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Benzofurazan *N*-Oxides as Mild Reagents for the Generation of α-Imino Gold Carbenes: Synthesis of Functionalized 7-Nitroindoles

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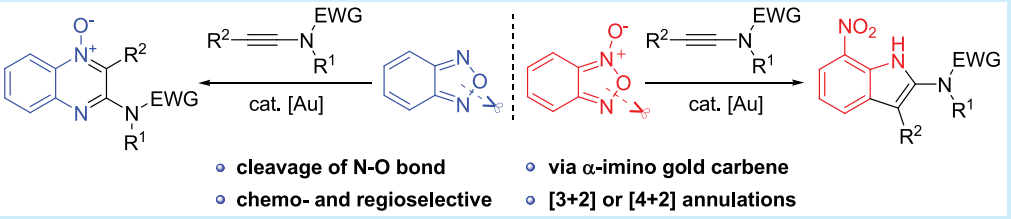
Supporting Information



ABSTRACT: An efficient gold-catalyzed [3 + 2] annulation of benzofurazan *N*-oxides with ynamides has been developed, which provides a concise and regioselective access to highly functionalized 7-nitroindoles. Although *N*-oxides are often considered as oxygen transfer reagents in gold catalysis, benzofurazan *N*-oxide was found to act as a facile precursor for an α-imino gold carbene intermediate. Benzofurazan can also react with ynamides to afford quinoxaline *N*-oxides via a [4 + 2] annulation process.

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7-Nitroindoles are important heterocyclic units that exist as the core structures of numerous biologically active molecules.[1−4] For example, 7-nitroindole **a** exhibits potent xanthine oxidase inhibitory activity[1] (Figure 1). 7-Nitroindole **b** serves as a chk2

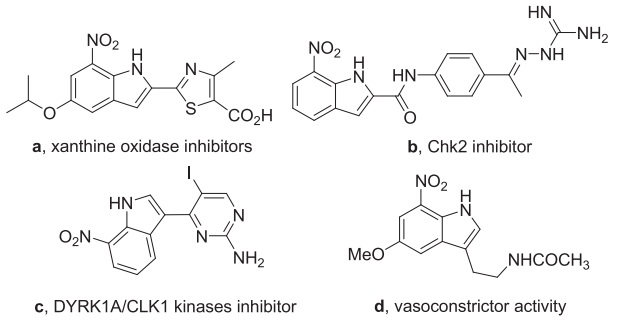

Figure 1. Biologically active 7-nitroindole derivatives.

inhibitor for the treatment of cancer.[2] 7-Nitroindole **c** with a pyrimidine ring was found to be an inhibitor of DYRK1A and CLK1 kinases, which displays in vitro antiproliferative activities.[3] Compound **d** shows good MT_1 and MT_2 affinities, which may be involved in the vasoconstrictor activities on animal vessels.[4] However, only limited methods are available for the synthesis of 7-nitroindoles such as direct nitration of indoles,[5a,b] nitration of 7-chloroindoles,[5c] Fischer indole synthesis of *o*-nitrophenylhydrazones,[5d,e] cyclization of 1,2-dinitrobenzene with vinylmagnesium bromides, etc.[5f] These methods usually suffer from various disadvantages such as low regioselectivity, limited substrate scope, and harsh reaction conditions. Therefore, it is highly desirable to develop efficient methods for the synthesis of 7-nitroindoles from easily available starting materials under mild reaction conditions.

In recent years, gold-catalyzed oxygen[6] and nitrene[7−16] transfer reactions have attracted considerable attention due to their wide applications in the construction of diversely functionalized carbo- or heterocycles (Scheme 1, eqs 1 and 2). Mechanistically, these reactions proceed through the nucleophilic attack of the oxygen or nitrogen atom from the nucleophilic reagents on the alkynes followed by elimination of a neutral organic framework. In this context, *N*-oxides such as pyridine- and quinoline-*N*-oxides have been commonly employed as oxygen transfer reagents to trigger a facile generation of highly electrophilic α-oxo gold-carbene intermediates.[6] On the other hand, great achievements have also been made based on the development of novel nitrene transfer reagents. For example, azides,[7] 2*H*-azirines,[8] *N*-iminopyridium ylides,[9] isoxazoles,[10] benzoisoxazoles,[11] 1,4,2-dioxazoles,[12] 4,5-dihydro-1,2,4-oxadiazoles,[13] triazapentalene,[14] benzo[*d*]-isoxazoles,[15] and sulfilimines[16] have been disclosed to show high reactivities in nitrene transfer reactions reported by Gagosz, Davies, Zhang, Ye, Hashmi, Liu, us, and others. In these reactions, α-imino gold-carbene complexes have been recognized as possible reaction intermediates. However, to the best of our knowledge, *N*-oxides have never been used as the precursors of α-imino gold-carbene intermediates. During our studies on the use of N−O-containing heterocycles as α-imino

