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DOI: 10.1039/C8CC00330K

Journal Name

COMMUNICATION

Gold-catalyzed *N*,*O*-functionalizations of 1,4-diyn-3-ols with *N*-hydroxyanilines to form highly functionalized pyrrole derivatives

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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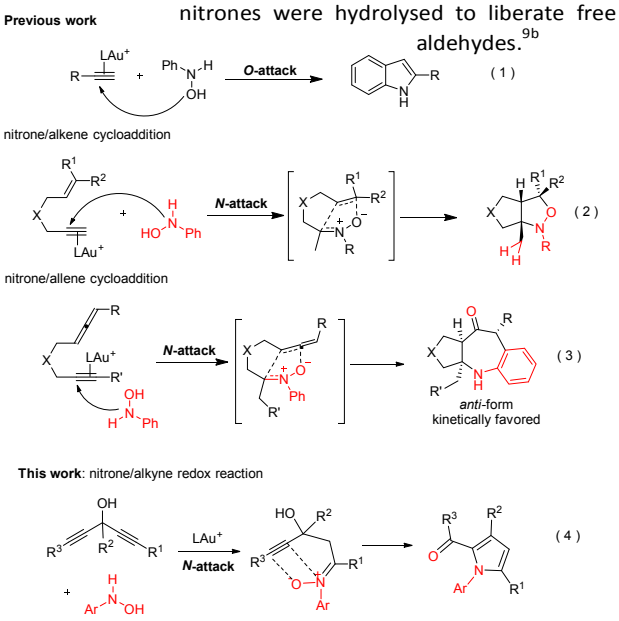
This work describes new *N*,*O*-functionalizations of 1,4-diyn-3-ols with *N*-hydroxyanilines to yield highly functionalized pyrrole derivatives. In a postulated mechanism, *N*-hydroxyaniline attacks at the more electron-rich alkynes via a *N*-attack regioselectivity to form unstable ketone-derived nitrones that react their tethered alkynes via an intramolecular oxygen-transfer to form *α-oxo* gold carbenes. This new method is applicable to a short synthesis of an bioactive molecule, PDE4 inhibitor.

Nitrones are versatile building blocks to access *N*,*O*-containing molecules through their stereoselective [3+2]-cycloadditions with alkene and allenes.[1] Nitrone species are commonly generated in situ from a mixture of *N*-hydroxyanilines with aldehydes; in contrast, ketone-derived nitrones are generally kinetically unstable[2a] unless an electron-withdrawing group is present.[2b-2e] Zhang and coworkers reported gold-catalyzed intermolecular reactions of *N*-hydroxyanilines with terminal alkynes to afford indole products; the key step involves an *O*-attack of *N*-hydroxyanilines at gold π-alkynes [Eq. (1)].[3,4] As opposed to the *O*-attack mode, we reported an alkene-controlled *N*-attack of *N*-hydroxyanilines at the π-alkynes of 1,6-enynes to generate unstable ketone-derived nitrones that reacted instantaneously with their tethered alkenes to enable novel [2+2+1]-annulation products [Eq. (2)].[5,6] Such gold-catalyzed *N*,*O*-functionalizations with *N*-hydroxyanilines is further applicable to 6-allenyl-1-ynes to form the same nitrones that were trapped with their tethered allenes to afford benzoazepin-4-ones stereoselectively [Eq. (3)].[7] This work reports new gold-catalyzed *N*,*O*-functionalizations of 1,4-diyn-3-ols with *N*-hydroxyanilines, delivering pyrrole derivatives efficiently [Eq. (4)]. Notably, the key ketone-derived nitrones reacted with the tethered alkynes in a non-cycloaddition route, notably through a distinct oxygen-transfer reaction.[8,9] In our previous work, gold catalysed reactions of nitrones with ynamides proceeded through different 1,2-oxoamination reactions, in which nitrones were hydrolysed to liberate free aldehydes.[9b]



The utility of this synthesis provides a short entry to highly functionalized pyrrole frameworks, which are found as the core structures in several bioactive and natural products; the examples are shown in Figure 1.[10] Herein, a short synthesis of PDE4 inhibitor is demonstrated in this work.

