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Gold(I)-Catalyzed Oxidative 1,4-Additions of 3-En-1-ynamide with Nitrones via Carbon- versus Nitrogen-Addition Chemoselectivity

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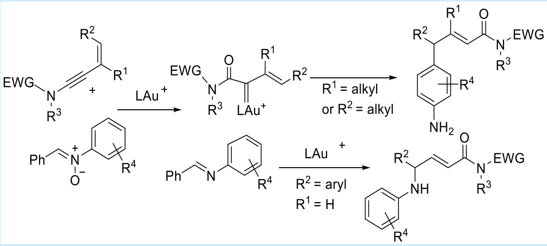
ABSTRACT: This work reports gold-catalyzed 1,4-oxofunctionalizations of 3-en-1-ynamides with nitrones, yielding two distinct *E*-configured products. We obtained 1,4-oxoarylation products from 3-en-1-ynamides bearing C(4)-electron-donating substituents and 1,4-oxoamination products from those analogues bearing C(4)-aryl substituents. We propose that if vinylgold carbenes are stable, imines undergo a *para*-arylation on these gold carbenes. If vinylgold carbenes are highly electron-deficient, this *N*-attack is irreversible to enable 1,4-oxoaminations.



One notable innovation in gold catalysis is catalytic alkyne oxidations using pyridine-based oxides,[1] generating versatile *α*-oxo gold carbenes (**I**) to achieve 1,2-oxidative functionalizations.[2] Such alkyne oxidations provide numerous cyclic and acyclic molecules via treatment of these carbenes with suitable nucleophiles (Scheme 1, eq 1). Despite their synthetic significance, pyridines released in these oxidations were treated as waste to render the reactions unable to meet atom economy. We recently developed distinct alkyne oxidations using nitrones as oxidants; this process releases imines that are more chemically active than pyridines.[1,3] Furthermore, the oxidations of alkynes with nitrones can deliver various 1,2-oxidative addition products from not only gold carbene intermediates but also a noncarbene process such as oxoarylation,[3] further manifesting the reaction diversity. Equation 2 shows one instance of gold carbene reactions in which *α*-oxo gold carbenes reacted with released imines, furnishing 1,2-oxoamination products.[4] In this work, we report 1,4-oxidative additions of 3-en-1-ynamides[5] with nitrones via two independent routes. In the case of 3- or 4-alkyl-3-en-1-ynamides, we obtained *E*-configured 1,4-oxoarylation products in which the released imines attack at the vinylgold carbenes via a *p*-aryl attack (eq 3), but for 5-aryl-3-en-1-ynamides, imines attack at gold carbenes via a nitrogen (N)-attack, yielding 1,4-oxoamination products with *E*-selectivity (eq 4). Noteworthy is the use of 4-chlorophenyl-derived nitrone (R^4 = 4-Cl); the oxidation still proceeds through a *p*-aryl attack path, leading to a chloro substitution.