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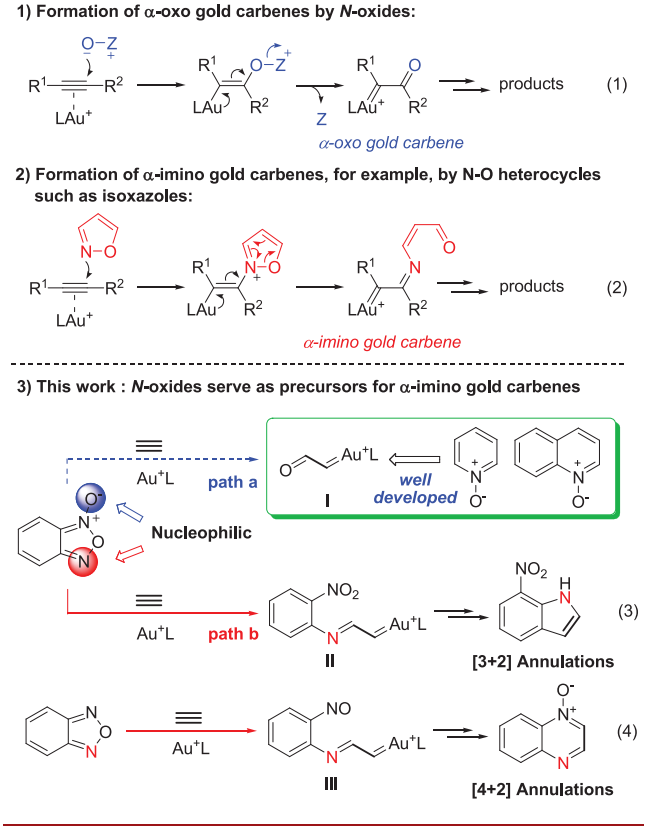
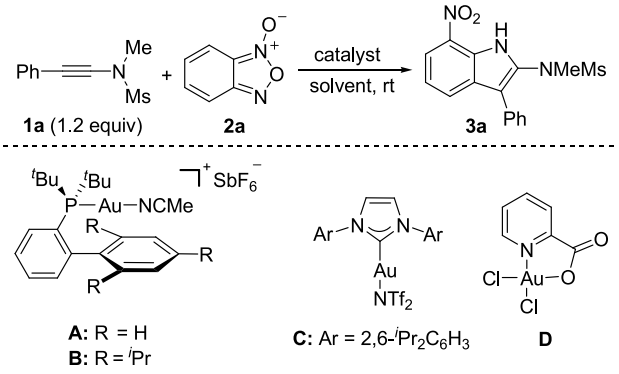
Scheme 1. Generation of α-Oxo/Imino Gold Carbenes



gold-carbene precursors,[12,13,15b] we envisioned that if an *N*-oxide reagent derived from N−O heterocycles bearing an additional nucleophilic site is used as the substrate, the reaction pathway might be altered since both the N^+-O^- and the other nucleophilic moiety can attack the alkyne. We are therefore quite interested in clarifying whether an α-oxo gold-carbene would still be formed by using these substrates and its transformations. To test our hypothesis, benzofurazan *N*-oxide was chosen as the appropriate substrate (Scheme 1, eq 3). Benzofurazan *N*-oxides are easily available heterocyclic compounds[17] which have been used for the synthesis of quinoxaline 1,4-di-*N*-oxides through the reaction with 1,3-dicarbonyl compounds[18a,b] and 2*H*-benzimidazole 1,3-dioxides.[18c] However, these heterocycles have not been applied in gold-catalyzed reactions. Herein, we report our success on gold-catalyzed cyclization of benzofurazan *N*-oxides with ynamides, which provides an efficient route to 7-nitroindole derivatives. Interestingly, the expected oxygen transfer reaction did not take place; instead, an α-imino gold-carbene intermediate **II** was produced to deliver a [3 + 2] annulation product. In addition, we find that benzofurazan[19] can also react with ynamides to afford quinoxaline *N*-oxides via an α-imino gold-carbene intermediate **III** (Scheme 1, eq 4).