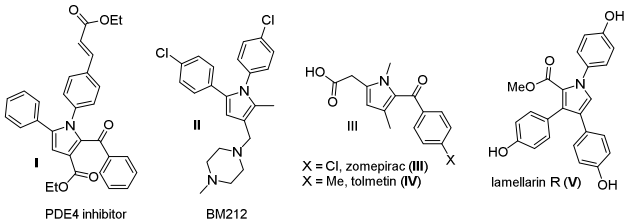


Fig.1 Representative bioactive and natural products

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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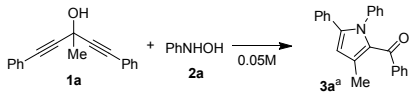
Table 1 optimizes the reactions of 3-methyl-1,5-diphenylpenta-1,4-diyn-3-ol (**1a**) with *N*-hydroxyaniline (**2a**) using various gold catalysts. We tested the reaction with *t*BuMePhosAuCl/$AgNTf_2$ (10 mol %) in DCE at room temperature, affording pyrrole **3a** in only 11% with a 69% recovery of initial **1a**. To improve the product yields, $Zn(OTf)_2$ (30 mol%) was added to this reaction to increase the yield of **3a** to 43% (entry 2). A high loading, 20 mol % of *t*BuMePhosAuCl/$AgNTf_2$ together with $Zn(OTf)_2$ led to a high consumption of **1a** to deliver **3a** in 58% (entry 3). With *t*BuMePhosAuCl (20 mol%), we employed $AgNTf_2$ with 50 mol % to obtain **3a** in 71% yield. With 50 mol % $AgNTf_2$, we altered gold catalysts LAuCl (20 mol %, L = IPr, P(*t*-Bu)$_2$(*o*-biphenyl), PPh_3), finding that P(*t*-Bu)$_2$(*o*-biphenyl)AuCl was the best catalyst to produce **3a** in 78% yield (entries 5-7). We tested the reactions with 10 mol % P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgNTf_2$, but giving **3a** in 20-21% yields at 25 ^{0}C and 60 ^{0}C (entries 8-9). The use of P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgSbF_6$ maintained the same high efficiency (entry 10). We employed a low loading (15 mol %) of P(*t*-Bu)$_2$(*o*-biphenyl)AuCl and $AgNTf_2$ (50 mol %) to decrease the yield of **3a** in 48% yield (entry 11). The use of this catalyst composition in other solvents gave **3a** in the following results: 41% in DCM, 8% in THF and 47% in CH_3NO_2. We also performed catalytic reactions with *p*-TSA, $Zn(OTf)_2$, $Cu(OTf)_2$ and $Sc(OTf)_3$, with $Zn(OTf)_2$ being the most productive to afford **3a** in 39% yield (see Table S1). The molecular structure of compound **3a** was determined by X-ray diffraction.[11]

Table 1. Optimization of the reaction condition



Entry	Catalyst (mol%)	Lewis acid (mol%)	Solvent	Temp (°C)	Time (h)	isolated yield (%) 1a	3a
1	$L_1AuCl(10)/AgNTf_2(10)$[b]	—	DCE	rt	9	69	11
2	$L_1AuCl(10)/AgNTf_2(10)$	$Zn(OTf)_2$ (30)	DCE	rt	5	34	43
3	$L_1AuCl(20)/AgNTf_2(20)$	$Zn(OTf)_2$ (30)	DCE	rt	5	15	58
4	$L_1AuCl(20)/AgNTf_2(50)$	—	DCE	rt	3	8	71
5	$IPrAuCl(20)/AgNTf_2(50)$	—	DCE	rt	7	56	28
6	$L_2AuCl(20)$[c]$/AgNTf_2(50)$	—	DCE	rt	2	0	78
7	$PPh_3AuCl(20)/AgNTf_2(50)$	—	DCE	rt	5	48	39
8	$L_2AuCl(10)/AgNTf_2(10)$	—	DCE	rt	8	62	21
9	$L_2AuCl(10)/AgNTf_2(10)$	—	DCE	60	6	53	20
10	$L_2AuCl(20)/AgSbF_6(50)$	—	DCE	rt	2	0	77
11	$L_2AuCl(15)/AgNTf_2(50)$	—	DCE	rt	4	30	48
12	$L_2AuCl(15)/AgNTf_2(50)$	—	C_6H_6	rt	4	35	45
13	$L_2AuCl(15)/AgNTf_2(50)$	—	DCM	rt	4.5	43	41
14	$L_2AuCl(15)/AgNTf_2(50)$	—	THF	rt	7	76	8
15	$L_2AuCl(15)/AgNTf_2(50)$	—	CH_3NO_2	rt	4	36	47

1a (0.05M, 1.0 equiv). **2a** (3.0 equiv). [a] Product yields are given after purification from a silica column. [b] L_1 = 2-Di-*tert*-butylphosphino-2'-methylbiphenyl. [c] L_2 = P(*t*-Bu)$_2$(*o*-biphenyl). [d] IPr = 1,3-bis (diisopropylphenyl) imidazol-2-ylidene.

