

Generation of α -Imino Gold Carbenes through Gold-Catalyzed Intermolecular Reaction of Azides with Ynamides

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S Supporting Information

ABSTRACT: The generation of α -imino gold carbenes via gold-catalyzed intermolecular reaction of azides and ynamides is disclosed. This new methodology allows for highly regioselective access to valuable 2-aminoindoles and 3-amino- β -carboline in generally good to excellent yields. A mechanistic rationale for this tandem reaction, especially for the observed high regioselectivity, is supported by DFT calculations.

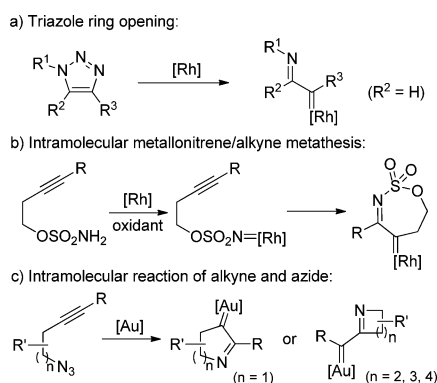
Primarily obtained by metal-catalyzed decomposition of α -diazocarbonyl compounds, α -oxo metal carbenes are versatile intermediates in organic synthesis and have attracted much attention over the past decades.¹ However, the nitrogen counterpart of α -oxo metal carbenes, α -imino metal carbenes, has seldom been explored as they are not readily accessible from typical diazo precursors, which often undergo facile cyclization to form 1,2,3-triazoles.² Nonetheless, considering that α -imino carbene chemistry would offer the great potential to build structurally complex nitrogen-containing molecules, several complementary approaches have been established recently. For example, the strategy that generates α -imino Rh carbenes from 1,2,3-triazoles has been used in various efficient synthetic methods by Gevorgyan, Fokin, and others (Scheme 1a).³ Notable is that only aldimine carbenes are accessible by this strategy. In addition, Blakey et al. showed that α -imino metal carbenes could be generated via Rh-catalyzed metallonitrene-initiated alkyne oxidation, but requiring the nitrene precursors to

be tethered to the C \equiv C triple bond in fixed distance (Scheme 1b).⁴

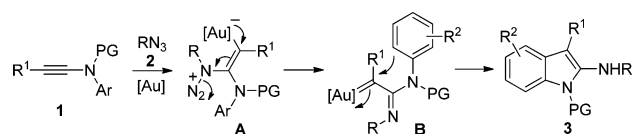
Recent rapid development in homogeneous gold catalysis offers an alternative and particularly attractive approach for the generation of α -imino gold carbenes⁵ through gold-catalyzed amination of alkynes, allowing the assembly of synthetically useful heterocycles in a remarkably efficient manner.^{6–8} In 2005, Toste et al. reported generation of α -imino gold carbene via gold-catalyzed nitrene-transfer reactions of alkynes with tethered azide moieties.^{6a} Such an intramolecular protocol (Scheme 1c) has been aptly exploited in the synthesis of functionalized indoles,^{6b,c} pyrroles,^{6c} and quinolines^{6f} from alkynyl azides by Zhang and Gagosz, respectively. Intermolecular protocols to approach α -imino gold carbenes, undoubtedly offering much higher degree of synthetic flexibility, have been recently attempted and, however, limited in a far not atom-economic way via nitrene transfer from pyridinium ylides to alkynes with release of stoichiometric amount of pyridines as wastes.⁷ Therefore, the exploration of intermolecular approaches to the generation of α -imino gold carbenes, especially in an economic and environmental friendly way, is highly desirable.