We initially focused on the cyclization of ynamide **1a** with benzofurazan *N*-oxide **2a** in the presence of various gold catalysts. To our delight, when in situ prepared PPh_3AuNTf_2 was employed as the catalyst, 7-nitroindole **3a** could be formed at room temperature in 73% yield within 4 h (Table 1, entry 1). The results indicated that an efficient N−O bond cleavage occurred during the process. Since the steric and electronic effects of the ligands played an important role in gold-catalyzed reactions, we expected that the yield of **3a** might be improved by variation of the ligands on gold. By changing the catalyst to

Table 1. Optimization of the Reaction Conditions



entry	catalyst (mol %)	solvent	time (h)	yield (%)[a]
1	$PPh_3AuCl/AgNTf_2$ (5)	DCE	4	73
2	**A** (5)	DCE	4.5	97 (95[b])
3	**B** (5)	DCE	4	89
4	**C** (5)	DCE	4	72
5	**D** (5)	DCE	4	82
6	$AuBr_3$ (5)	DCE	4	78
7	**A** (5)	THF	1	41[c]
8	**A** (5)	DCM	4	66
9	**A** (5)	MeCN	24	54
10	**A** (5)	toluene	4	71
11[d]	**A** (5)	DCE	12	78
12	$AgSbF_6$ (5)	DCE	24	7
13	$HNTf_2$ (10)	DCE	4	20
14[e]	none	DCE	24	-[f]

[a]Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [Substrate] = 0.1 M. [b]Isolated yield. [c]The solvent became viscous. [d]1.0 equiv of **1a** and 1.2 equiv of **2a** were used. [e]50 °C. [f]98% NMR yield of unreacted **1a** was observed.

JohnPhosAu(MeCN)SbF_6 (catalyst **A**), a significant increase of the yield was observed (entry 2, 97%). The use of more crowded ^{t}BuXPhos (catalyst **B**) resulted in a slight decrease in yield (entry 3). *N*-Heterocyclic carbene gold(I) complex **C** ($IPrAuNTf_2$) provided **3a** in 72% yield (entry 4). Gold(III) complexes such as $PicAuCl_2$ (catalyst **D**) or $AuBr_3$ could also catalyze the reaction, furnishing **3a** in 78−82% yields (entries 5−6). When the reactions were performed in other solvents such as THF, DCM, MeCN, or toluene, **3a** was formed in up to 71% yield (entries 7−10). The results indicated that DCE was the best solvent (compared with entry 2). It was noted that, in the case of THF, the reaction mixture became viscous as the reaction proceeded. Possibly partial polymerization of THF occurred as being initiated by some cation species and propagated by a cationic mechanism.[20] Turning the ratio of **1a**:**2a** to 1:1.2 gave a lower yield of **3a** (entry 11, 78%). Employing $AgSbF_6$ or $HNTf_2$ as the catalyst afforded **3a** in ≤20% yields (entries 12−13). The reaction did not take place in the absence of any catalyst, even at 50 °C for 24 h (entry 14).

With the optimized reaction conditions in hand (Table 1, entry 2), the scope of this novel cycloaddition reaction was examined. The scope of ynamides **1** was first studied by using **2a** as the reaction partner (Scheme 2). Tosyl-protected substrate **1b** gave **3b** in a lower yield of 78% (compared with **3a**). In the case of Ns-protected ynamide **1c**, the product **3c** precipitated easily from the reaction medium due to its low solubility, which can be simply purified by filtration and