Under the optimized condition, we examined the effects of the alkoxy groups of diynols **1aa**-**1ac** (R = Me, Bu and $PhCH_2$), yielding compound **3a** in relatively low yields (52-59%) [Eq. (5)]. The high efficiency of a hydroxyl group as in species **1a** is probably attributed to its good leaving property.

We assessed the scope of this pyrrole synthesis with various 3-alkyl-1,4-diyn-3-ol **1** and *N*-hydroxyaniline **2a** using P(*t*-Bu)$_2$(*o*-biphenyl)AuCl (10-20 mol %)/$AgNTf_2$ (50 mol %); the results are summarized in Table 2. As the tertiary carbon were substituted with R^2 = *n*-propyl, *i*-propyl and styryl, the resulting products **3b**-**3d** were obtained in 48-73% yield (entry 2-4). In entries 5-8, different symmetric aryl-substituted diynols **1e**-**1h** were tested; electron-donating substituents $R^1 = R^3$ = 4-XC_6H_4 (X = Me, OMe) were operable with 10 mol % LAuCl to afford compounds **3g** and **3h** in 58% and 66% yields respectively whereas electron-withdrawing analogues **3e** and **3f** (X = Cl, CF_3)

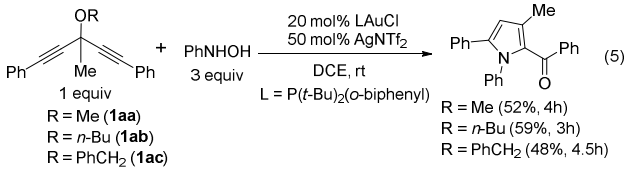
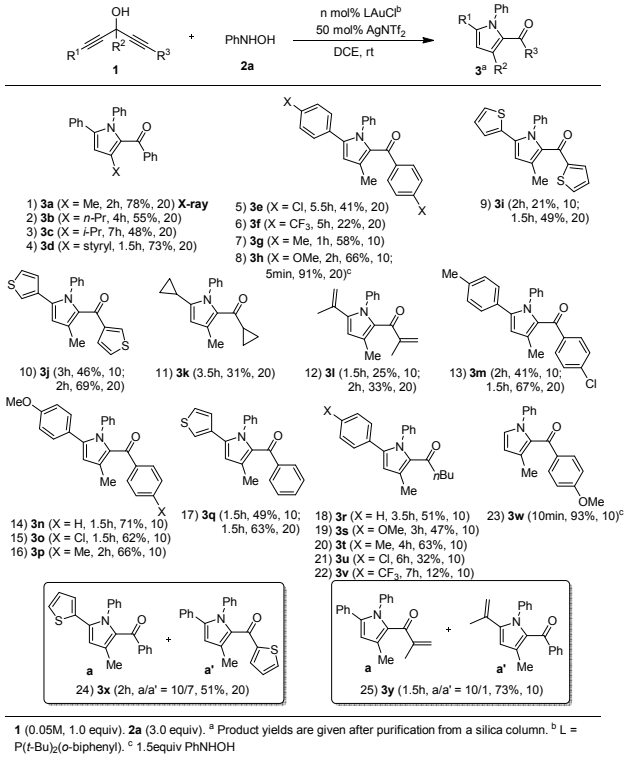


Table 2. Reactions with various 3-alkyl-1,4-diyn-3-ols



1 (0.05M, 1.0 equiv). **2a** (3.0 equiv). [a] Product yields are given after purification from a silica column. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl). [c] 1.5equiv PhNHOH

required 20 mol % gold catalysts to deliver the desired products **3e** and **3f** in 41% and 22% yields respectively. For diynol **1h,** gold catalyst at a 20 mol % loading enabled a complete reaction within 5 minutes, yielding **3h** in 91% yield. We tested the reaction of species **1i** (R^1, R^3 = 2-thienyl) and **1j** (R^1, R^3 = 3-thienyl), delivering the desired products **3i** and **3j** in 49% and 69% yields respectively (entries 9 and 10). For alkyl-substituted diyne and alkenyl diyne derivatives **1k** and **1l,** their corresponding reactions were performed with 20 mol % catalyst to afford pyrrole derivatives **3k** and **3l** in poor yields (31-33% entries 11 and 12). In the non-symmetric aryl-substituted diynes, we tested substrates **1m**-**1p** with 10-20 mol % catalysts to afford the following products in satisfactory