Scheme 1. 1,*n*-Oxidative Functionalizations of Alkynes

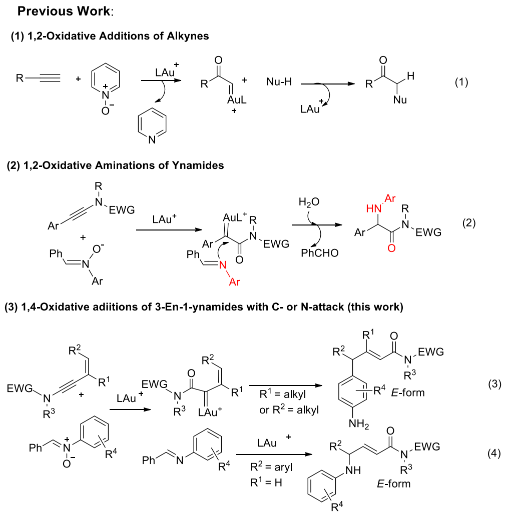


Table 1 summarizes the results for catalytic oxidations of 3-en-1-ynamide (**1a**) with nitrone (**2a**) using various gold catalysts; our target **3a** in these tests was obtained as only an *E*-configured isomer. Our initial test of LAuCl/AgNTf$_2$ (L = IPr and P(*t*-Bu)$_2$(*o*-biphenyl)) in dry 1,2-dichloroethane near 25 °C delivered 1,4-oxoarylation product **3a** in 53−55% yield, together with diazene oxide **3′** and benzaldehyde in small proportions (entries 1 and 2). For PPh$_3$AuCl/AgNTf$_2$ in 1,2-DCE, compound **3a** was obtained in 31% yield (entry 3). With (PhO)$_3$PAuCl/AgNTf$_2$, we observed an enhanced efficiency, giving compound **3a** in 67% yield (entry 4). Variations of silver salts as in (PhO)$_3$PAuCl/AgX, (X = OTf, SbF$_6$, BF$_4$) in 1,2-dichloroethane afforded compound **3a** with satisfactory yields (65−72%) with X = SbF$_6$ being the most effective (entries 5−

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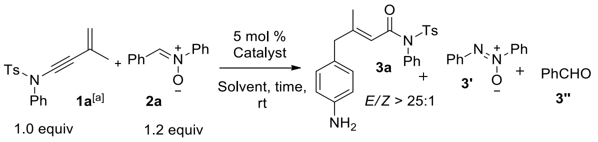
Table 1. Optimization of Gold Catalysts



entry	catalyst	solvent	time (h)	yield[b] (%) 3a	3′	1a	2a
1	IPrAuCl/AgNTf$_2$	DCE	24	55	12	10	15
2	LAuCl/AgOTf	DCE	24	53	11	11	17
3	PPh$_3$AuCl/AgNTf$_2$	DCE	24	31	27		36
4	(PhO)$_3$PAuCl/AgNTf$_2$	DCE	05	67	5		8
5	(PhO)$_3$PAuCl/AgOTf	DCE	06	65	6		9
6	(PhO)$_3$PAuCl/AgSbF$_6$	DCE	04	73	2−3		trace
7	(PhO)$_3$PAuCl/AgBF$_4$	DCE	05	72	2−3		trace
8	(PhO)$_3$PAuCl/AgSbF$_6$	DCM	06	76	2−3		trace
9	(PhO)$_3$PAuCl/AgSbF$_6$	THF	24	25	35	47	30
10	(PhO)$_3$PAuCl/AgSbF$_6$	toluene	24	8	35	56	45
11	(PhO)$_3$PAuCl/AgSbF$_6$	DMF	24	trace	6	78	75
12	AgSbF$_6$	DCM	24	38	15	20	10
13	(PhO)$_3$PAuCl/NaBARF	DCM	18	72	2−3		trace

[a][**1a**] = 0.08 M. [b]Isolated yields are obtained after purification from a silica column. L = P(t-Bu)$_2$(o-biphenyl).

7). For (PhO)$_3$PAuCl/AgSbF$_6$ in other solvents, the yields of compound **3a** were as follows: DCM (76%), THF (25%), toluene (8%) and DMF (trace) (entries 8−11). AgSbF$_6$ alone in DCM was also active for this transformation, rendering compound **3a** in 38% yield (entry 12). To verify the catalytic activity of the gold catalyst, we prepared Ag^{1+}-free (PhO)$_3$PAuCl/NaBARF, which afforded the desired product **3a** in 72% yield (entry 13). X-ray diffraction of compound **3a** confirmed a 1,4-oxidative arylation product bearing an E-configured skeleton.