Inspired by our recent study on the ynamide chemistry,^{9,10,8c} we envisioned that the α -imino gold carbene might be generated via gold-catalyzed intermolecular reaction of ynamide **1** with suitable azide compound **2**. The carbene intermediate **B**, likely highly electrophilic, could be further trapped by the aryl ring on the nitrogen of ynamide to yield the final 2-aminoindole **3** (Scheme 2). Herein, we report the successful implementation of

Scheme 1. Typical Ways for the Generation of α -Imino Metal Carbenes



Scheme 2. Initial Design



this mechanistic design to a highly regioselective synthesis of a wide range of polysubstituted 2-aminoindoles, which represents the first generation of α -imino gold carbenes via gold-catalyzed intermolecular reaction of azides and alkynes. Moreover, this chemistry can also be successfully extended to the site-selective synthesis of 3-amino- β -carboline through gold-catalyzed formal [4 + 2] cycloaddition between azides and ynamides. Most

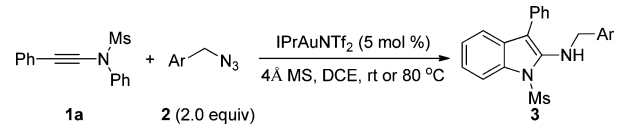
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importantly, a mechanistic rationale for the observed high regioselectivity is also strongly supported by DFT calculations.

At the outset, ynamide **1a** was used as the model substrate to react with a broad range of substituted azides. However, in most cases, only hydration product¹¹ was obtained probably due to the decreased nucleophilicity of the azide compared with the *N*-oxide.^{5a-c} To our delight, it was found that benzyl azide **2a** could serve as an external nitrene-transfer reagent to react with ynamide **1a** in the presence of 5 mol % IPrAuNTf₂ to afford the desired 2-aminoindole **3aa** in 65% yield (Table 1, entry 1).¹¹

Table 1. Reaction of Ynamide **1a** with Benzyl Azides **2**^a



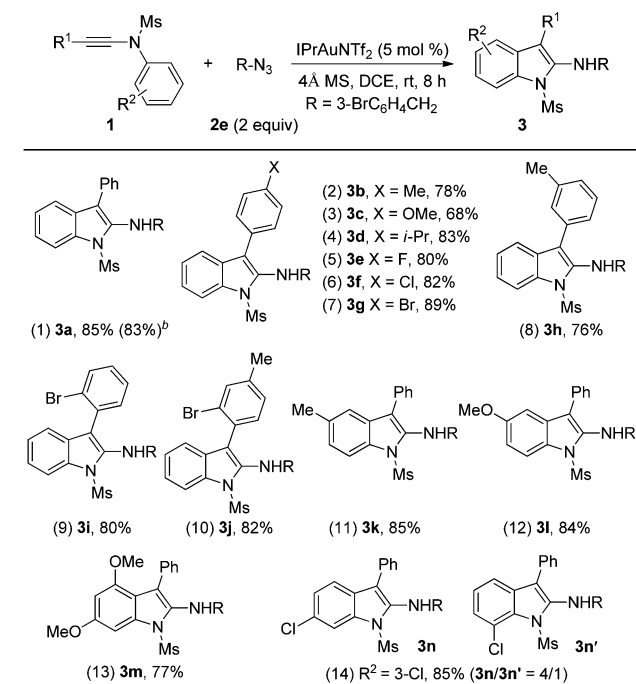
entry	Ar	2	T (°C)	3	yield (%) ^b
1	Ph	2a	80	3aa	65
2	4-FC ₆ H ₄	2b	80	3ab	60
3	4-ClC ₆ H ₄	2c	80	3ac	50
4	4-BrC ₆ H ₄	2d	80	3ad	75
5 ^c	3-BrC ₆ H ₄	2e	80	3a	89
6 ^c	2-BrC ₆ H ₄	2f	80	3af	80
7	4-NO ₂ C ₆ H ₄	2g	80	3ag	81
8	4-CH ₃ C ₆ H ₄	2h	80	3ah	30 ^d
9	3-BrC ₆ H ₄	2e	rt	3a	85

^aReaction conditions: IPrAuNTf₂ (9.0 mg, 0.010 mmol), **1a** (54.3 mg, 0.20 mmol), **2** (0.40 mmol), 4 Å MS (40 mg), DCE (4.0 mL), 8 h.
^bIsolated yields. ^c**3ah** was isolated in 45% yield.