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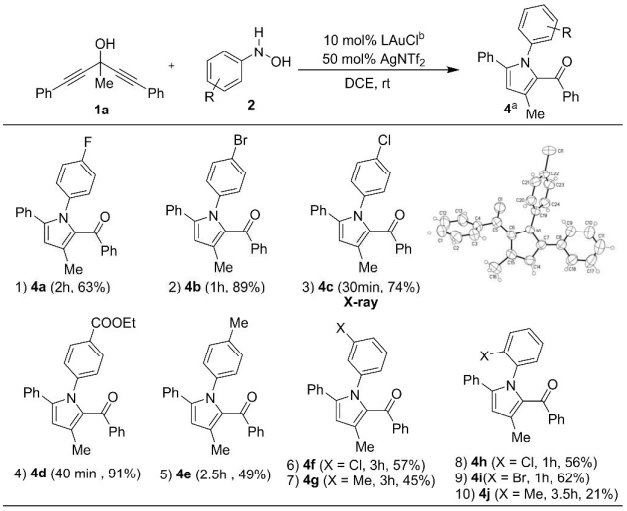
yields: **3m** (67%, 20 mol %), **3n** (71%, 10 mol %), **3o** (62%, 10 mol %) and **3p** (66%, 10 mol %, entries 13-16); herein, the more electron rich alkynes of substrates were attacked by *N*-hydroxyaniline to attain high efficiency. We also prepared 1,4-diyn-3-ol **1q** (R^1 = 3-thienyl, R^3 = phenyl) to yield compound **3q** in 63% yield. We tested additional non-symmetric diynols **1r**-**1v** bearing a butyl and an aryl group respectively, and with a 10 mol % catalyst, electron-donating group R^1 = 4-XC_6H_4 (X = H, Me, OMe) provided yields (47-63%) better than those of electron-withdrawing analogues **3u** (R^1 = Cl, 32%; CF_3, 12% entries 18-22). To our pleasure, we examined the reaction on a terminal alkyne **1w** to afford the desired product **3w** up to 93% in a brief period (10 min) using a 10 mol % catalyst. Interestingly, we prepared substrates **1x** bearing one phenyl and one-thienyl group respectively, yielding two regioisomers **3x** (51%, a/a' = 10/7, entry 24). For 1,4-diyn-1-ol **1y** bearing a phenyl and an alkenyl, the reaction afforded two regioisomers **3y** in good regioselectivity (73%, a/a' = 10/1, entry 25). Among these products, the molecular structure of compounds **3a** was characterized by X-ray diffraction.[11]

Table 3 shows the compatibility of these reactions with various *N*-hydroxyanilines that were operable with 10 mol % catalysts; reasonable yields of products were obtained in most instances. For *N*-hydroxyanilines **2b**-**2e** bearing various *para*-phenyl substituents including R = F, Cl, Br and CO_2Et, their resulting **4a-4d** were obtained in satisfactory yields (61-91%, entries 1-4). We also prepared *N*-hydroxyaniline **2f** bearing R = Me, giving the desired product **4e** in low yield (49%, entry 5).

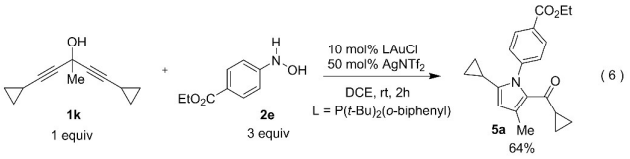
Table 3. Reactions with various *N*-hydroxyanilines



1a (0.05M, 1.0 equiv). **2** (3.0 equiv). [a] Product yields are given after purification from a silica column. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl)