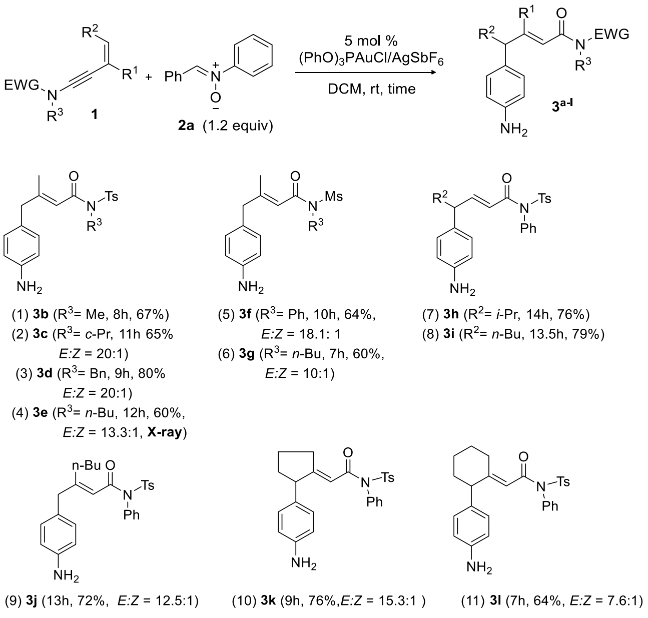
We prepared various 3-en-1-ynamides **1** to test the substrate scope; the results are summarized in Table 2. With nitrone **2a** and (PhO)$_3$PAuCl/AgSbF$_6$ (5 mol %) in DCM, the resulting 1,4-oxidative arylation products **3b**−**3l** were obtained in E-configurations predominantly (Table 2, entries 1−11). For substrates **1b**−**1d** bearing varried tosyl-derived sulfonamides such as NTs(Me), NTs(c-Pr), and NTs(Bn), their 1,4-oxoarylation products **3b**−**3d** were obtained in 67−80% yields with exclusive E-selectivity (E/Z > 25:1) (Table 2, entries 1−3). We tested also the reaction on 3-en-1-ynamide **1e** bearing NTs(n-Bu), further delivering compound **3e** with 60% yield and E/Z = 13.3:1 (Table 2, entry 4). The molecular structure of compound **3e** was characterized with X-ray diffraction.

For 3-en-1-ynamides **1f** and **1g** bearing mesyl-derived sulfonamides NMsPh, NMs(n-Bu), their resulting compounds **3f** and **3g** were obtained in 60−64% yields with a preferable E-selectivity (E/Z > 10:1, entries 5−6). 3-En-1-ynamides **1h** and **1i** bearing various C(4)-alkyl groups (R^2 = i-Pr and n-Bu) were also applicable to these oxidative arylations, giving compounds **3h** and **3i** in 76−79% yields (entries 7−8). 3-En-1-ynamide **1j** bearing C(3)-substituted n-butyl afforded compound **3j** in 72% yield (E/Z = 12.5:1) (entry 9). We also prepared cyclopentene- and cyclohexene-derived 3-en-1-ynamides **1k** and **1l**; their corresponding products **3k** and **3l** were obtained in 64−76% yield, with E/Z = 15.3:1 and 7.6:1, respectively (entries 10−11).

We assessed the substrate scope using various nitrones bearing *meta*- and *ortho*-substituents on aniline moieties; these results are summarized in Table 3. We first tested the reactions on nitrones **2b**−**2d**, bearing varied *meta*-substituents (R^2 = Br, Cl, Me); their corresponding desired products **4a**−**4c** were obtained with 58−79% yields (Table 3, entries 1−3). We also examined *ortho*-substituted analogues **2e**−**2i**, (R^1 = Br, Cl, I, F, Me), further affording the desired 1,4-oxoarylation products **4d**−**4h** in 65−88% yields (entries 4−8). Finally, we examined 2-naphthyl-derived nitrone **2j**, delivering compound **4i** in 73% yield (entry 9).

