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Gold(I)-Catalyzed Formal Intramolecular Dehydro-Diels−Alder Reaction of Ynamide-ynes: Synthesis of Functionalized Benzo[*b*]carbazoles

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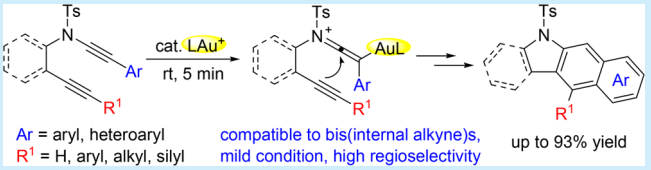
Supporting Information

ABSTRACT: A gold-catalyzed cycloisomerization of ynamide-ynes via a formal dehydro-Diels−Alder reaction has been developed, providing an attractive route to diversely substituted benzo[*b*]carbazoles. The reaction likely proceeds via regioselective attack of the pendant alkyne moiety to a keteniminium ion intermediate followed by benzannulation. The method offers several advantages such as high efficiency, mild reaction conditions, and wide functional group tolerance and serves as a highly useful complement to the thermal DDA reactions of ynamide-ynes.



Benzo[*b*]carbazoles, including aryl- and heteroaryl[*b*]-carbazoles, are an important class of nitrogen-containing heterocyclic compounds, which have been found in a wide variety of biologically active substances and have also received much attention in the fields of organic functional materials as fluorescent chemosensors,[1] organic light-emitting diodes (OLEDs),[2] and organic field effect transistors (OFETs).[3] For instance, ellipticine A and its analogues have been intensively studied over the past 50 years because of their anticancer properties.[4] Due to the structural similarity of benzo[*b*]-carbazoles to the ellipticines, it is widely concerned whether such compounds have similar biological activities. In this context, 5*H*-benzo[*b*]carbazole **B** with an indolyl group at the C-6 position was found to be an Aβ1−40 aggregation inhibitor that may be potentially useful for the treatment of progressive neurodegenerative diseases.[5] *N*-Methyl-substituted benzo[*b*]-carbazole **C** was discovered to have in vitro anticancer activity[6] (Figure 1). Although many methods have been developed for the synthesis of carbazoles, the efficient synthesis of benzo[*b*]-carbazoles is quite limited. These compounds have been commonly prepared from substituted indoles[7] or naphthalenes.[8] Recently, a number of synthetic approaches to benzo[*b*]carbazoles have been reported[1,4c,9] such as intramolecular dehydro-Diels−Alder reaction of ynamides,[9a−c] biradical cyclization of *N*-(2-alkynylphenyl)ketenimines,[9d,e] radical cyclization through imidoyl selanide intermediates,[4c] Pd-catalyzed cyclization of 2-alkynylbenzaldehydes with indoles,[9f] iron-catalyzed isomerization/cyclodehydration of 2-[(indoline-3-ylidene)(methyl)]benzaldehyde derivatives,[9g] etc. However, these methods usually have some limitations such as harsh conditions, being restricted to special substituted substrates, lack of flexibility, low product yields, etc. Thus, enhancing the efficiency of the synthetic methods that allow selective formation of benzo[*b*]carbazoles with wide substrate diversity under mild reaction conditions is still highly attractive. One important result of these previous efforts concerns thermal intramolecular dehydro-Diels−Alder reactions.[10] In 2005, Saá et al. reported that dehydro-Diels−Alder reactions of ynamide-tethered alkynes provided benzo[*b*]carbazoles in generally low to moderate yields at 150 °C.[9a−c] However, this method was incompatible with the substrates bearing substituents (except for a silyl substituent) on both ends of the alkyne terminals (three examples, yields <24%). In addition, the regioselectivity was also difficult to control, since both the arenynamide and arenyne moieties might undergo a cycloaddition reaction.[9a−c] During our study on the gold-catalyzed transformation of ynamides,[11,12] we envisioned that the synthesis of nitrogen heterocycles might be accessed through cyclization of ynamide-ynes involving regioselective attack of a nucleophile to keteniminium ion intermediate **I** or a gold−alkyne complex. Such reactions have been reported using furan, indole, alkene, or a hydride as the nucleophiles;[13] however, alkynes have rarely been utilized[15b] as the nucleophile in this type of reaction.[14,15]

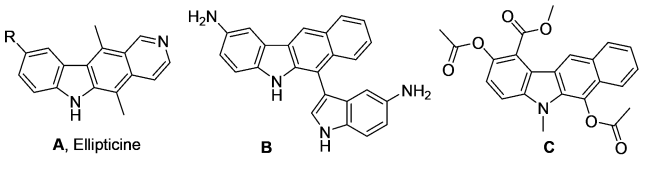


Figure 1. Biologically active benzo[*b*]carbazole derivatives.