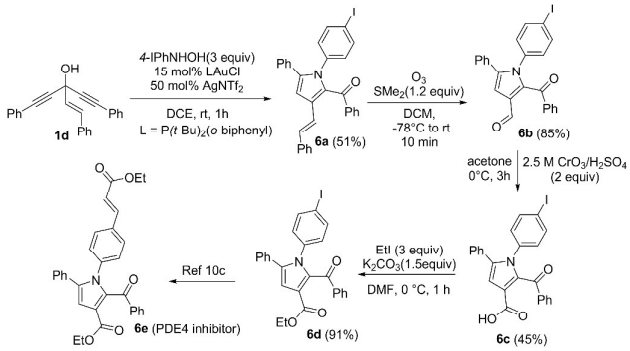
Clearly, basic *N*-hydroxyaniline is not an efficient substrate. In entries 6 and 7, we used meta-substituted *N*-hydroxyanilines to test this reaction, affording the desired products **4f** and **4g** in 57% and 45% respectively. We also prepared *ortho*-substituted *N*-hydroxyanilines; herein, electron-withdrawing group **4h** and **4i** (R = Cl, Br) were obtained in 56-62% yields (entries 8-9), better than that of electron-donating analogues **4j** (R = Me, 21%, entry 10). The molecular structure of compound **4c** was again confirmed by X-ray diffraction.[11]

As noted in Table 2 (entry 11), the gold catalyzed reaction of 1,4-diyn-1-ol **1k** with *N*-hydroxyaniline **1a** gave pyrrole **3k** in only 31% yield with 20 mol % catalyst. But with ester-substituted *N*-hydroxyaniline **2e**, the yield of compound **5a** was increased to 64% with 10 mol % catalyst [Eq. (6)]. Accordingly, product yields in Table 3 can be significantly improved with 10 mol % catalyst if a less basic N-hydroxyaniline like **2e** is used.

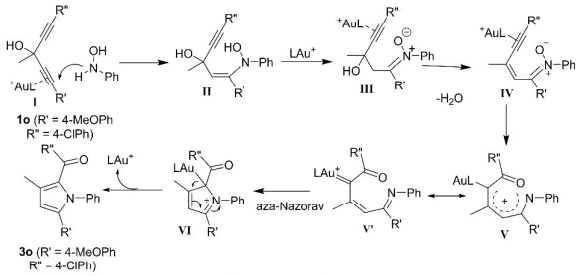


(6)

Scheme 1 manifests the utility of our new catalytic reactions to achieve a formal synthesis of **6e**, a PDE4 inhibitor. Treatment of species **1d** with 4-IC_6H_4NHOH (3.0 equiv) with gold catalysts yielded the desired pyrrole product **6a** in 51% yield. A subsequent oxidative cleavage of species **6a** with O_3/Me_2S afforded an aldehyde derivative **6b** that was convertible to an acid **6c** and finally to the ester **6d**. The transformation of species **6d** into **6e** via Heck reactions has been documented in the literature.[10c]



Scheme 1. Formal synthesis of PDE4 inhibitor



Scheme 2. A Postulated Mechanism

An electron-rich alkyne is preferable for this pyrrole synthesis because LAu^+ can complex such alkynes strongly. Scheme 2 depicts a postulated mechanism involving a preferable π-coordination of gold at the more electron-rich alkyne as in species **I** before a nucleophilic attack of *N*-hydroxyaniline. The regioselectivity proceeds with an *N*-attack

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of amine, as facilitated by its tethered alkyne.[5,7] Resulting ketone-derived nitrones **II** again coordinates with gold to effect a dehydration; this step is facilitated with $AgNTf_2$ or $Zn(OTf)_2$ to ionize a hydroxyl leaving group. A subsequent intramolecular oxygen transfer of species **IV** yields α-*oxo* gold carbenes **V** that undergoes an aza-Nazorav cyclization[12] to yield observed products **3o** via intermediate **VI**.

In summary, we have developed novel gold-catalyzed *N,O*-functionalizations of 1,4-diyn-3-ols[13,14] with *N*-hydroxyanilines to form highly functionalized pyrrole derivatives. The loading of gold catalysts relies on the types of *N*-hydroxyanilines; electron-deficient types can be catalysed satisfactorily with a 10 mol % loading. The mechanism of these reactions proceeds via an initial formation of nitrones, but their reactions with the tethered alkynes occur via an oxygen-transfer process.

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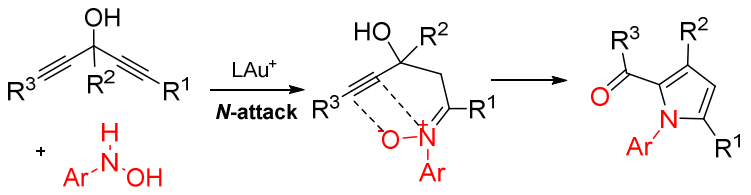

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