Apart from 1,4-oxoarylations, we have developed new 1,4-oxoaminations with those enynes bearing 4-aryl substituents; the results are provided in Table 4. Among these 1,4-oxoamination products, X-ray diffraction of representative **5f**

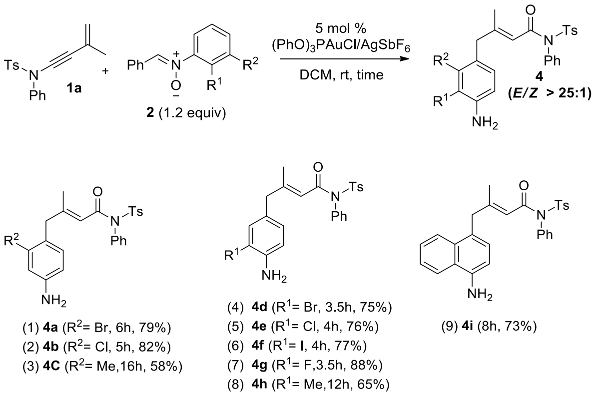
Table 2. Reactions of Various 3-En-1-ynamides[a,b]



(1) **3b** (R^3= Me, 8h, 67%)
(2) **3c** (R^3= c-Pr, 11h 65% E:Z = 20:1)
(3) **3d** (R^3= Bn, 9h, 80% E:Z = 20:1)
(4) **3e** (R^3= n-Bu, 12h, 60%, E:Z = 13.3:1, **X-ray**)
(5) **3f** (R^3= Ph, 10h, 64%, E:Z = 18.1: 1
(6) **3g** (R^3= n-Bu, 7h, 60%, E:Z = 10:1)
(7) **3h** (R^2= i-Pr, 14h, 76%)
(8) **3i** (R^2= n-Bu, 13.5h, 79%)
(9) **3j** (13h, 72%, E:Z = 12.5:1)
(10) **3k** (9h, 76%,E:Z = 15.3:1)
(11) **3l** (7h, 64%, E:Z = 7.6:1)

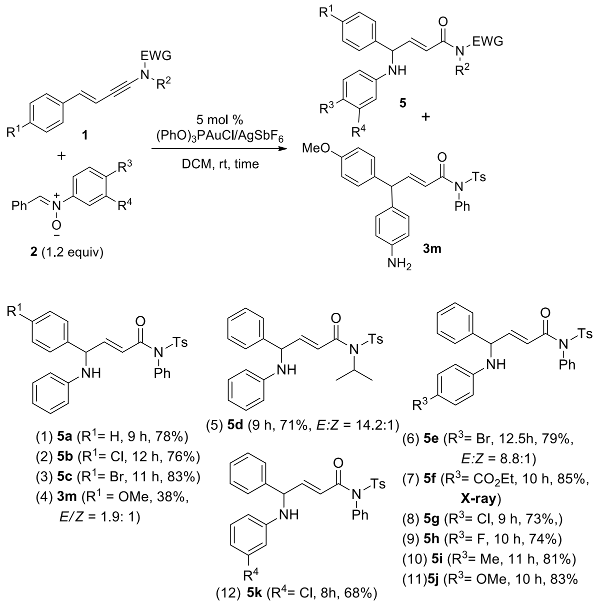
[a][**1a**] = 0.08 M. [b]Isolated yields are obtained after purification from a silica column.

Table 3. Nitrone Substrate Scope[a,b]



[a][**1a**] = 0.08 M. [b]Isolated yields are obtained after purification from a silica column.

Table 4. Gold-Catalyzed 1,4-Oxoaminations[a,b]



[a][**1**] = 0.08 M. [b]Isolated yields are obtained after purification from a silica column.