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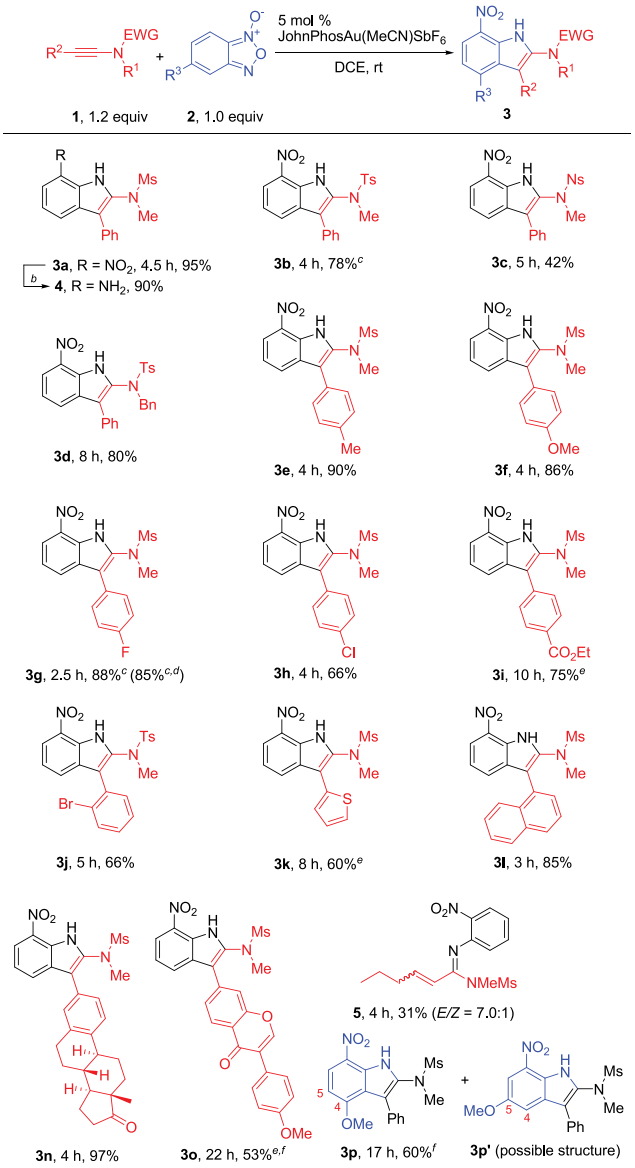
Scheme 2. Synthesis of 7-Nitroindoles by Gold-Catalyzed [3 + 2] Annulations[a]

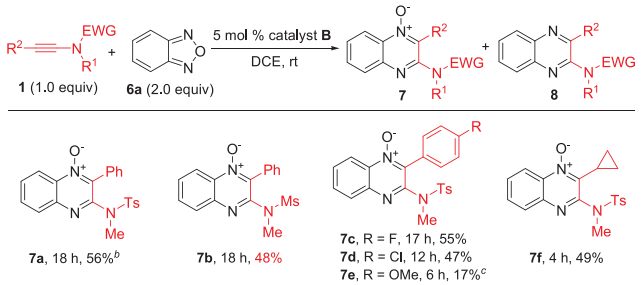


[a]Isolated yields. [b]5 mol % Pd/$CaCO_3$, 5.0 equiv of HCO_2NH_4, EtOH, reflux. [c]Reaction was performed at 50 °C. [Substrate] = 0.033 M. [d]1 mmol scale. [e]5 mol % $PicAuCl_2$ was used as the catalyst. [f][Substrate] = 0.05 M.

washing (42% yield). These results suggest that the protecting groups on nitrogen have a dramatic impact on the product yields. *N*-Benzyl substituted ynamide was also compatible (**3d**). Next, the substituent effects of the aryl groups on ynamide terminus were investigated. Electron-donating groups such as *p*-methyl and *p*-methoxy on the aryl ring were well suited, furnishing **3e** and **3f** in 90% and 86% yields, respectively. Substrates bearing electron-withdrawing groups such as *p*-F and *p*-Cl worked well, leading to **3g**–**3h** in 66–88% yields. In addition, a reaction of **1g** on 1 mmol scale also provided a high yield of **3g**. Several products were observed under the standard conditions when ynamide **1i** with a *p*-CO_2Et-substituted aryl group was used as the substrate. Switching the gold catalyst to $PicAuCl_2$ was found to give better results, leading to **3i** in 75% yield. A substrate bearing a sterically encumbered *o*-Br substituted aryl ring could also be easily transformed to the desired product **3j** in 66% yield. A heteroaryl-substituted ynamide such as a 2-thienyl-substituted one was well compatible, which also required $PicAuCl_2$ to afford a satisfactory yield (**3k**). Ynamide with a 1-naphthyl substituent proceeded smoothly (**3l**). When alkyl-substituted ynamide was used, the desired 7-nitroindole **3m** was not observed, instead, vinyl imine **5** was formed in 31% yield via 1,2-H shift. The reaction could be applied to natural product related derivatives. For example, ynamides derived from 1,3,5(10)-estratrien-3-ol-17-one or formononetin transformed to **3n** and **3o** in moderate to high yields. Furthermore, when benzofurazan *N*-oxide **2b** with a methoxy substituent at the R^3 position was employed, 4-OMe-substituted **3p** was obtained in 60% yield, along with a small amount of a byproduct **3p′** and alkyne hydration product (ca. 12% combined yield). It is suggested that **3p′** is a 7-nitroindole isomer in which the MeO group locates at the C-5 position due to the tautomerization of the substrate **2b**.[21] To demonstrate the utility of the product, reduction of **3a** under the conditions of cat. Pd/HCO_2NH_4 was performed, which delivered 7-aminoindole **4** in 90% yield. The structures of 7-nitroindoles **3** were confirmed by X-ray crystallographic analyses of **3b** (CCDC-1940164) and **3p** (CCDC-1940167).