Notably, the nucleophilic addition of the phenyl on the **2a** to α -imino gold carbene was not observed. The feasibility of the parent benzyl azide encouraged us to screen various typical benzyl azides with a range of electronic and steric characteristics. As shown in Table 1, benzyl azides with the electron-withdrawing groups generally worked well (entries 1–7), and 3-bromobenzyl azide **2e** gave the best yield of the desired **3a** even at room temperature (entry 5 and entry 9). Instead, when the benzyl azide was substituted with an electron-donating group such as methyl (**2h**), the desired **3ah** was obtained in low yield (30%) together with 2-aza-1,3-butadiene **3ah'** as a significant byproduct (45%, entry 8).

The reaction scope was then explored by using 3-bromobenzyl azide **2e** as the nitrene precursor. As summarized in Table 2, the reaction proceeded smoothly with various ynamides **1**, allowing the facile synthesis of 2-aminoindoles **3** in generally good to excellent yields. For example, different aryl-substituted ynamides (R¹ = aryl) were suitable substrates for this tandem reaction, affording the corresponding 2-aminoindoles **3a**–**3j** in 68–89% yields (entries 1–10, **3a** was confirmed by X-ray diffraction). However, with an alkyl-substituted (R¹ = Cy) substrate, the reaction failed to give the desired indole, and an α,β -unsaturated imidamide **3o'** was isolated in 30% yield instead.^{11,12} This outcome manifested an in situ generated gold carbene as key intermediate in such a gold-catalyzed intermolecular reaction. In addition, the substrates bearing both electron-withdrawing and electron-donating groups on the aromatic ring also underwent smooth cyclization to deliver products **3k**–**3n** with yields ranging from 77% to 85% (entries 11–14). Of note, when the substrate with chloro substituent at the meta-position was employed, a 4/1 regioselectivity was observed, and the main isomer was **3n** formed through cyclization on the less hindered

Table 2. Reaction Scope Study^a

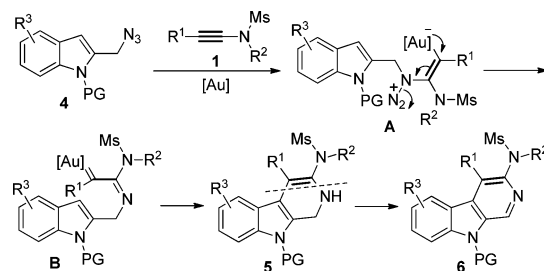


^aReactions run in vials; isolated yields are reported. ^b5.0 mmol scale, 2 mol % IPrAuNTf₂ was used, 20 h.

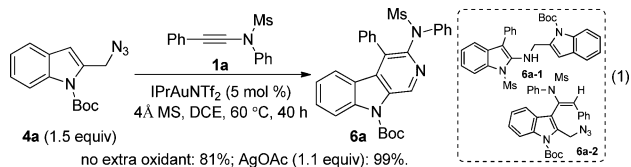
position (entry 14). To further test the practicality of the current catalytic system, a gram-scale reaction of 1.36 g of ynamide **1a** and 2.11 g of azide **2e** was carried out in the presence of 2 mol % IPrAuNTf₂, and 1.88 g of the desired 2-aminoindole **3a** was furnished in 83% yield, highlighting the synthetic utility of this chemistry (entry 1). Thus, this protocol provides an efficient and practical route for the construction of the 2-aminoindole scaffold, which is an important structural motif in an array of bioactive molecules^{13,14} and not readily accessible by known methods.¹⁴

We then considered the possibility of extending the above protocol to other gold-catalyzed intermolecular alkyne amination-initiated tandem reactions. In particular, the utilization of the transferred amino group may lead to the development of the formal cycloaddition reaction. We envisioned that the reaction of ynamide **1** with indolyl azide **4** would generate the α -imino gold carbene intermediate **B**, which could be further trapped by the more nucleophilic indolyl part but not the aryl group on nitrogen of ynamide **1** to give the corresponding 1*H*-pyrido[3,4-*b*]indole **5**, thus constituting a gold-catalyzed formal [4 + 2] cycloaddition (Scheme 3). Notably, **5** might undergo further dehydrogenative oxidation to deliver the 3-amino- β -carboline **6**.

