

Platinum-Catalyzed Oxoarylations of  
Ynamides with Nitrones

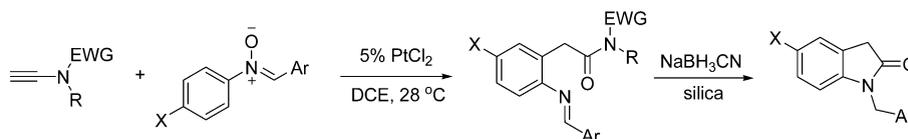
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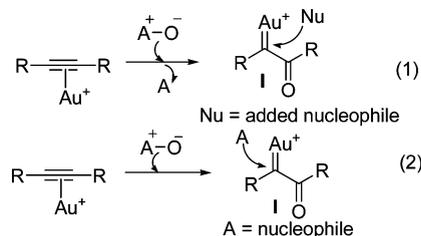
## ABSTRACT



A new platinum-catalyzed oxoarylation of ynamides with nitrones is reported. Cascade sequences for the synthesis of indolin-2-ones via  $\text{NaBH}_3\text{CN}$  reduction in situ of the initially formed oxoarylation products are also developed.

Gold-catalyzed intermolecular oxidations of alkynes with organic oxides presumably involve the generation of  $\alpha$ -oxo gold carbenes **I**,<sup>1–6</sup> pyridine-based oxides<sup>2</sup> are superior to sulfur oxides<sup>3</sup> for generating such reactive intermediates. This new synthetic method provides potential access to valuable  $\alpha$ -functionalized carbonyl compounds through a subsequent attack on the gold carbenes **I** with an external nucleophile, as depicted in eq 1. Nevertheless, at the outset of the present study, there

was only one successful example<sup>7</sup> of such a conversion because of the following problems: (1) a competitive attack of this external nucleophile at the gold- $\pi$ -alkyne; (2) a complexation of gold-carbene **I** with newly released pyridine, and (3) a second oxidation of gold carbenes **I** with organic oxides.<sup>8</sup> Recently, we proposed a distinct route, as depicted in eq 2, in which a nucleophile is embedded within the organic oxide  $\text{A}^+-\text{O}^-$  ( $\text{A}$  = nucleophile).<sup>4a</sup> At the end of the initial alkyne oxidation, the released nucleophile **A** is easily trapped with gold-carbene **I** within an inner sphere, so eliminating the preceding problems. This new approach also fulfills atom economy because the reduced form **A** is a part of product skeleton.



Shown in Scheme 1 is our recent practice<sup>4a</sup> of this new 1,2-difunctionalization on arenynamide **1**. In this transformation, gold-catalyzed nitrone oxidation of alkyne **1** produces an imine that reacts efficiently with carbene **I** to give the  $\alpha$ -aminoamide **3**. In a further development of this chemistry, we report a new discovery that applies platinum catalysis to ynamides **4**, to deliver products **5** through an

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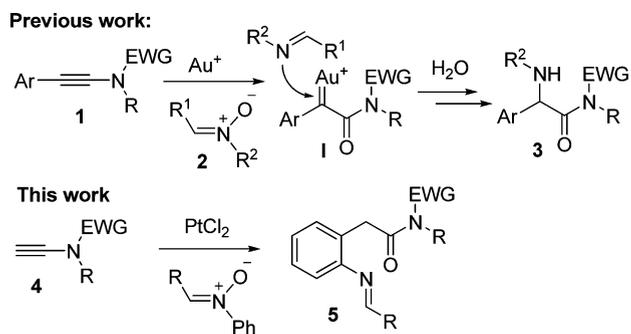
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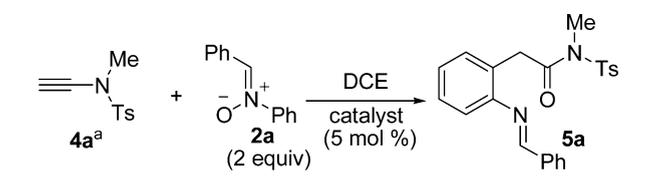
**Scheme 1.** Gold-Catalyzed 1,2-Difunctionalization of Activated Alkynes



oxoarylation reaction. Notably, this new alkyne 1,2-difunctionalization proceeds via a distinct mechanism that excludes the intermediacy of gold carbenes **I**.