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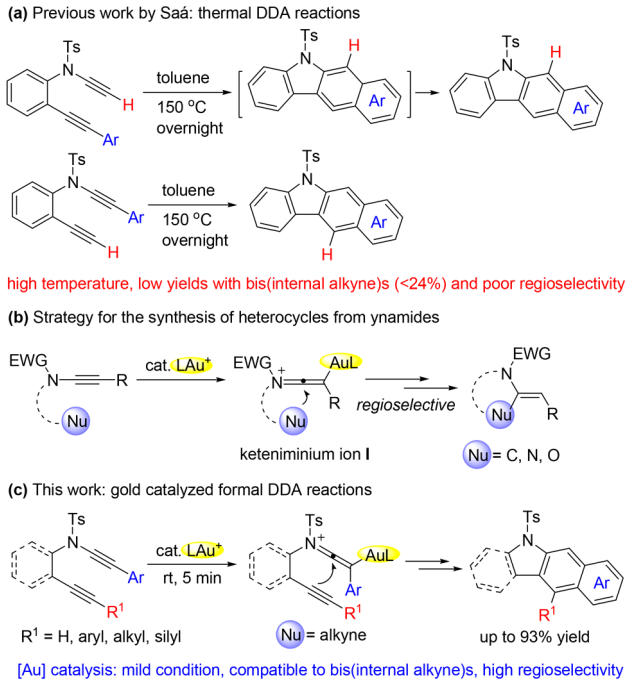
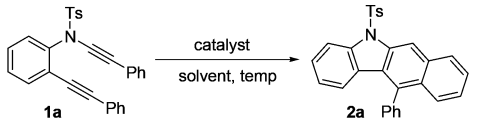
Herein, we describe a highly efficient and regioselective cyclization of ynamide-ynes to benzo[*b*]carbazoles under extremely mild reaction conditions via a formal dehydro-Diels–Alder reaction (Scheme 1). In this reaction, the cycloaddition occurs selectively at the arenynamide moiety.

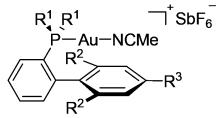
Scheme 1. Synthesis of Benzo[*b*]carbazoles from Ynamide-Tethered Alkynes



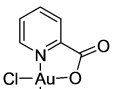
To test our hypothesis, we initially investigated the cyclization reaction of ynamide **1a** bearing two phenyl groups at the alkyne terminus by using 5 mol % PPh_3AuNTf_2 as the catalyst. To our delight, benzo[*b*]carbazole **2a** could be obtained in 72% NMR yield within 2.5 h at room temperature in DCE (Table 1, entry 1). Switching the catalyst to PPh_3AuCl/$AgSbF_6$ resulted in a similar yield of **2a** (entry 2). Gratifyingly, it was found that JohnphosAu(MeCN)SbF_6 (catalyst **A**) was highly efficient for this transformation, leading to **2a** in 93% yield within 5 min (entry 3). The results indicate that the nature of the ligands played an important role in promoting catalytic activity. It is worth noting that the isolated product **2a** contained a trace amount of coloring material by direct separation on a silica gel column. The coloring material could be removed by treatment of the reaction mixture with H_2O_2 solution at 80 °C before column chromatography. The use of more crowded ^{t}BuXphos (catalyst **B**) also resulted in an excellent yield of 91% (entry 4). A gold(III) complex of $PicAuCl_2$ (catalyst **C**) provided **2a** in a low yield with a longer reaction time (24 h, 31%, entry 5). High product yields could also be observed when the reactions were carried out in DCM, THF, and toluene, whereas only 75% of **2a** was formed in MeCN (entries 6–9). Employing Lewis acids such as $AgSbF_6$, $Zn(OTf)_2$, $ZnCl_2$, $FeCl_3{\cdot}6H_2O$, and $Cu(OTf)_2$ as the catalyst afforded **2a** in yields ranging from 6% to 39% after stirring for 1–10 h at 50 °C (entries 10–14). When Brönsted acids such as TfOH, MsOH, or $HNTf_2$ were used as the catalyst, **2a** was formed in low yields (entries 15–17). These results indicate that gold catalysts displayed superior reactivity for this reaction, compared to that of the other catalysts. The reaction proceeded slowly at 80 °C without adding any catalyst, furnishing **2a** in 62% yield after 17 h (entry 18).

