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Gold-Catalyzed Direct Assembly of Aryl-Annulated Carbazoles from 2-Alkynyl Arylazides and Alkynes

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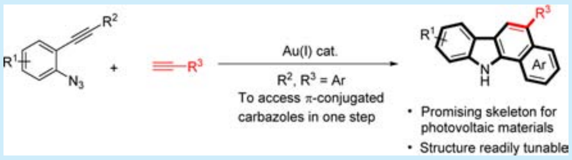
Ⓢ *Supporting Information*

ABSTRACT: An unprecedented gold-catalyzed synthetic method for the direct assembly of aryl-annulated carbazoles from 2-alkynyl arylazides and alkynes is described. The reaction is proposed to proceed via a sequential cyclopropenation and intramolecular metal carbene/arene Friedel–Crafts-type reaction, respectively, mediated by two gold carbene intermediates.



Carbazole chemistry has seen continuous growth in the last several decades.[1] The importance of carbazoles and related derivatives lies in their exceptional biological and pharmacological activities and unique electrical and thermal properties.[2,3] Specifically, aryl-annulated carbazoles are of great synthetic significance due to their potential as highly promising antitumor agents and promising building blocks in the synthesis of organic materials.[2a,c,4] For example, dihydrobenzo[*a*]carbazole **A** and benzo[*a*]carbazoles **B** and **C** have been potent anticancer agent against various tumor cell lines (Figure 1).[5] Moreover, aryl-annulated carbazoles, as π-extended carbazole derivatives, which have strong electron delocalization, have gained increasing attention in organic light-emitting diodes[6] and fluorescence reagents.[7] Notably, very recently, Qian and co-workers employed benzo[*a*]carbazole-containing compound **D** in dye-sensitized solar cells, providing a power conversion efficiency of 7.54%, which is very close to the result of commercially available dye N719.[8]

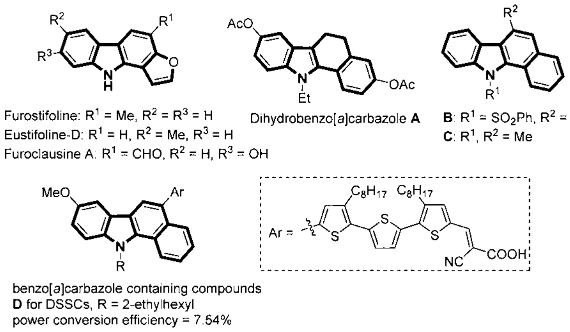


Figure 1. Natural products, bioactive compounds, and photovoltaic materials containing aryl-annulated carbazoles.

Over the past decades, dozens of methods for the synthesis of carbazoles have been developed.[9−15] However, the reports for direct and general synthesis of aryl-annulated carbazoles are quite limited.[16] Recently, gold catalysis has become a general concept for the creation of efficient synthetic methods to rapidly build up molecular complexity.[17] In particular, the gold catalyst allows an alkyne and an azide functionality to undergo a redox process, leading to the formation of an active α-imino gold carbene intermediate, which is able to subsequently participate in a wide range of transformations (eq 1). Toste and co-workers first discovered this reaction mode in a gold(I)-catalyzed intramolecular acetylenic Schmidt reaction (eq 2).[18] Zhang and co-workers developed a gold-catalyzed synthesis of 2,3-dihydro-1*H*-pyrrolizines with electron-withdrawing groups at the 5-postion from linear azidoenynes (eq 3).[19] The groups of Zhang and Gagosz independently reported a nucleophilic trapping of α-imino gold carbene and a Claisen rearrangement sequence between 2-alkynyl arylazides and allyl alcohol for the synthesis of indolin-3-ones (eq 4).[20] Employing propargyl alcohols as the nucleophiles, we recently established a gold-catalyzed cascade reaction for the synthesis of pyrroloindolone derivatives (eq 5).[21] Using alkene-tethered (azido)ynamides as substrates, the groups of Fujii and Ohno reported a gold-catalyzed cascade cyclization of (azido)ynamides proceeding through the formation of an α-amidino gold carbenoid.[22] As aforementioned, the in situ generation of α-imino gold carbenes followed by nucleophilic trapping and subsequent cascade reaction has proven to be a versatile platform for the synthesis of nitrogen-containing heterocycles. Herein, we will describe an unprecedented gold(I)-catalyzed direct assembly of benzocarbazoles from simple alkynes and 2-alkynyl arylazides, which could be easily prepared from 2-halogen aniline derivatives (eq 6).