Scheme 3. Further Design: Gold-Catalyzed Formal [4 + 2] Cycloaddition between Azides and Ynamides

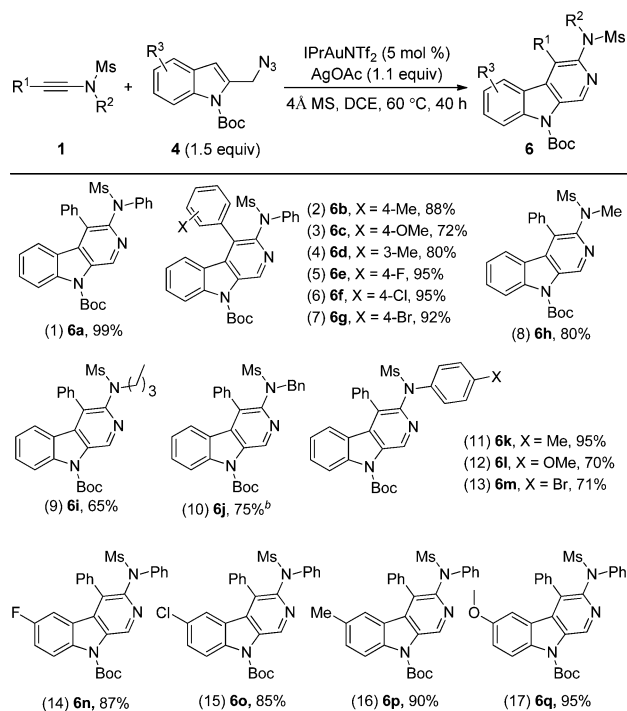


To our delight, the reaction of ynamide **1a** with indolyl azide **4a** in the presence of 5 mol % IPrAuNTf_2 indeed afforded the desired product **6a** in 81% yield, and almost quantitative yield was achieved by using 1.1 equiv of AgOAc as oxidant eq 1.¹¹ Significantly, neither 2-aminoindole **6a-1** nor background enamide **6a-2** formation was observed in this case.



We then examined the scope and generality of this novel [4 + 2] cyclization reaction under the optimized reaction conditions (Table 3).¹¹ The reaction of azide **4a** with various R^1 -substituted

Table 3. Reaction Scope Study^a

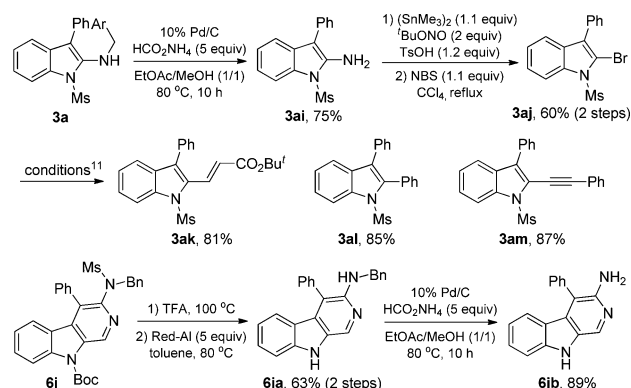


^aReactions run in vials; isolated yields are reported. ^bTime = 72 h.

ynamides **1** was first examined. The corresponding 3-amino- β -carboline **6a-6g** were obtained in generally good to excellent yields (entries 1–7). Importantly, no background 2-aminoindole formation was detected in all cases. In the case of ynamides with different R^2 groups, the reaction also worked well to deliver the desired **6h-6m** in 65–95% yields (entries 8–13, **6l** was confirmed by X-ray diffraction). In addition, substituents with different electronic nature on the indole ring were also readily tolerated, leading to the efficient formation of products **6n-6q** in excellent yields (entries 14–17). This transformation thus makes it a straightforward way to synthesize the 3-amino- β -carboline, known as the lead compounds for antitumor agents, that conventionally demand rather tedious synthesis.¹⁵ Notably, for alkyl substituted ($\text{R}^1 = \text{Cy}$) ynamide, the reaction failed to give the desired β -carboline but afforded the α,β -unsaturated imidamide **6r'** (25% yield).^{11,12}

Further transformation of the as-synthesized amination products was explored (Scheme 4). For example, benzyl group

