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Platinum-Catalyzed Oxoarylations of Ynamides with Nitrones

Sabyasachi Bhunia, Chin-Jung Chang, and Rai-Shung Liu*

Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan, ROC

rsliu@mx.nthu.edu.tw

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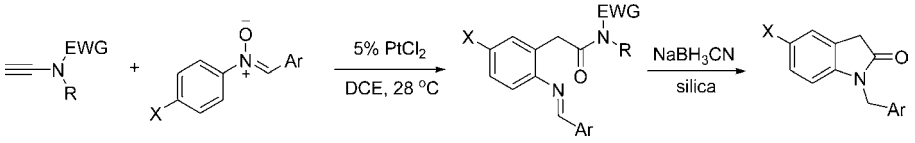
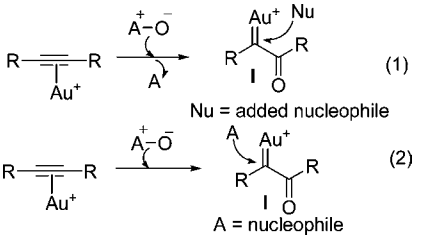
ABSTRACT



A new platinum-catalyzed oxoarylation of ynamides with nitrones is reported. Cascade sequences for the synthesis of indolin-2-ones via $NaBH_3CN$ 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 α-oxo gold carbenes **I**;[1−6] pyridine-based oxides[2] are superior to sulfur oxides[3] for generating such reactive intermediates. This new synthetic method provides potential access to valuable α-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[7] of such a conversion because of the following problems: (1) a competitive attack of this external nucleophile at the gold-π-alkyne; (2) a complexation of gold-carbene **I** with newly released pyridine, and (3) a second oxidation of gold carbenes **I** with organic oxides.[8] Recently, we proposed a distinct route, as depicted in eq 2, in which a nucleophile is embedded within the organic oxide A^+-O^- (A = nucleophile).[4a] 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[4a] 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 α-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

(1) Xiao, J.; Li, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 7226.

(2) For pyridine-based oxides, see selected examples: (a) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (b) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550. (c) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482. (d) Davies, P. W.; Cremonesi, A.; Martin, N. *Chem. Commun.* **2011**, *47*, 379. (e) Lu, B.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *132*, 14070. (f) Dateer, R.-B.; Pati, K.; Liu, R.-S. *Chem. Commun.* **2012**, *48*, 7200. (f) Dateer, R. B.; Shaibu, B. S.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2012**, *51*, 113.

(3) For sulfur oxides, see: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (b) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156. (c) Cuenca, A. B.; Montserrat, S.; Hossain, K. M.; Mancha, G.; Lledós, A.; Medio-Simón, M.; Ujaque, G.; Asensio, G. *Org. Lett.* **2009**, *11*, 4906. (d) Davies, P. W.; Albrecht, S. J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 8372. (e) Li, C.-W.; Pati, K.; Lin, G.-Y.; Sohel, S. M. A.; Hung, H.-H.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891.

(4) For nitrones, see: (a) Mukherjee, A.; Dateer, R. B.; Chaudhuri, R.; Bhunia, S.; Karad, S. N.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 15372. (b) Yeom, H. S.; Lee, J. E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040. (c) Yeom, H. S.; Lee, Y.; Lee, J. E.; Shin, S. *Org. Biomol. Chem.* **2009**, *7*, 4744. (d) Yeom, H. S.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J. E.; Lee, S. S.; Shin, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1611.

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(6) For nitro group, see: Jadhav, A. M.; Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 1769–1771.

(7) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *13*, 1738.

(8) Xu, C.-F.; Xu, M.; Jia, Y.-X.; Li, C.-Y. *Org. Lett.* **2011**, *13*, 1556.

