

# Gold-Catalyzed Cascade Cyclization of (Azido)ynamides: An Efficient Strategy for the Construction of Indoloquinolines

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#### **Supporting Information**

**ABSTRACT:** (Azido)ynamides were efficiently converted into indoloquinolines by the use of a gold catalyst. While ynamides bearing an allylsilane gave terminal alkenes, ynamides bearing a simple alkene gave cyclopropanes. This reaction proceeds through the formation of an  $\alpha$ -amidino gold carbenoid.



uring the past decade, gold has attracted considerable attention as an effective  $\pi$ -acid for the activation of alkynes and allenes,<sup>1</sup> and the gold-catalyzed reactions of alkynes and alkenes have been used extensively to synthesize a broad range of natural products and complex molecules in an efficient and chemoselective manner.<sup>2</sup> In addition to its ability to activate  $\pi$ bonds, gold ions bearing alkenyl or alkynyl ligands are electrondonating and have the ability to form gold-carbenoid species, which have been reported as intermediates in the reactions of enynes,<sup>3</sup> diynes,<sup>4</sup> and alkynes with N-oxides,<sup>5</sup> as well as the rearrangement reactions of 1,2-propargylic esters.<sup>5a,6</sup> In 2005, Toste et al.<sup>7a</sup> reported the use of azide as an effective nitrene equivalent for the generation of a gold-carbenoid species in their synthesis of pyrroles. Following on from this pioneering work, Gagosz<sup>7b</sup> and Zhang<sup>7c</sup> independently reported the development of a novel method for the synthesis of indoles from alkynyl azides by the nucleophilic addition of alcohols or arenes to gold carbenoids. In contrast to these studies, there have been no reports in the literature to date pertaining to the reactivity of ynamides with azides, despite the potential utility of this reaction in the synthesis of  $\alpha$ -carboline-type fused indoles.

As a part of our ongoing research toward the development of gold-catalyzed reactions for the construction of the core structures of pharmaceutically important compounds,<sup>8</sup> we became interested in the direct synthesis of the  $\alpha$ -carbolines and indoloquinolines. These heterocyclic frameworks can be found in numerous bioactive natural products (Figure 1),<sup>9</sup> as well as a wide range of synthetic derivatives exhibiting antimalarial



**Figure 1.** Natural products containing an  $\alpha$ -carboline/indoloquinoline framework.

and antitumor activities.<sup>10</sup> It was envisaged that the goldcatalyzed reaction of (azido)ynamide **A** would lead to the formation of an  $\alpha$ -amidino gold-carbenoid **B**, which could be used to produce various indoloquinolines **C**-**E** through an intramolecular trapping reaction with an alkene or arene (Scheme 1). For example, the reaction of the carbenoid **B** with

## Scheme 1. Concept of This Work



an allylsilane or simple alkene moiety would give terminal alkene **C** or cyclopropane **D**, respectively. It was also envisaged that the reaction of carbenoid **B** with an arene would be effective for the formation of fused indole **E**. Herein, we report the development of a novel method for the construction of indoloquinoline compounds by the gold-catalyzed cascade cyclization of (azido)ynamides.

The (azido)ynamide **1a** was prepared by the reaction of tosylamides with a Waser-type alkynylating reagent (Scheme 2).<sup>11</sup> It is noteworthy that bromoalkyne, which has been widely used as an alkynylating reagent for the preparation of ynamides,<sup>12</sup> was ineffective in our hands for the preparation of (azido)-ynamides. Ynamides **1b**-**g** were also prepared in a similar manner (see Supporting Information).

