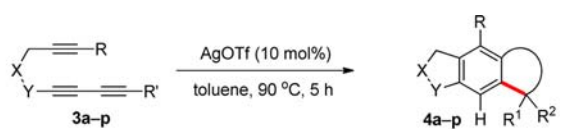
| entry	catalyst	yield (%)[a]	entry	catalyst	yield (%)[a]
1	AgOTf	91[b]	8	Sm(OTf)$_3$	62
2	AgSbF$_6$	88	9	In(OTf)$_3$	78
3	AgNO$_3$	82	10	Sc(OTf)$_3$	63
4	AgOAc	85	11	Ru$_3$(CO)$_{12}$	53[c,d]
5	AgO	23	12	PPh$_3$AuCl	0
6	Cu(OTf)$_2$	86	13	PtCl$_2$	0
7	Zn(OTf)$_2$	73	14	none	0

[a]Determined by ^{1}H NMR. [b]No conversion at 60 °C. [c]HBF$_4$·OEt$_2$ (15 mol%) was used. [d]No conversion without HBF$_4$·OEt$_2$

were found to promote the C−H activation in only slightly lower yields (62−86%, entries 6−10). A cationic ruthenium carbonyl complex, known for hydroamination and C−H bond activation, generated from Ru$_3$(CO)$_{12}$ and HBF$_4$·OEt$_2$,[18] also promoted the reaction smoothly, providing 53% yield of the C−H insertion product (entry 11), but Ru$_3$(CO)$_{12}$ alone was ineffective, and the starting material decomposed. In conrast, other metal complexes known for their high affinity for alkynes, such as PPh$_3$AuCl and PtCl$_2$,[19] generated only intractable material (entries 12 and 13). Without catalysts[13] under otherwise identical conditions, the substrate decomposed with no vestige of the product (entry 14).

The scope of this catalytic C−H insertion reaction was further explored with various unsymmetrical and symmetrical bis-1,3-diyne substrates (Table 2). In general, 1°, 2°, and 3° C−H bonds were activated to afford 5-membered-ring products, yet the substituent pattern in the alkyl chain significantly affected the reaction efficiency. While the insertion of the 1° C−H bond of **3a** was best achieved with AgSbF$_6$ (10 mol%) in iodobenzene to form **4a** in 62% yield, substrate **3b** containing a geminal dimethyl 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.[20] The reactions of **3c** and **3d** were also performed with AgSbF$_6$ 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 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**.[21] 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 and alkene and alkyne functionalities were tolerant if the functional groups were not directly attached to the carbon center where the C−H insertion occurs.[22] An 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**

Table 2. Reaction Scope of Primary, Secondary, and Tertiary C−H Bond Insertion[a]

[a]Isolated yields are indicated below each entry. *Reactions were performed with AgSbF$_6$ (10 mol%) in iodobenzene and the reported yields were measured by ^{1}H NMR with an internal standard.

that possess two different kinds of available C−H bonds for insertion, the environments of which are 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).

To gain mechanistic insights into the C−H activation process, a deuterium-labeled substrate **3s** was employed (eq 4). Under the typical C−H insertion conditions, nearly complete deuterium incorporation (>98%) at the C2 position of product **4s** was observed. When a competition experiment was performed with an equimolar mixture of a deuterium-labeled substrate **3s** and the unlabeled substrate **3j**, no crossover products were detected (Scheme S1). These results
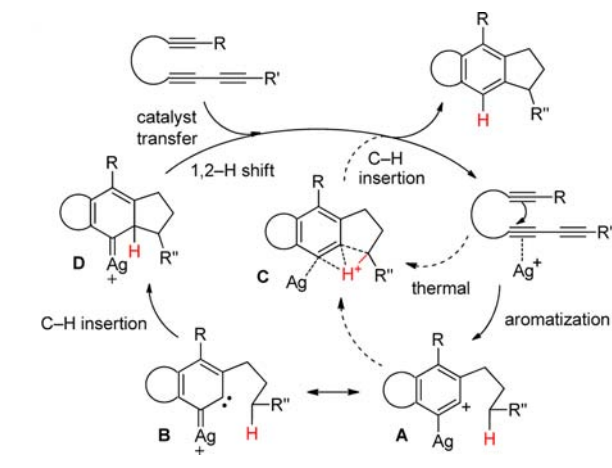
$$(2)$$