Shown in Table 1 is the reaction of nitrone **2a** (2 equiv) with ynamide **4a** (1 equiv) in dichloroethane (DCE) in the presence of various gold and platinum catalysts at 5 mol % loading. We observed the complete consumption of starting ynamide **4a** under the reaction conditions. We tested first the reactions with gold catalysts including P(*t*-Bu)<sub>2</sub>(*o*-biphenyl)AuNTf<sub>2</sub>, IPrAuNTf<sub>2</sub> (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene), and AuCl<sub>3</sub> in DCE at 28 °C, and all gave rise to a messy mixture, due to rapid decomposition

**Table 1.** Catalytic Activity over Gold and Platinum Catalysts

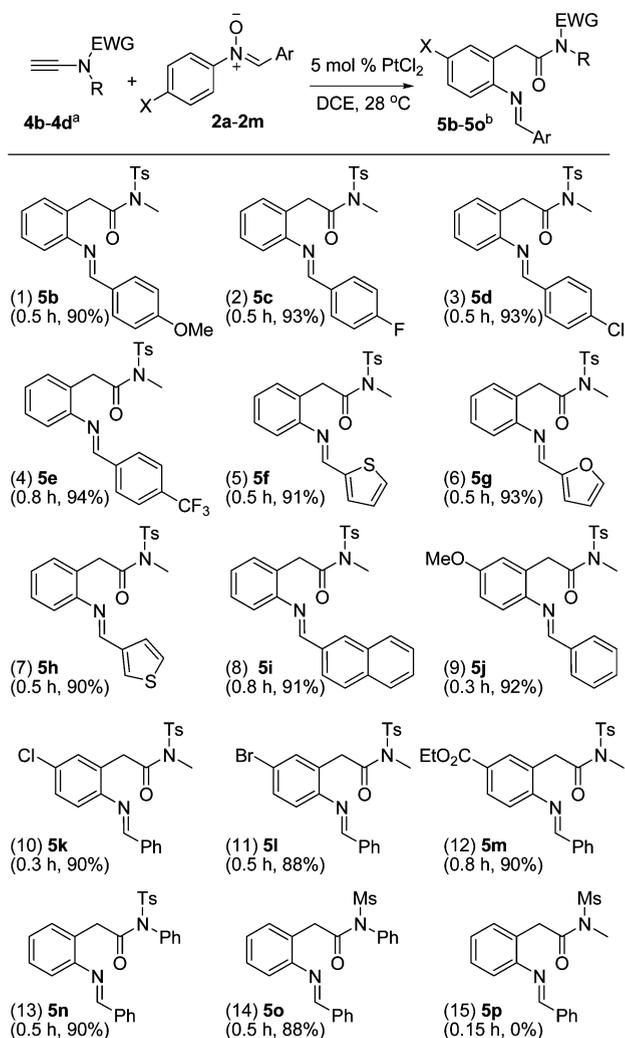


entry	catalyst <sup>b</sup>	temp (0 °C)	time (h)	<b>5a</b> (yields, %) <sup>c</sup>
1	LAuCl/AgNTf <sub>2</sub>	28	2	—
2	IPrAuCl/AgNTf <sub>2</sub>	28	3	—
3	AuCl <sub>3</sub>	28	2	—
4	AuCl	28	0.3	57
5	PtCl <sub>2</sub>	28	0.5	95
6	PtI <sub>2</sub>	80	0.7	15
7	PtCl <sub>4</sub>	28	0.5	65

<sup>a</sup>[**4a**] = 0.17 M. <sup>b</sup>L = P(*t*-Bu)<sub>2</sub>(*o*-biphenyl), IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene. <sup>c</sup>Product yields are reported after purification from silica column.

of the starting ynamide **4a** (entries 1–3). To our delight, use of the less acidic AuCl gave an oxoarylation product **5a** in 57% yield. The yield of desired **5a** was further increased up to 95% with PtCl<sub>2</sub> in DCE at 28 °C (entry 5). In contrast, PtI<sub>2</sub> led only to unreacted ynamide **4a** with a 32% recovery, in DCE at 28 °C, but a thermal activation gave the desired **5a** in 15% yield (entry 6). We also tested

**Scheme 2.** Reaction Scope for Pt-Catalyzed Oxoarylation Reactions<sup>a</sup>



<sup>a</sup>[Ynamide] = 0.17 M, reactions performed at 28 °C. <sup>b</sup>Product yields are reported after purification from silica column.