As the starting point, a variety of gold complxes were evaluated for the reaction of **1a** with **2a** in dichloroethane at 60 °C. The ligands were found to have a considerable impact on the catalytic

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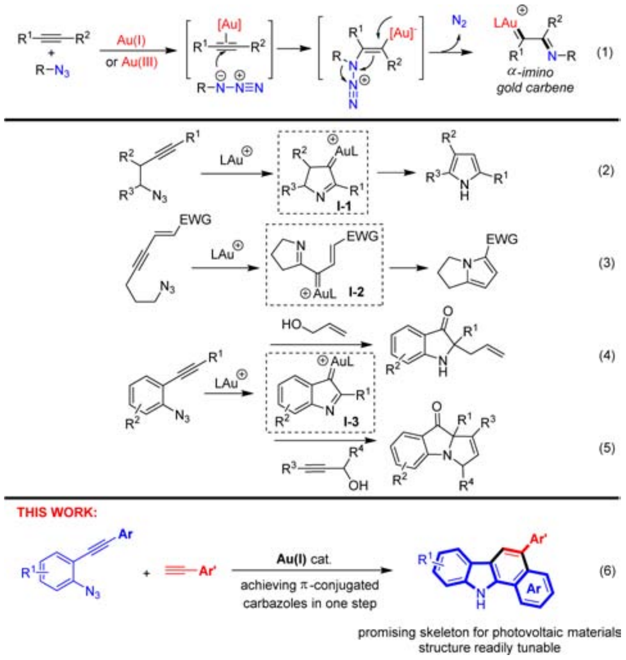
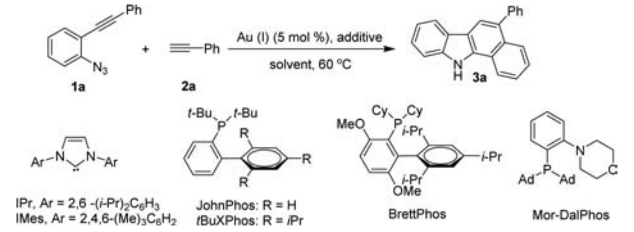


activity (Table 1, entries 1−6). For instance, $IPrAuNTf_2$ was able to give 65% yield, while a structurally similar catalyst, $IMesAuNTf_2$, provided **3a** in 46% yield (entry 2). Although the gold complexes with bulky biphenyl phosphine ligands were also capable of promoting the transformation, the product was isolated in moderate yields ranging from 44 to 51% (entries 3−5). The use of Mor-DalPhos, however, led to a significantly diminished yield (entry 6). Variation of the counterion of gold catalyst from NTf_2^- to SbF_6^- resulted in a slightly lower yield (entry 7). As reported by Ye, in some gold-carbene-mediated transformations, water could have a positive effect on the conversion and selectivity.[23] In our case, the addition of a small portion of water to the reaction led to considerable improvement in the yield when $IPrAuNTf_2$ was the catalyst (entry 8). The presence of 10 mol % of benzoic acid in the system led to a slightly improved yield (78% GC yield and 70% isolation yield, entry 9). The addition of 4 Å MS to the reaction led to a very diminished yield (35% yield). Although the actual role of water is not fully understood, we tend to believe that water and benzoic acid may accelerate the reaction by weakening the coordination effect (deactivation effect) of imino intermediates (**I−IV**) to the gold catalyst and also by facilitating the protonation and tautomerization of intermediate **IV** (see the mechanism description).

Table 1. Optimization of Catalysts and Reaction Conditions[a]