For our initial experiments, we investigated the optimization of the reaction conditions for the synthesis of indoloquinoline **2a** 

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## Scheme 2. Preparation of (Azido)ynamide 1a



Table 1. Optimization of Reaction Conditions



 $^a$ Isolated yield.  $^b$  The catalyst was used following filtration through a pad of Celite.  $^c1$  mol % of the catalyst was used.



using ynamide 1a as a model substrate (Table 1). The reaction of 1a with 5 mol % of IPrAuCl/AgNTf<sub>2</sub> in 1,2-dichloroethane at 50 °C gave the desired product 2a, albeit in a low yield of 11% (entry 1). The use of PPh<sub>3</sub>AuCl/AgNTf<sub>2</sub> as the catalyst led to a significant improvement in the yield, with 2a being isolated in 64% yield within 10 min at rt (entry 2). Several other phosphine ligands were also screened in the reaction (entries 3–7) with the use of the triarylphosphine L2 providing 2a in 78% yield after 10 min at rt (entry 7). PtCl<sub>4</sub> was also found to catalyze the reaction, whereas PtCl<sub>2</sub> showed barely any activity (entries 8 and 9). Following an extensive period of screening, we found that a combination of L2AuCl/AgOTf in nitromethane provided the highest level of activity with 2a being formed in 94% yield with a

decreased loading of the catalyst (1 mol %) (entries 10-12). To the best of our knowledge, this reaction represents the first example of the use of allylsilane as a nucleophilic trapping agent for the capture of a gold-carbenoid species.<sup>13</sup>

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With the optimal reaction conditions in hand (Table 1, entry 12), we proceeded to evaluate the substituent effect of the (azido)ynamide 1 (Table 2). Ynamide 1b bearing an electron-

#### Table 2. Evaluation of the Substituent Effect

	TMS			
R <sup>1</sup> R <sup>2</sup>	Ts N <sub>3</sub> 1	[L2AuCI/AgOTf] (1 mol %) CH <sub>3</sub> NO <sub>2</sub> rt	R <sup>1</sup> R <sup>2</sup>	
entry	substrate $(E/Z)$	$\mathbb{R}^1$	$\mathbb{R}^2$	product $(\%)^a$
1	1b (Z)	OMe	Н	<b>2b</b> (91)
2	lc(Z)	CF <sub>3</sub>	Н	<b>2c</b> (60)
3	1d (Z)	Н	Me	2d (97)
4	1e (Z)	Н	CO <sub>2</sub> Me	<b>2e</b> $(90)^b$
5	$\mathbf{1f}(Z)$	Н	Cl	$2f(86)^{b}$
6	1g (E)	Н	Н	<b>2a</b> (95)
<sup>4</sup> Icolated v	riald by mal %	of the catalust r	ma usad	

<sup>a</sup>Isolated yield. <sup>b</sup>2 mol % of the catalyst was used.

donating methoxy group as the  $R^1$  substituent reacted smoothly under the optimized conditions to give the desired product in 91% yield (entry 1). In contrast, ynamide 1c bearing an electronwithdrawing trifluoromethyl group at the same position reacted much less efficiently and gave the corresponding product in only 60% yield (entry 2). Electron-donating and -withdrawing groups (i.e., methyl, and methoxycarbonyl and chloro groups, respectively) positioned para  $(R^2)$  to the alkyne were well tolerated (entries 3-5), although the electron-deficient ynamides 1e and 1f required an increase in the loading of the catalyst to 2 mol % (entries 4 and 5). The application of the optimized reaction conditions to (E)-allylsilane **1g** resulted in the formation of 2a in 95% yield (entry 6), which was the same product as that obtained from the corresponding (Z)-isomer 1a (Table 1). These reaction conditions were also successfully applied to the allylamine-type ynamide 3, where they gave exomethylene derivative 4 in 66% yield (Scheme 3).<sup>1</sup>