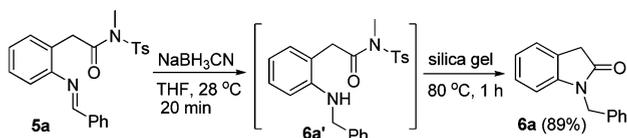
the reaction with PtCl<sub>4</sub>, which gave compound **5a** in 65% yield (entry 7).

Shown in Scheme 2 is the generalization of this platinum-catalyzed oxoarylation reaction with various ynamides **4b–4d** (1.0 equiv) and nitrones **2b–2m** (2.0 equiv). The reactions were performed with PtCl<sub>2</sub> catalyst (5 mol %) in dichloroethane at 28 °C. The duration of the reaction (0.3–0.8 h) determines whether there is a complete consumption of the ynamides **4b–4d**. We examined first the reactions using nitrones **2b–e** bearing alterable 4-substituted phenylimines (Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, and 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>); these afforded the desired products **5b–5e** in satisfactory yields (90–94%, entries 1–4). The reaction was further applied to the additional nitrones **2f–2h**, bearing heteroaryl imines (Ar = 2,3-thienyl and 2-furanyl). These delivered the oxoarylation products **5f–5h** in excellent yields (90–93%, entries 5–7). For nitrone **2i**, bearing a naphthylimine, its corresponding product

**5i** was obtained in 91% yield (entry 8). Such reactions also worked for the nitrones **2j–2m** with various 4-substituted anilines (X = MeO, Cl, Br, and CO<sub>2</sub>Et); these gave the desired products **5j–5m** in 88–92% yield (entries 9–12). We tested this reaction on other ynamides **4b–4d** and found their reactivities varied with the sulfonamide functionalities. For ynamides **4b** and **4c** bearing –NTs(Ph) and –NMs(Ph), the resulting products **5n** and **5o** were obtained in 88–90% yields (entries 13–14). In contrast, ynamide **4d** gave many minor products because of its facile decomposition with the PtCl<sub>2</sub> catalyst within 0.15 h (entry 15). The reactions failed to work with other sulfonamides including NMs(*n*-Bu), NTs(*n*-Bu).

Scheme 3 depicts an efficient transformation of an oxoarylation product **5a** into indolin-2-one **6a**. In this process, initially present **5a** was reduced with NaBH<sub>3</sub>CN (1 equiv) in THF under ambient conditions (28 °C, 20 min), and the solution was filtered through a Celite bed. The THF filtrate was heated with silica gel (SiliaFlashG60) at 80 °C for 1 h to ensure a complete conversion to the indolin-2-one **6a** (89%).

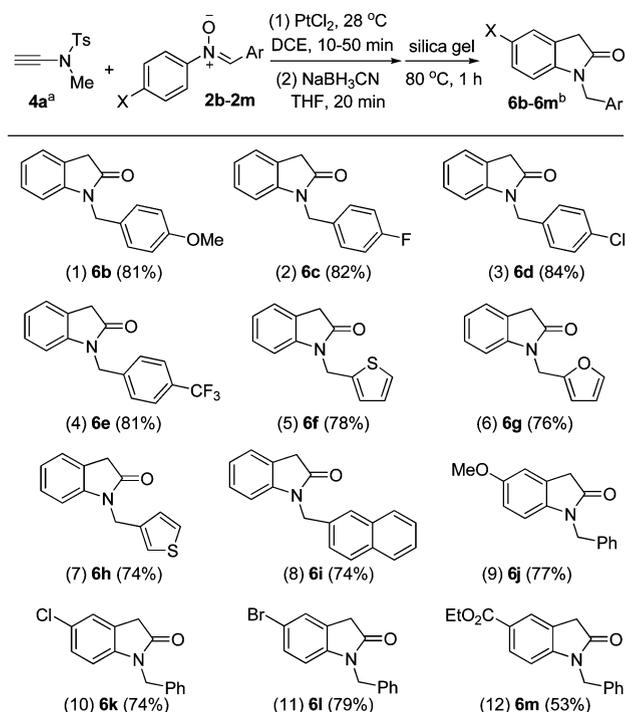
**Scheme 3.** Formation of an Indolin-2-one