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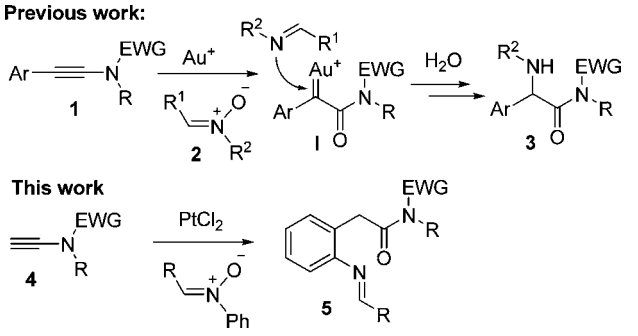
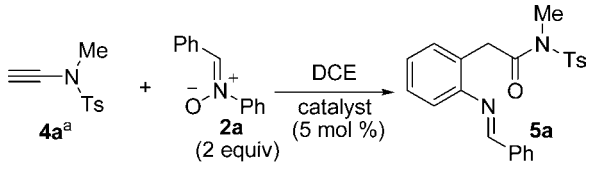
Scheme 1. Gold-Catalyzed 1,2-Difunctionalization of Activated Alkynes



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 $P(t\text{-Bu})_2$-(o-biphenyl)$AuNTf_2$, $IPrAuNTf_2$ (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene), and $AuCl_3$ 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

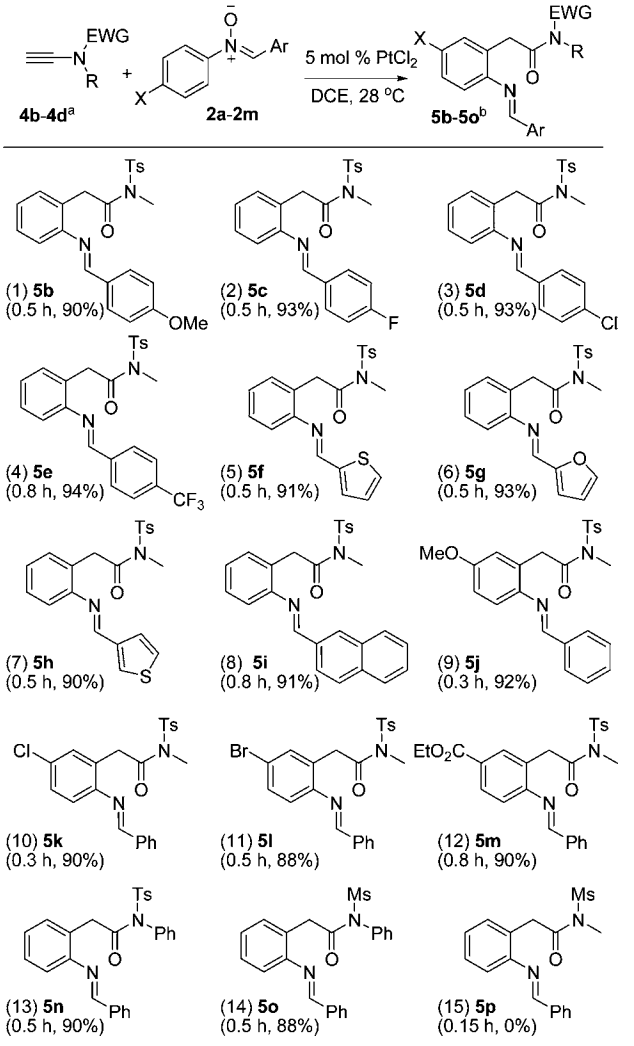


entry	catalyst[b]	temp (0 °C)	time (h)	**5a** (yields, %)[c]
1	$LAuCl/AgNTf_2$	28	2	–
2	$IPrAuCl/AgNTf_2$	28	3	–
3	$AuCl_3$	28	2	–
4	AuCl	28	0.3	57
5	$PtCl_2$	28	0.5	95
6	PtI_2	80	0.7	15
7	$PtCl_4$	28	0.5	65

[a] [**4a**] = 0.17 M. [b] L = $P(t\text{-Bu})_2$(*o*-biphenyl), IPr = 1,3-bis-(diisopropylphenyl)imidazol-2-ylidene. [c] 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 $PtCl_2$ in DCE at 28 °C (entry 5). In contrast, PtI_2 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[a]



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

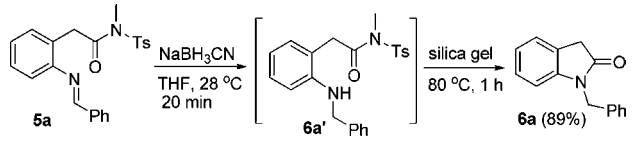
the reaction with $PtCl_4$, which gave compound **5a** in 65% yield (entry 7).