To compare the reactivity of benzofurazan *N*-oxide **2** and benzofurazan **6**, we next investigated the gold-catalyzed reactions of **6a** with ynamides (Scheme 3). To our delight,

Scheme 3. Scope of Gold-Catalyzed [4 + 2] Annulations with Ynamides[a]



[a]Isolated yields. Only the yields of **8** which could be purified by column chromatography are given. [b]**8a** was also isolated in 15% yield. [c]**8e** was also isolated in 25% yield.

quinoxaline *N*-oxides **7** could be formed in the presence of ^{t}BuXPhosAu(MeCN)SbF_6 (catalyst **B**). Quinoxaline derivative **8** was also observed as a side product in most cases. Obviously, **8** can be envisioned to be formed during the oxidative reaction of quinoxaline *N*-oxide **7** with ynamide (*vide infra*). A series of ynamides were smoothly converted into the corresponding quinoxaline *N*-oxides. Tosyl and mesyl groups on nitrogen were well tolerated (**7a**, CCDC-1940169; **7b**). Electron-withdrawing groups (e.g., *p*-F and *p*-Cl) on the aryl ring of the ynamides were compatible (**7c** and **7d**), while electron-donating groups (e.g., *p*-OMe) resulted in a low yield of **7e** (17%), along with the formation of **8e** in 25% yield. The results indicated that electron-rich ynamides turned out to be easily oxidized by *N*-oxide **7**. Cyclopropyl-substituted ynamide afforded **7f** in 49% yield.

Interestingly, when the above reaction (for example, **1b** with **6a**) was carried out at 80 °C, quinoxaline *N*-oxide **7a** was almost consumed, furnishing quinoxaline **8a** (CCDC-

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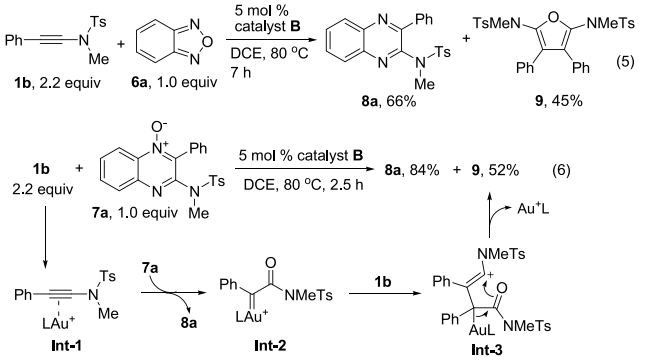
1940168) in 84% yield and 2,5-diaminofuran **9** (CCDC-1940166) in 45% yield (based on **6a**) (Scheme 4, eq 5). To

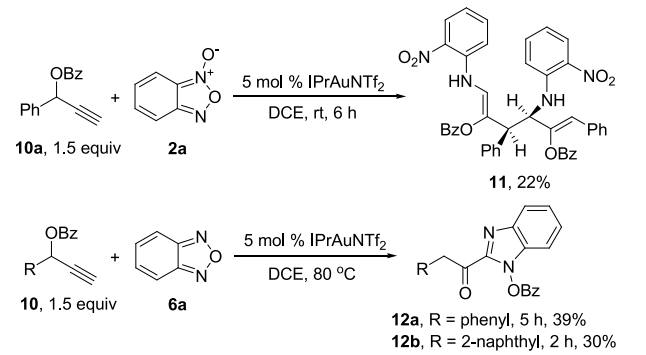
Scheme 4. Formation of 2,5-Diaminofuran



understand the reaction outcome between ynamide **1** and *N*-oxide **7**, the reaction of **1b** with **7a** was also performed (Scheme 4, eq 6). The same products of **8a** and **9** were formed. The results indicated that **7a** acts as an oxidant to initiate an oxygen transfer reaction with ynamide. The *in situ* generated α-oxo gold carbene **Int-2** is trapped by an additional ynamide molecule to deliver the furan product **9**. According to the literature, when ynamide was oxidized by 8-methylquinoline *N*-oxide, only the over-oxidized product of α-ketoimide was observed.[22] Thus, quinoxaline *N*-oxide displays unique reactivity compared to well-used *N*-oxides.