We then moved on to investigate the reaction of (azido)ynamides with simple alkenes with the aim of synthesizing cyclopropane-fused indoloquinolines (Table 3). As expected, ynamides **5a**–**d**, which had a phenyl or *n*-butyl group as one of their alkene substituents, provided the corresponding cyclopropane compounds **6a**–**d** in good to excellent yields (entries 1–4).<sup>15</sup> PPh<sub>3</sub>AuCl/AgNTf<sub>2</sub> was used as the catalyst for the reaction of ynamide **5b** because the reaction did not proceed to completion with **L2**AuCl/AgOTf (entry 2). These reactions were found to be stereospecific and provided different products depending on the geometry of the alkene (compare entry 1 vs 3 or entry 2 vs 4). In contrast, the reaction of ynamide **5e** bearing a Table 3. Reaction Scope for the Synthesis of Cyclopropanes<sup>a</sup>



<sup>*a*</sup>Reactions were conducted with 5 mol % of [L2AuCl/AgOTf] in 1,2dichloroethane. <sup>*b*</sup>Isolated yield. <sup>*c*</sup>5 mol % of PPh<sub>3</sub>AuCl/AgNTf<sub>2</sub> was used as the catalyst. <sup>*d*</sup>Produced as an inseparable mixture.

terminal alkene moiety afforded cyclopropane **6e** as an inseparable mixture of products, presumably because of its instability (entry 5).

We also investigated the ring-opening reactions of cyclopropane 6c to evaluate the synthetic utility of these cyclopropane-fused indoloquinolines 6 (Scheme 4). The use of



ethanol, NaN<sub>3</sub>, and TMSCl as nucleophiles for the ring-opening reaction of **6c** led to the efficient diastereoselective cleavage of the cyclopropane ring to give the corresponding indoloquinoline derivatives 7a-c in excellent yields.<sup>15</sup> These results demonstrated that oxygen, nitrogen, and halogen functional groups could be introduced stereoselectively to the  $\alpha$ -position of the side chain.

To complete this research, we examined the reaction of (azido)ynamides **8** bearing an aryl group as the trapping functional group (Scheme 5). As expected, the (azido)ynamides **8** underwent a cascade cyclization reaction via the arylation of the corresponding gold carbenoids with a benzene or indole ring to give the azocine- or azepine-fused pentacyclic indoles **9a** and **9b**, respectively, in moderate yields.

Plausible reaction mechanisms for the formation of 2a, 6, and 9 by the intramolecular reactions of (azido)ynamides are shown in Scheme 6. Coordination of the gold catalyst to the alkyne as shown in 10 would induce the nucleophilic attack of the azide nitrogen to form 11. The gold-carbenoids 12a-c would then be formed by the release of molecular nitrogen. Ynamide 1a bearing an allylsilane moiety would undergo an electrophilic cyclization reaction through the gold carbenoid 12a to give a carbocation, and subsequent elimination of the TMS group followed by deauration with concomitant aromatization would give indoloquinoline 2a. The carbenoid 12b without a silyl group would undergo cyclopropanation of the corresponding gold carbenoid to give 6.<sup>16</sup> Compound 2a could also be formed from the

Scheme 5. Construction of Medium-Sized Rings through Arylation







cyclopropane intermediate **6** ( $R^1 = H$ ,  $R^2 = CH_2TMS$ ) by the desilylative cleavage of the cyclopropane ring. In the case of ynamides bearing an aryl group, arylation of the carbenoid moiety would take place from **12c** to give **9** via a nucleophilic addition or C–H insertion pathway.<sup>17</sup>

In summary, we have developed a novel method for the synthesis of indoloquinoline compounds via the gold-catalyzed cascade cyclization of (azido)ynamides. We have shown that a variety of trapping functional groups can be used for this reaction, including allylsilane, simple alkenes, and arenes. This reaction provides a new approach for the synthesis of biologically interesting  $\alpha$ -carboline and indoloquinoline-type compounds. Further studies focused on the application of this reaction to the total synthesis of indoloquinoline alkaloids are currently underway in our laboratory.

# ASSOCIATED CONTENT

#### **S** Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available freely via the Internet at http://pubs.acs.org.

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## Notes

The authors declare no competing financial interest.

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