$$(3)$$

$$(4)$$

$$(5)$$

$$(6)$$

Scheme 2. Possible Mechanism for C−H Insertion
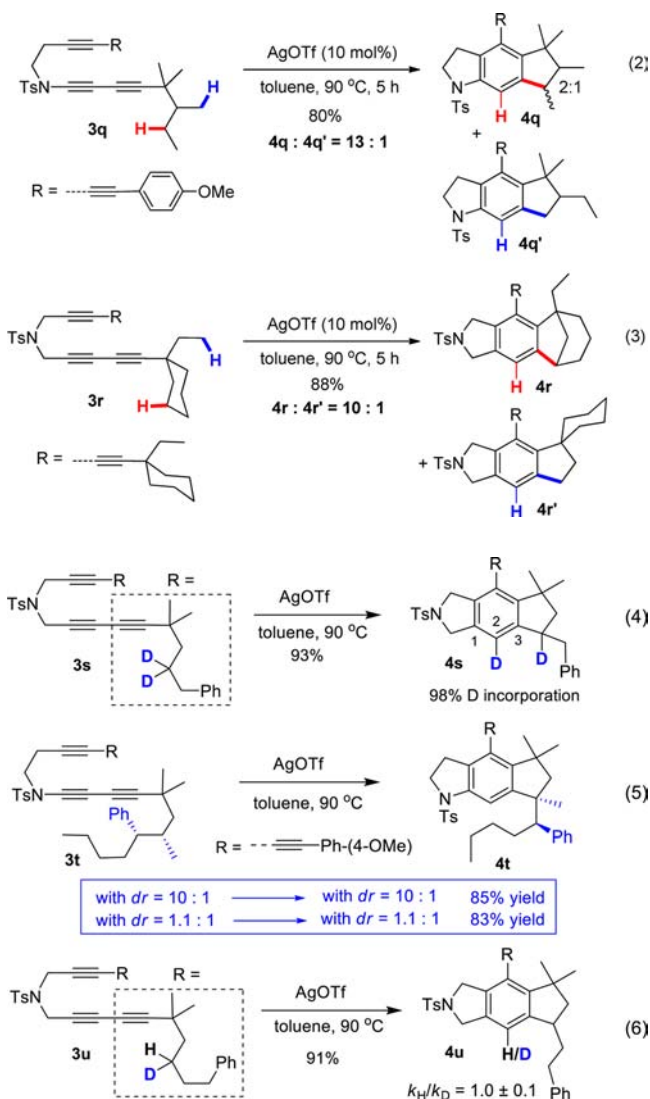
taken together imply that C(sp^3)−H bond-breaking and C(sp^2)−H bond-forming events take place in a concerted rather than a stepwise manner.

In addition, diastereomerically enriched substrate **3t** (dr = 10:1 and 1.1:1) provided **4t** with diasteromeric ratio identical to that of starting material **3t** (eq 5). The conserved stereochemistry in these two experiments is more favorably in line with a concerted mechanism for the C−H activation step than a stepwise process via a radical or cationic intermediate.

Finally, the transformation of monodeuterated substrate **3u** to the insertion product **4u** showed a negligible magnitude of deuterium kinetic isotope effect[23] ($k_H/k_D = 1.0 \pm 0.1$), 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**,[24] 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.

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 should inspire the synthesis of various molecular structures in green and atom-economical manners.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
Experimental details, characterization data, and 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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(21) See Supporting Information for details.

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