Table 1. Optimization of the Reaction Conditions





A, R^1 = ^{t}Bu, R^2 = R^3 = H
B, R^1 = ^{t}Bu, R^2 = R^3 = ^{i}Pr



C

entry	catalyst (mol %)	solvent	temp	time	yield (%)[a]
1	PPh_3AuNTf_2 (5)	DCE	rt	2.5 h	72
2	$PPh_3AuCl/AgSbF_6$ (5)	DCE	rt	2 h	75
3	**A** (5)	DCE	rt	5 min	93 (90[b])
4	**B** (5)	DCE	rt	5 min	91
5	**C** (5)	DCE	rt	24 h	31
6	**A** (5)	DCM	rt	5 min	91
7	**A** (5)	THF	rt	5 min	91
8	**A** (5)	toluene	rt	0.5 h	85
9	**A** (5)	MeCN	rt	17 h	75
10	$AgSbF_6$ (10)	DCE	50 °C	1 h	6
11	$Zn(OTf)_2$ (10)	DCE	50 °C	10 h	13
12	$ZnCl_2$ (10)	DCE	50 °C	10 h	15
13	$FeCl_3{\cdot}6H_2O$ (10)	DCE	50 °C	7 h	11
14	$Cu(OTf)_2$ (10)	DCE	50 °C	7 h	39
15	TfOH (10)	DCE	50 °C	22 h	18
16	MsOH (10)	DCE	50 °C	18 h	22
17	$HNTf_2$ (20)	DCE	50 °C	3 h	9
18	none	DCE	80 °C	17 h	(62)

[a]0.2 mmol scale. NMR yields using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are shown in parentheses. [b]After treatment with H_2O_2 solution.

With the optimized reaction conditions in hand (Table 1, entry 3), we then focused our attention on the investigation of the substrate scope of this novel cyclization reaction. The results are shown in Scheme 2. To begin with, the effects of aryl substituents on the Ar ring were first studied. Electron-donating groups such as *p*-methyl or 3,5-dimethyl on the aryl ring were well compatible, leading to **2b** and **2c** in 75% and 85% yields, respectively. The presence of a *p*-methoxy substituent on the aryl ring resulted in a low yield of the desired **2d** (18%), possibly due to undesired side reactions caused by a methoxyphenyl group.[16] Substrates bearing electron-withdrawing aryl groups such as *p*-Cl, *p*-CO_2Et, and *p*-NO_2 were well tolerated in the reaction, furnishing **2e**–**2g**[17] in 84–90% yields within 10 min. In addition, a reaction of **1f** at 1 mmol scale also provided a high yield of **2f**. It was noted that thermal cyclization of **1g** at 150 °C overnight afforded **2g** in only 16% yield.[9a–c,18] The results demonstrate the superior advantage of gold catalysis over thermal reactions for internal alkynes. Cyclization of 2-pyridyl-containing substrate **1h** proceeded slowly, even at 80 °C, and the desired **2h** was formed in 29% yield. This is possibly due to the competing coordination of the pyridyl moiety with gold, causing deactivation of the catalyst. Next, the effects of the substituents on the R^1 group were evaluated. For aryl substituents, both the electron-rich and electron-deficient substituents were compatible, furnishing **2i**–**2j** in 89–93%