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 $PtCl_2$ 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-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, and 4-$CF_3C_6H_4$); 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_2Et); 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 $PtCl_2$ 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 $NaBH_3CN$ (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%).

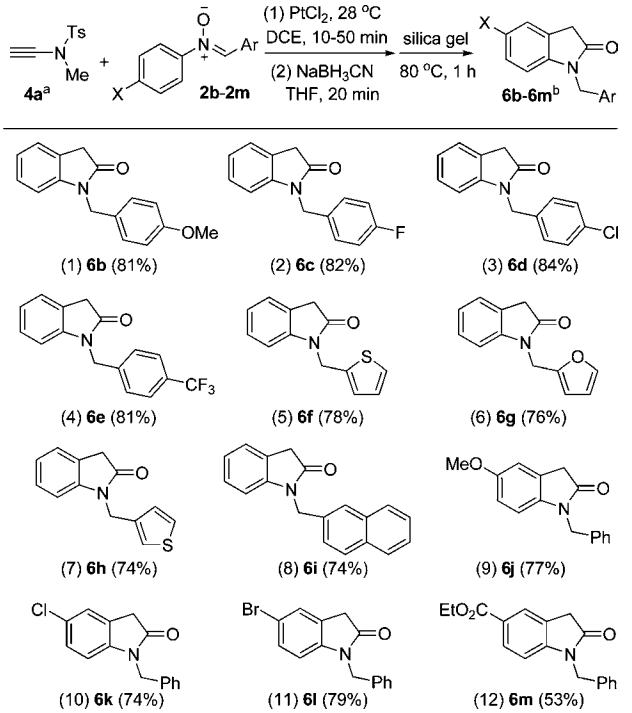
Scheme 3. Formation of an Indolin-2-one



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 $NaBH_3CN$ 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-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, and 4-$CF_3C_6H_4$), heteroaryl imines **2f**–**2h** (Ar = 2,3-theinyl and 2-furanyl), and 2-naphthylimine **2i**. For nitrones **2j**–**2m** bearing varied aniline substitutents, 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 nitrone **d_5-2a** with $PtCl_2$ under our standard conditions afforded the desired **d_5-5a** with one methylene proton bearing X = 0.70 D. We performed this platinum-catalyzed reaction on ynamide **4a** and **d_0-2a** (2 equiv) in the presence of deuterated imine **d_5-7a** (2 equiv), but the resulting oxoarylation product

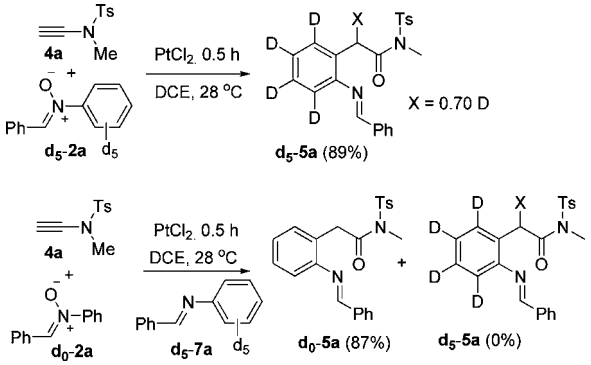
Scheme 4. Cascade Sequence for the Synthesis of Indolin-2-ones[a]



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

d_0-5a had no deuterium content at all. Nitrone **2a** is clearly the source of both the oxygen and imine groups of the resulting product **5a**.

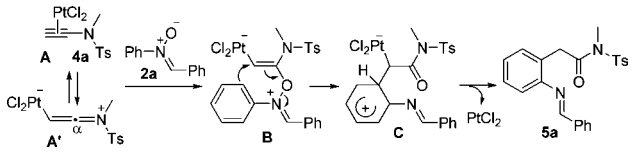
Scheme 5. Deuterium-Labeling Experiments



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

(9) For chemistry of ynamides, see reviews: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840–2859.

Scheme 6. A Plausible Reaction Mechanism



form **A′**.[9,10] A subsequent [3,3]-sigmatropic shift of the β-oxy alkenylplatinum intermediate **B** generates the 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.[3c,e,11]

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 $NaBH_3CN$ 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 β-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.

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(11) Wang, Y.; Ye, L.; Zhang, L. *Chem. Commun.* **2011**, *47*, 7815.