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Gold-catalyzed 1,2-iminonitronation of electron-deficient alkynes with nitrosoarenes to afford α-imidoyl nitrones†

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Gold-catalyzed 1,2-iminonitronation of propiolate derivatives with nitrosoarenes to give α -imidoyl nitrones is described; this new reaction is applicable to diverse propiolate derivatives and nitrosoarenes.

Although alkenes and alkynes are two important unsaturated hydrocarbon motifs in organic synthesis, catalytic oxidation of alkynes¹ is much less explored than for alkenes.^{2,3} One important advent in Au- and Pt-catalyzed reactions is the functionalization of electrophilically activated alkynes with diverse nucleophiles.⁴ Pyridine N-oxides or sulfoxides allow gold-catalyzed 1,2-double oxidation of alkynes to afford 1,2-dicarbonyl products (I) efficiently⁵ (eqn (1)). Metal-catalyzed reactions of terminal alkynes with nitrosoarenes were reported to produce indole derivatives.⁶ To implement 1,2-oxidative difunctionalization of alkynes, we reported 1,2-oxoimination of ynamides using nitrosoarenes to enable a reaction of meta thesis type (eqn (2)).⁷ We are aware of no precedent for catalytic 1,2-dual imination reactions of alkynes using suitable nitrogen sources. Here we report gold-catalyzed 1,2-iminonitronation reactions using electron-deficient alkynes, nitrosoarenes and a suitable gold catalyst, which represent a special case of 1,2-dual imination reactions. The contrasting outcome in eqn (2) and (3) is due to their distinct mechanisms involving noncarbene⁷ versus carbene routes.

Table 1 presents conditions to achieve a 1,2-iminonitronation using various metal catalysts (5 mol%) and solvents. We tested this reaction first involving ethyl propiolate **1a** and PhNO (**2a**, 2.3 equiv.) in dichloroethane (25 °C, 6 h) with LAuCl/AgNTf₂ (L = P(*t*-Bu)₂(*o*-biphenyl)), leading to a complete conversion to afford an α -imidoyl nitrone **3a** in 77% yield together with α , β -dioxo ester **4** (13%) and diazene oxide **4**' (0.14 equiv.) in minor proportions

$\begin{array}{c} O \\ OEt (5 \text{ mol } \%) \\ Ph \\ \textbf{1a} \\ \textbf{2at (2.3 equiv)} \\ \textbf{2at (2.3 equiv)} \\ \end{array} \begin{array}{c} Ph \\ Ph \\ \textbf{1a} \\ \textbf{2at (2.3 equiv)} \\ Ph \\ \textbf{2at (2.3 equiv)} \\ \end{array} \begin{array}{c} Ph \\ Ph \\ \textbf{2at (2.3 equiv)} \\ Ph \\ P$						
				Yield ^{b} (%)		
Entry	Catalyst	Solvent ^a	Time (h)	1a	3a	4
1	LAuCI/AgNTf ₂	DCE	6	_	77	13
2	LAuCI/AgSbF6	DCE	6	_	67	21
3	AuCIPPh ₃ /AgNTf ₂	DCE	6	_	64	19
4	IPrAuCI/AgNTf2	DCE	10	_	71	9
5	AuCI ₃	DCE	7	_	63	22
6	AgNTf ₂	DCE	12	65		_
7	PtCI ₂ /CO	DCE	12	71		_
8	LAuCI/AgNTf ₂	DCM	24	_	75	14
9	LAuCI/AgNTf2	CH_3NO_2	12	12	63	13
10	LAuCI/AgNTf2	Toluene	18	45	27	28

L = $P(t-Bu)_2(o-biphenyl)$, IPr = 3-bis(diisopropylphenyl)imidazol-2ylidene. ^{*a*} [1a] = 0.20 M. ^{*b*} Product yields are reported after purification from a silica column. ^{*c*} Diazene oxide 4' was isolated in 0.14 equiv. in entry 1 whereas this species was undetermined in other entries.