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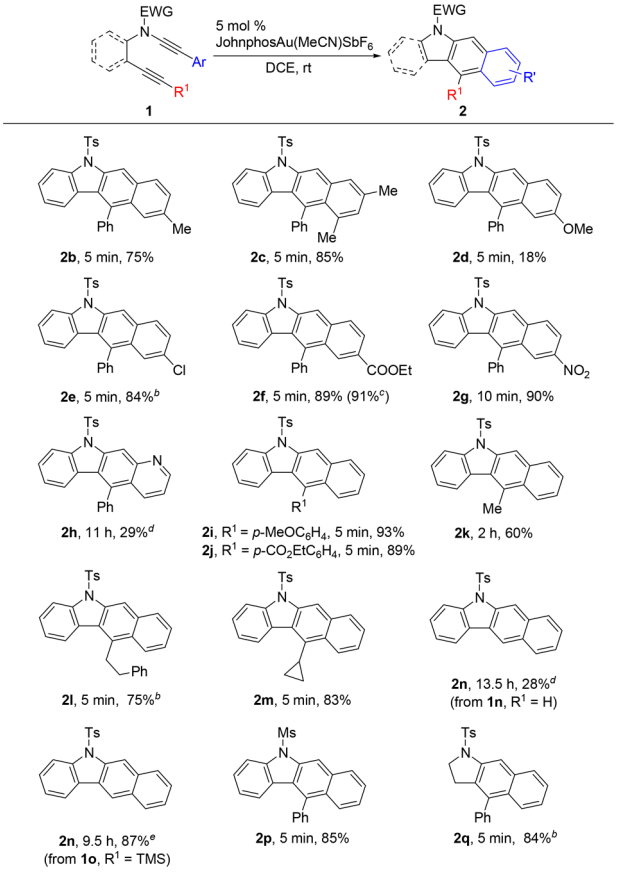
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Scope of Gold-Catalyzed Cyclization of Ynamide-ynes[a]



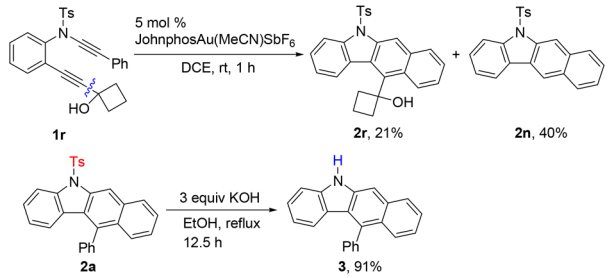
[a]0.2 mmol scale. Isolated yields. [b]After treatment with H_2O_2 solution. [c]Reaction was run at 1 mmol scale. [d]50 °C. [e]80 °C.

yields. Alkyl substituents were also well suited for this reaction. For example, employing methyl-substituted substrate **1k** led to the formation of **2k** in 60% yield. The reaction of a phenethyl-substituted alkyne took place readily and efficiently to give **2l** in 75% yield. A substrate with a cyclopropyl group as R^2 was transformed into the corresponding product **2m** in 83% yield. Cyclization of **1n** bearing a bottom terminal alkyne moiety proceeded less efficiently to give **2n** in 28% yield at 50 °C, possibly due to the reduced stability of the resulting vinyl cationic species involved in the reaction. It was noted that when R^1 was a TMS group, the desilylated product **2n** was formed in a high yield of 87%.[19] Thus, the TMS group can be used as a hydrogen equivalent in this reaction. *N*-Mesyl-substituted substrate **1p** afforded **2p** in a good yield of 85%, indicating that the protecting group has little effect on this reaction. In addition, the reactivity of a linear substrate **1q** was also examined, and the corresponding cyclized product **2q** was formed in a high yield of 84%.

Interestingly, when substrate **1r** bearing a cyclobutanol moiety was employed as the substrate, the desired product **2r** was obtained only in 21% yield, along with benzo[*b*]carbazole **2n** in 40% yield. The results indicate that a C−C bond cleavage reaction occurred during the reaction. In addition, the protecting group on the nitrogen can be facilely removed though base-promoted detosylation (Scheme 3).

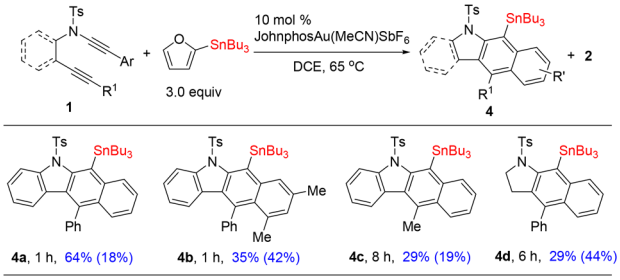
Our original mechanistic proposal suggested that an aryl-gold intermediate might be formed during the process. To verify this