To highlight the utility of this platinum-catalyzed oxoarylation of ynamides, we developed a one-pot synthesis of useful indolin-2-ones **6b–6m** from ynamide **4a** and nitrones **2b–2m**, as depicted in Scheme 4. In a typical operation, when the oxoarylation reaction of ynamide **1a** was complete in dichloroethane, a THF solution of NaBH<sub>3</sub>CN was added. The mixture was stirred for 20 min before being filtered through a Celite bed. The filtrate was heated with silica gel (SiliaFlashG60) at 80 °C for 1 h before workup. We used the same nitrones **2b–2m** as those in Scheme 2 to exemplify the generality of this indolin-2-one synthesis. Entries 1–8 show the efficient production of indolin-2-ones **6b–6i** in 74–84% yield, from nitrones **2b–2i** bearing alterable phenylimines **2b–2e** (Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, and 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>), heteroaryl imines **2f–2h** (Ar = 2,3-thienyl and 2-furanyl), and 2-naphthylimine **2i**. For nitrones **2j–2m** bearing varied aniline substituents, the resulting indolin-2-ones **6j–6m** were obtained in 53–79% yields (entries 9–12).

Scheme 5 shows deuterium labeling experiments that assist our understanding of the reaction mechanism. Treatment of ynamide **4a** and the deuterated nitron **d<sub>5</sub>-2a** with PtCl<sub>2</sub> under our standard conditions afforded the desired **d<sub>5</sub>-5a** with one methylene proton bearing X = 0.70 D. We performed this platinum-catalyzed reaction on ynamide **4a** and **d<sub>0</sub>-2a** (2 equiv) in the presence of deuterated imine **d<sub>5</sub>-7a** (2 equiv), but the resulting oxoarylation product

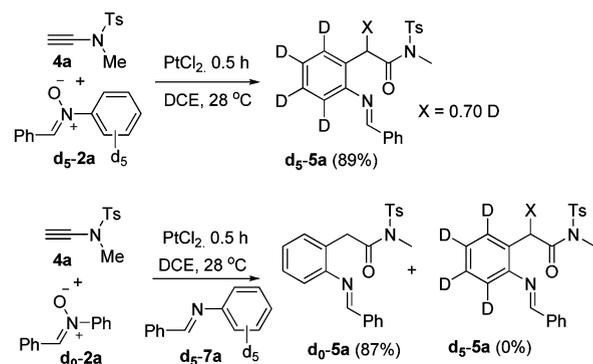
**Scheme 4.** Cascade Sequence for the Synthesis of Indolin-2-ones<sup>a</sup>



<sup>a</sup> [Ynamide] = 0.17 M, reactions performed at 28 °C. <sup>b</sup> Product yields are reported after purification from silica column.

**d<sub>0</sub>-5a** had no deuterium content at all. Nitron **2a** is clearly the source of both the oxygen and imine groups of the resulting product **5a**.

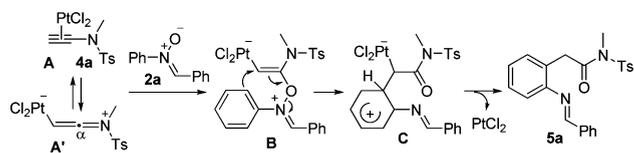
**Scheme 5.** Deuterium-Labeling Experiments



We propose the mechanism as depicted in Scheme 6 to rationalize our resulting oxoarylation compound **5a**. We postulate that nitron **2a** initially attacks at the C $\alpha$ -carbon of  $\pi$ -ynamide **4a**, which also has a ketene resonance hybrid

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### Scheme 6. A Plausible Reaction Mechanism



form **A'**.<sup>9,10</sup> A subsequent [3,3]-sigmatropic shift of the  $\beta$ -oxy alkenylplatinum intermediate **B** generates the

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platinum-containing amide **C**, ultimately giving the observed product **5a** through a proton transfer. This noncarbene route is analogous to that proposed for the 1,2-difunctionalization of alkynes via diphenylsulfur oxide.<sup>3c,e,11</sup>

In summary, a new platinum-catalyzed oxoarylation of ynamides with nitrones is reported. These reactions work well with a reasonable range of substrates. Cascade sequences for the synthesis of indolin-2-ones via  $\text{NaBH}_3\text{CN}$  reduction *in situ* of the initially formed oxoarylation products are also developed. On the basis of deuterium labeling experiments, we postulate a noncarbene route, in which the key step is a [3,3]-sigmatropic shift of the  $\beta$ -oxy alkenylplatinum intermediate **B**.

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**Supporting Information Available.** Experimental procedures, NMR spectra, and characterization data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.