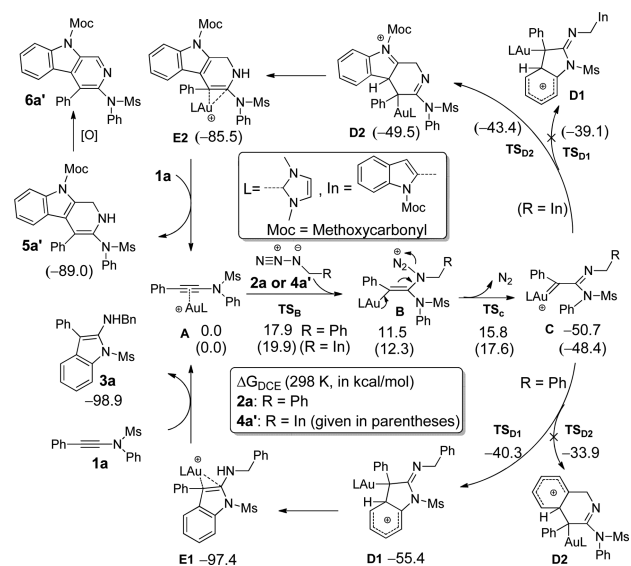
Scheme 4. Transformation of the Products



in **3a** was easily removed to give 2-aminoindole **3ai**, which could be transformed into **3aj** by means of deamination and bromination. The 2-bromoindole **3aj** could be further subjected to Heck, Suzuki, and Sonogashira reactions to produce the corresponding functionalized indoles **3ak-3am** in 81–87% yields. In addition, deprotection of **6j** could afford 3-benzylamino- β -carboline **6ja**, which shows high antitumor activity.^{15a,b} **6ja** could be readily transformed into free amine **6jb**.

To further confirm the mechanism, we calculated the free energies of two possible pathways for the reactions of ynamide **1a** with azide **2a** and **4a** using density functional theory (DFT) as shown in Scheme 5. The azide **2a** and **4a** first attacked Au-

Scheme 5. M06(SMD, DCE)/6-31G(d,p)/SDD Free Energies for the Reactions of **1a** with **2a** and **4a**



activated alkyne **A** leading to the generation of Au-substituted alkene **B** by overcoming a moderate barrier of 17.9 and 19.9 kcal/mol, respectively. Subsequent departure of N_2 with a small barrier of 4.3 or 5.3 kcal/mol gave the gold carbene intermediate **C**, a bifurcation point. The gold carbene could be trapped either by the *N*-phenyl or by R group leading to intermediate **D1** or **D2**. For $\text{R} = \text{Ph}$, the gold carbene was regioselectively trapped by the *N*-phenyl to form intermediate **D1** by overcoming a barrier of

10.4 kcal/mol; while for R = In, the gold carbene was regioselectively trapped by the more nucleophilic indolyl to form intermediate **D2** by overcoming a barrier of 5.0 kcal/mol. Finally, intermediate **D1** or **D2** was readily converted into product **3a** or **5a** through proton transfer¹¹ and ligand exchange, and **5a** could be further converted into product **6a** through dehydrogenative oxidation.

In summary, the challenging generation of α -imino gold carbenes via gold-catalyzed intermolecular reaction of azides and alkynes has been achieved, leading to the site-selective synthesis of versatile 2-aminoindoles and 3-amino- β -carbolines in generally good to excellent yields. In addition, a mechanistic rationale for the observed regioselectivity is also strongly supported by DFT computations. In comparison with the intermolecular alkyne oxidation approach to the generation of gold carbenes, this strategy is not only more atom economic but also more flexible, as it can introduce various amino groups while only the oxygen is transferred in case of the related oxidation approach. Further application of this gold-catalyzed intermolecular alkyne amination will be pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06015.

Experimental procedures (PDF)

Characterization data (CIF)

Characterization data (CIF)

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Notes

The authors declare no competing financial interest.

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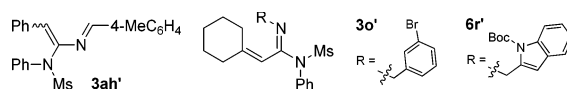
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(11) For details, please see the Supporting Information (SI).

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