Scheme 3. Transformation of 1r and Detosylation Reaction



intermediate, and also demonstrate its further utility through functionalization of the C−Au bond, Au/Sn transmetalation reactions using 2-tributylstannylfuran as the tin reagent were performed.[20] To our delight, treatment of **1a** with 3 equiv of 2-tributylstannylfuran and 10 mol % JohnphosAu(MeCN)SbF_6 at 65 °C in DCE for 1 h formed stannylated benzo[*b*]carbazole **4a** in 64% yield, along with 18% of nonstannylated product **2a** (Scheme 4). This result represents an important extension of

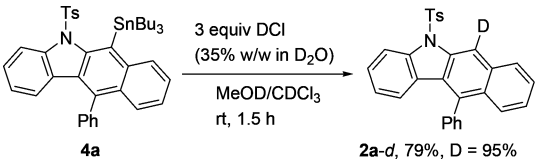
Scheme 4. Gold-Catalyzed Stannyl Transfer Reaction



[a]Isolated yields. The yields of nonstannylated products **2** are shown in parentheses after treatment with H_2O_2.

our previous work in which *β*-stannyl naphthalenes were synthesized.[20a] The scope of the reaction was briefly investigated, and the yields ranged from 29 to 35% for stannylated products in the cases of **4b**−**4d**. These products might be further functionalized through a Stille coupling reaction. The C-6 position of the Bu_3Sn group on the benzo[*b*]carbazole was confirmed by a deuterium-labeling experiment through the reaction of **4a** with DCl in a mixed solvent of MeOD/$CDCl_3$ (Scheme 5).

Scheme 5. Deuterium Labeling Experiment



We propose the following reaction mechanism for this reaction (Scheme 6). Initially, the alkyne moiety attacks the gold-coordinated ynamide **5** or keteniminium ion intermediate **5′** regioselectively due to the polarity of the ynamide to afford vinylcation species **6**. Subsequent nucleophilic attack of the phenyl ring on the vinyl cation followed by aromatization leads to the formation of aryl gold intermediate **8**, which undergoes protodeauration to give the product **2**. To account for the formation of **2n** in the case of cyclobutanol-substituted aryl

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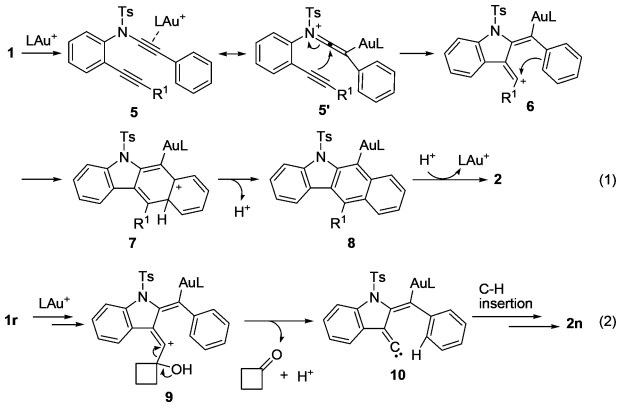
Scheme 6. Possible Reaction Mechanism



alkyne **1r**, a possible reaction pathway is shown in Scheme 6, eq 2. After formation of vinylcation **9**, a C−C bond cleavage reaction occurs to give carbene intermediate **10** with concomitant elimination of cyclobutanone. Insertion of the carbene to the C−H bond of the aryl ring generates the benzo[*b*]carbazole **2n**.

In summary, we have disclosed a new reaction pattern of gold-catalyzed cycloisomerization of ynamide-ynes via a formal dehydro-Diels−Alder reaction, which provides an attractive route to diversely substituted benzo[*b*]carbazoles. The reaction likely proceeds via attack of the pendant alkyne moiety to a keteniminium ion intermediate followed by benzannulation. Functionalization of the resulting aryl gold intermediate via Au/Sn transmetalation was also performed to afford C-6-stannylated benzo[*b*]carbazoles. The method offers several advantages such as high efficiency, mild reaction conditions, and wide functional group tolerance and serves as a highly useful complement to the thermal DDA reactions of ynamide-ynes. Further studies to extend this chemistry for the synthesis of a wide variety of heterocycles are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01145.

Experimental details, spectroscopic characterization of all new compounds (PDF)

Accession Codes

CCDC 1836362 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(17) The X-ray crystal structure of **2g** is given in the Supporting Information.

(18) The correct structure of **2g** was shown in ref 9b and c.

(19) Reactions of **1n** or **1o** under the thermal conditions (DCE, 80 °C) afforded the same product **2n** in trace amounts or low yield, respectively; see Supporting Information for details.

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