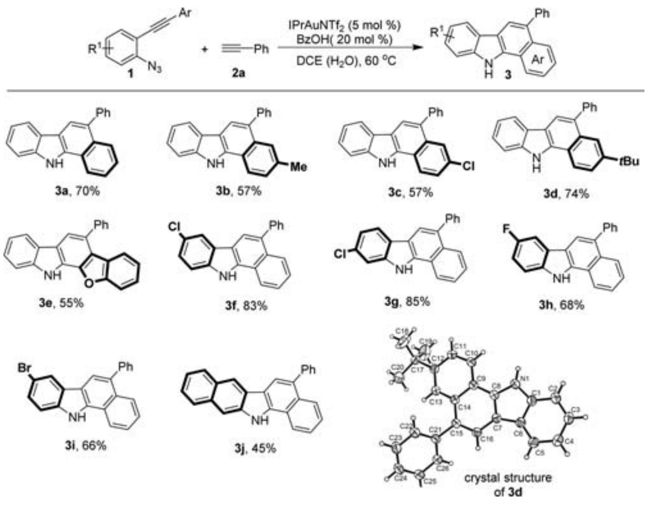


entry	cat/additive	solvent	yield (%)[b]
1	$IPrAuNTf_2$	DCE	65
2	$IMesAuNTf_2$	DCE	46
3	$tBuXPhosAuNTf_2$	DCE	51
4	$BrettPhosAuNTf_2$	DCE	44
5	$JohnPhosAuNTf_2$	DCE	51
6	Mor-$DalPhosAuNTf_2$	DCE	8
7	$IPrAu(NCMe)SbF_6$	DCE	63
8	$IPrAuNTf_2$	DCE+H_2O[c]	73
9	$IPrAuNTf_2$+BzOH[d]	DCE+H_2O[c]	78 (70[e])
10	$IPrAuNTf_2$+BzOH[d]+MS[f]	DCE	35[e]

[a] Unless indicated otherwise, the reaction of **1a** (0.1 mmol) and **2a** (0.4 mmol) was carried out at 60 °C in the presence of catalysts (5 mol %) in DCE (1 mL). [b] GC yield. [c] 1 mL of DCE and 1 mmol of H_2O were used. [d] 10 mmol % of BzOH was added. [e] Isolated yield. [f] 200 mg of 4 Å MS was added.

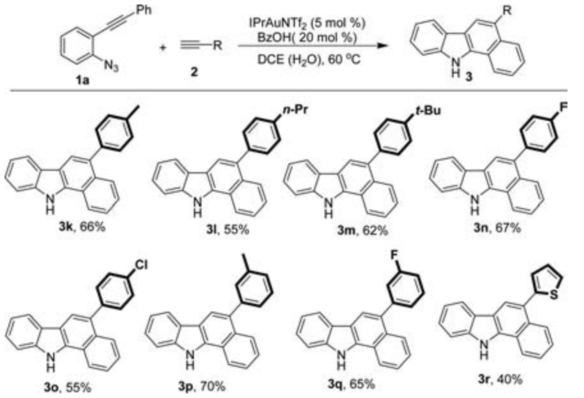
The optimized conditions were then applied to various azido alkynes and alkynes to examine the substrate scope of this reaction (Scheme 1). The variation of substituents at the alkyne terminus of **1** was initially investigated. Electron-donating (**3b**), electron-withdrawing (**3c**), and bulky (**3d**) substituents were all tolerated for this transformation, providing the corresponding products in 55−74% yields. A heteroaryl-substituted substrate **1e** also underwent the reaction smoothly, leading to benzofuro[2,3-*a*]carbazole **3e** in a moderate yield. The structure of one of the products, **3d**, was identified by single-crystal XRD analysis (see SI for details). Subsequently, the substitution variation at the azido alkyne core was investigated. For 4-Cl- and 5-Cl-substituted compounds **1**, the products were isolated in high yields (83−85%, **3f** and **3g**). 4-Fluoro- and 4-bromo-substituted substrates were also well-tolerated, giving rise to the desired products with fairly good yields (**3h** and **3i**). Notably, the tolerance of the bromo group, which is basically incompatible with the palladium catalysis based methodologies for carbazole synthesis, offers the possibility for the modulation of the structure of related products via cross-coupling reactions to further increase the structural complexity. Under the standard conditions, **3j**, which has a greater π-conjugated system, could also be obtained, albeit with a slightly lower yield. The generality for the alkyne substrates was finally examined. As shown in Scheme 2, all of the phenylacetylene derivatives tested, either bearing electron-withdrawing or -donating groups, were able to undergo the desired reaction to afford carbazole products in

Scheme 1. Scope of Azido Alkynes[a]



[a] Reaction of **1** (0.1 mmol) and **2a** (0.4 mmol) was carried out at 60 °C in the presence of $IPrAuNTf_2$ (5 mol %) and BzOH (10 mol %) in DCE/H_2O (1 mL/0.018 mL).