To further explore the utility of benzofurazan derivatives in gold catalysis, we also made efforts to examine their reactions with propargyl esters (Scheme 5). Interestingly, a four-

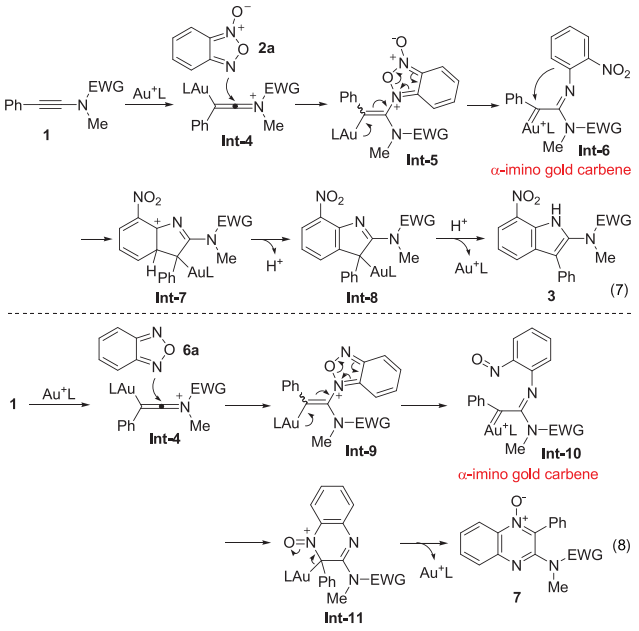
Scheme 5. Reaction of Propargyl Esters with 2a or 6a



component reaction involving two molecules of benzolyl-protected substrate **10a** and two molecules of benzofurazan *N*-oxide **2a** was observed, leading to the product **11** (CCDC-1940163) bearing *o*-nitroaniline moieties in 22% yield. Reaction of **10a** with benzofurazan **6a** resulted in the formation of *N*-OBz protected benzimidazole **12a** in 39% yield. 2-Naphthyl-substituted propargyl ester **10b** underwent a similar reaction with **6a** (**12b** in 30% yield, CCDC-1940165). Possible reaction mechanisms for these transformations are shown in the Supporting Information. Both reactions involve the nucleophilic attack of the nitrogen moiety of benzofurazan *N*-oxide or benzofurazan to a vinyl gold carbene intermediate generated through 1,2-acyloxy migration of propargyl ester.[23]

Based on the above results, a possible reaction mechanism is given for the formation of 7-nitroindole **3** (Scheme 6, eq 7)

Scheme 6. Possible Reaction Mechanism



and *N*-oxide **7** (Scheme 6, eq 8). Initially, ynamide **1** is activated by gold to afford keteniminium ion intermediate **Int-4**, which is attacked by the imino nitrogen of **2a** to give an intermediate **Int-5**. Ring fragmentization of **Int-5** affords the α-imino gold carbene **Int-6**. Subsequent nucleophilic attack of the phenyl ring on gold carbene leads to intermediate **Int-7**. This is followed by aromatization and deauration to give the product **3**.[24,25] When benzofurazan **6a** is used, **Int-9** is formed through the nucleophilic attack of the imino nitrogen on intermediate **Int-4**. **Int-9** fragmentizes into the α-imino gold carbene **Int-10** via N−O bond cleavage. Then nucleophilic attack of the nitroso nitrogen to gold-carbene[26] followed by elimination of the gold catalyst leads to the products **7**.

In summary, we have developed a novel and efficient protocol for the synthesis of 7-nitroindoles through gold-catalyzed [3 + 2] annulations of benzofurazan *N*-oxides with ynamides. Although *N*-oxides are often considered as oxygen transfer reagents, benzofurazan *N*-oxide was found to act as a facile precursor to initiate the generation of an α-imino gold carbene intermediate. In addition, gold-catalyzed reactions of benzofurazans with ynamides provide quinoxaline *N*-oxides via [4 + 2] annulation process. Further extensions by exploring the reactivity of *N*-oxides derived from other N−O heterocycles are currently underway 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.9b02893.

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

Accession Codes

CCDC 1940163−1940169 contain 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

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Notes

The authors declare no competing financial interest.

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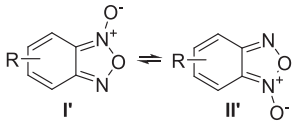

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