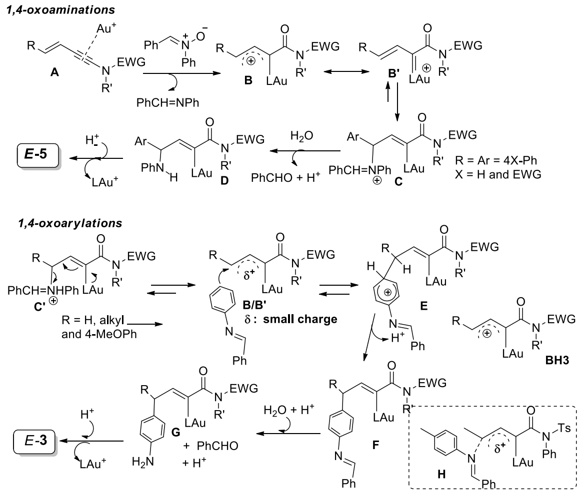
was performed to verify the proposed structure. Most 1,4-oxoamination products prefer only *E*-selectivity with *E*/*Z* > 20:1; those products with *E*/*Z* < 25:1 are indicated in Table 4. We first tested 4-phenyl-3-en-1-ynamide **1m** (R^1 = Ph) with nitrone **2a**, affording amination product **5a** in 78% yield (entry 1). We examined electron-withdrawing phenyl analogues **1n**–**1o** (R^1= Cl and Br) that reacted with nitrone **2a** to produce compounds **5b**–**5c** in 76–83% yields (Table 4, entries 2 and 3). When we tested the ynamide-containing electron-donating group **1p** (R^1 = OMe) we obtained desired product **3m** in 38% yield with *E*/*Z* = 1.9:1 (entry 4). We also performed the reactions on species **1q**, bearing various sulfonamides NTs(*i*-Pr), delivering compound **5d** in 71% yield with *E*/*Z* = 14.2:1 (entry 5). Further, we tested several nitrones **2** with 4-phenyl-3-en-1-ynamides (**1m**); see entries 6–12. For *p*-bromophenyl-derived nitrone **2k**, corresponding product **5e** was obtained in 79% yield with *E*/*Z* = 8.8:1 (entry 6). We performed these reactions on other *para*-substituted nitrones (R^3 = CO_2Et, Cl, F, **2l**–**2n**); their resulting products **5f**– **5h** were obtained in 73–85% yields (Table 4, entries 7–9). X-ray diffraction of compound **5f** confirms our proposed 1,4-oxoamination structure and its *E*-configuration. For nitrones **2o**–**2p** bearing electron-donating *p*-phenyl moieties (R^3 = Me, O-Me), the resulting products **5i**–**5j** were obtained with 81–83% yields (entries 10–11). *m*-Chlorophenyl-containing nitrone **2q** (R^4 = Cl) afforded compound product **5k** in 68% yield (Table 4, entry 12). A summary of the results in Tables 2 and 4 indicates that alkyl and 4-methoxyphenyl at position C(4) of 3-en-1-ynamides prefer 1,4-oxoarylations, whereas their C(4)-phenyl and their electron-deficient analogues produce 1,4-oxoaminations.

We prepared nitrones **2m** and **2o** bearing 4-chloro- and 4-methylphenyl-derived nitrones to seek a switch of chemoselectivity to 1,4-oxoamination. Notably, we still obtained 1,4-oxoarylation product **3a** in 40% yield via an electrophilic substitution in which the phenylchloro moiety was replaced. In contrast, we observed no reaction occurring for nitrone **2o**. In the presence of water, we observed no change of reaction chemoselectivity for these two nitrones, but the yield of compound **3a** was slightly improved to 46%. In the case of species **2o**, we obtained no *C*- or *N*-addition product but a large recovery yield of starting **1a** and **2o**. In this case, we speculate that the gold catalyst is likely poisoned with the released imine (vide infra). We also performed the oxidation of 3-en-1-ynamide **1a** with a mixture of d_5-nitrone **2r** and its imine in equal proportions; the resulting product **d_4-3a** contained only deuterated aniline at the 4-carbon position, whereas its alkenyl proton was only protonated.

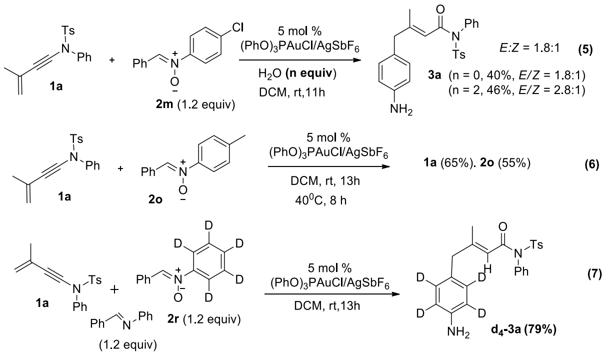
Accordingly, nitrone is the only source to provide oxygen and benzene for the 1,4-oxoarylation reaction of 3-en-1-ynamide **1a**. To measure the kinetic isotope effect, we ran a reaction containing **d_0-2a** (1.0 equiv), **d_5-2r** (1.0 equiv), and 3-en-1-ynamide **1a** (0.3 equiv); the resulting product was obtained with **d_0-3a**/**d_4-3a** = 1.00/1.00, showing no isotope effect.