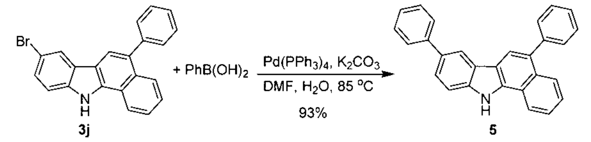
Scheme 2. Scope of Alkynes[a]



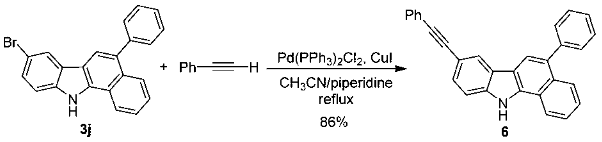
[a]Reaction of **1** (0.1 mmol) and **2a** (0.4 mmol) was carried out at 60 °C in the presence of $IPrAuNTf_2$ (5 mol %) and BzOH (10 mol %) in DCE/H_2O (1 mL/0.018 mL).

moderate to good yields. 2-Ethynylthiophene could also react with **1a** to offer the benzo[*a*]carbazole ring in 40% yield (**3r**). Aliphatic alkynes (e.g., 1-hexyne and cyclohexylacetylene) were unable to undergo the desired reaction.

Additionally, bromo-substituted product **3j** was subjected to palladium-catalyzed cross-coupling reactions to access more conjugated carbazole derivatives (eqs 7 and 8). Compounds **5** and **6** were successfully obtained in good yields through Suzuki coupling and Sonogashira coupling reactions, respectively.



(7)



(8)

A mechanism for this gold-catalyzed cascade reaction is proposed as shown in Figure 2. The *α*-imino gold carbene **I−3** initially formed from azido alkyne **1a** would be able to undergo a cyclopropenation with an acetylene[24] to generate a cyclopropene **II**. As a known vinyl metal carbene precursor,[25] cyclopropene **II**, in the presence of the gold catalyst, would be transformed into gold carbene intermediate **III**. After an intramolecular metal carbene/arene Friedel−Crafts-type reaction, intermediate **IV** could be generated, which would then be converted into benzo[*a*]carbazole **3** after protonation and tautomerization. One possible side reaction of this process might be the formation of **4a** via alkynyl C−H insertion of *α*-imino gold carbine **I−3a**.[26] A control experiment showed that presynthesized compound **4a** could not be transformed into **3a** under the reaction conditions. Thus, a gold-catalyzed intramolecular Friedel−Crafts-type reaction of **4a** to give **3a** can be ruled out.

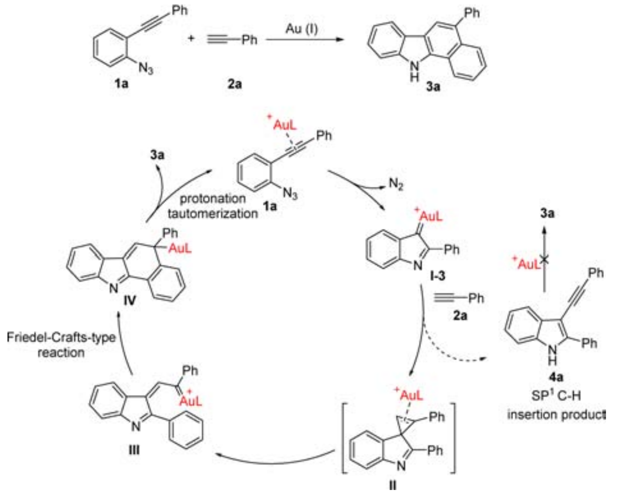


Figure 2. Proposed reaction mechanism.

In summary, we have established an unprecedented gold-catalyzed synthetic method for the direct assembly of aryl-annulated carbazoles from 2-alkynyl arylazides and alkynes. The reaction is mechanistically a cascade process proceeding sequentially via key reaction units, including cyclopropenation and intramolecular metal carbene/arene Friedel−Crafts-type reaction, which are mediated by two different gold carbene intermediates. This protocol provides a convenient route to aryl-annulated carbazoles from readily available starting materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01627.

Experimental procedures and characterization data (PDF)
X-ray data for compound **3e** (CIF)

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Notes

The authors declare no competing financial interest.

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