We postulate a mechanism for the 1,4-oxoarylation and 1,4-oxoamination reactions of 3-en-1-ynamides (Scheme 2). A summary of our results indicates that C(4)-alkyl and 4-methoxyphenyl substituents preferably form 1,4-oxoarylation products, whereas their phenyl and other electron-deficient phenyl analogues preferably yield 1,4-oxoamination products.

Scheme 2. Plausible Mechanism for 1,4-Oxoamination and 1,4-Oxoarylation Reaction



This mechanism also rationalizes the observed *E*-stereoselectivity of observed products **3** and **5**. We previously reported gold-catalyzed oxidations of ynamides with nitrones to generate gold carbenes and imines; herein, we postulate alkenylgold carbenes **B′** that are also characterized with an allylgold cation resonance **B**. These gold carbenes likely form complex pairs with imines according to our deuterium-labeling experiments. In the case of electron-withdrawing phenyl and their electron-deficient analogues, their positive charge is significant to react with imine at the more basic nitrogen, yielding an addition intermediate **C**. This route leads to 1,4-oxoamination product **5** via a subsequent hydrolysis intermediate **B**. In the case of C(4)-alkyl- and 4-methoxyphenyl-substituted analogues, the positive charge of allylgold cation **B** (or **B′**) is small and stable; *N*-imine or carbene complex **C′** is easily dissociative to allow a *p*-aryl of the released imine, forming species **E**. A subsequent loss of proton of species **E** is, however, expected to be facile because of its aromatization. This process produces 1,4-oxoarylation products if allylgold cations **B**/**B′** are highly stable with a small positive charge. We hypothesize that the C(4)-N-attack is kinetically favorable because the nitrogen of the imine is more nucleophilic than a benzene, whereas the *p*-aryl attack can occur in a slow but irreversible process. In eq 6, we observed no reaction between 3-en-1-ynamide **1a** and nitrone **2o**; we rationalize this outcome with a postulated and stable complex pair **H** because an alternative path is completely blocked. In the case of 4-chlorophenyl-derived nitrone **2m**, the mechanism can be rationalized in a similar path.[6] For the two paths, their initial intermediates **D** and **G** bear *Z*-configured skeletons but yield *E*-configured products **3** and **5** after protodeaurations.



In summary, we report gold-catalyzed oxidations of 3-en-1-ynamides with nitrones to yield two distinct products. We obtained 1,4-oxoarylation products[7] from those ynamides bearing electron-donating substituents at the alkene moieties to render vinylgold carbenes stable. Initial *N*-attack of imines at these gold carbenes is reversible; the chemoselectivity becomes switched to 1,4-oxoarylations via *p*-arylations of imines at gold carbenes. If substituents are less electron-donating, this initial *N*-attack becomes irreversible because of the highly electron-deficient nature of gold carbenes; the chemoselectivity is favorable for 1,4-oxoamination products.[8]

■ ASSOCIATED CONTENT

Supporting Information

n data, crystallography data, and ^{1}H NMR and ^{13}C NMR for representative compounds (PDF). The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00055.

Experimental procedures, characterization data, crystallography data, and ^{1}H NMR and ^{13}C NMR for representative compounds (PDF)

Accession Codes

CCDC 2048163, 2048168, and 2048171 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 Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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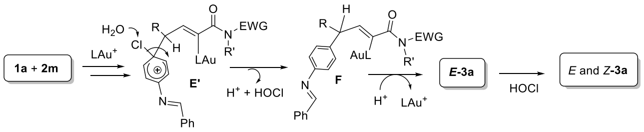

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