(entry 1). A switch of its silver source to LAuCl/AgSbF₆ (entry 2) gave compound 3a in a slightly decreased yield, ca. 64% whereas dicarbonyl product 4 was obtained in 19% yield. Other gold catalysts including PPh3AuCl/AgNTf2, IPrAuCl/ $AgNTf_2$ (IPr = 3-bis(diiso-propylphenyl)imidazol-2-ylidene) and AuCl₃ were also active, affording desired 3a in 63-71% yields with side product 4 in 9-22% yields (entries 3-5). AgNTf₂ and PtCl₂/CO were catalytically inactive to give initial 1a with 65–71% recovery (entries 6 and 7). For LAuCl/AgNTf₂, other solvents including dichloromethane (DCM), nitromethane and toluene yielded compound 3a in 75%, 63% and 27% yields respectively; its byproduct 4 was obtained in 13-28% yields (entries 8-10). Structural characterization of compound 3a relies on the X-ray diffraction study of its indole derivative 3j (Table 2, entry 9).8 Our control experiment indicates that α,β -dioxo ester 4 arises from the alkyne

Table 1 Reactions over various catalysts

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Table 2 Catalytic reactions with various alkynes^a



^{*a*} [1] = 0.20 M. Product yields are reported after purification from a silica column. $L = P(t-Bu)_2(o-biphenyl)$.

oxidation of initial 1a rather than from the hydration of product 3a (see eqn (5)).

1 2-dioxo additions

$$R \xrightarrow{R'} R' + \stackrel{A}{\to} \stackrel{O}{\longrightarrow} \xrightarrow{Au} R' \stackrel{V}{\longrightarrow} R'$$
sulfur oxides,
pyridine oxides
$$(1)$$

 \cap

NA

1,2-oxoiminations

$$R = -N_{R'}^{EWG} + Ar_{Ar}^{N=0} \xrightarrow{Au} R_{II}^{O} \xrightarrow{EWG} (2)$$

1,2-iminonitronations (this work)

$$R \xrightarrow{O}_{Ar'} A_{r'} \xrightarrow{N=0} A_{u} \xrightarrow{Au}_{Ar'} \xrightarrow{CO_2 R'}_{I+} (3)$$

$$R \xrightarrow{I}_{Ar'} A_{r'} \xrightarrow{R}_{R} = alkyl, aryl or heteroaryl$$

We prepared additional propiolate derivatives (**1b–1m**) to assess the scope of the reaction. The 1,2-iminonitronation of nitrosobenzene (2.3 equiv.) with various ethyl propiolate derivatives (**1b–1m**) is shown in Table 2. In most cases, α , β -dioxo esters were also produced in minor proportions, but we did not isolate them. The reactions were run with P(*t*-Bu)₂(*o*-biphenyl)AuCl/AgNTf₂ (5 mol%) in DCE (25 °C, 0.2 M). Entries 1–4 show the applicability of this catalytic reaction to several propiolate substrates **1b–1d** bearing various *p*-phenyl substituents (4-XC₆H₄, X = methyl, methoxy and 4-chloro); their corresponding α -imidoyl nitrones **3b–3d** were obtained in satisfactory yields (61–76%). For *ortho*-methyl substituted derivative **1e**, its corresponding product was obtained in 61% yield (entry 4). The scope of this catalysis is further extended to heteroaryl substrates including 2-thienyl, 3-furanyl, 3-benzothienyl 2-benzofuranyl, and *N*-tosyl indolyl, yielding desired products (**3f**-**3j**) in 64–74% yields (entries 5–9). This reaction was extendible to an alkenyl-substituted propiolate **1k**, providing desired **3k** in 79% yield (entry 10). To our delight, the reactions were also compatible with alkyl-substituted propiolates **1l** and **1m** (R = cyclohexyl and cyclopropyl), affording α -imidoyl nitrones **3l** and **3m** in satisfactory yield 63%–71% (entries **11** and **12**). Although the reaction was extendible to *n*-butyl-substituted propiolate, we were unable to obtain its product in pure form. For terminal alkyne propiolate, a complicated mixture of species **3j** is elucidated by X-ray diffraction to characterize its structure.⁸

We also studied the scope of the substrates of various nitrosoarenes **2b–2f** (2.3 equiv.); their reactions with ethyl propiolate **1a** were examined with P(*t*-Bu)₂(*o*-biphenyl) AuCl/AgNTf₂ (5 mol%) in DCE (25 °C, 7–9 h, Table 3). The catalytic reactions worked efficiently for electron-rich nitrosoarenes **2b–d** including 3,5-dimethylphenyl, *t*-butylphenyl and 4-methoxyphenyl analogues (entries 1–3); resulting products **5b–5d** were produced in 67–73% yields. For their electrondeficient phenyl analogues **2e** and **2f** (XC₆H₄, X = Br and Cl, entries 4 and 5), the same reactions afforded α -imidoyl nitrones **5e–5f** in 73% and 69% yields, respectively.

We tested the reaction of highly electron-deficient diethyl but-2-ynedioate (**1n**) to examine the reaction chemoselectivity (eqn (4)). The HRMS, ¹H and ¹³C-NMR data support the structure of a bis-nitrone species **6a** with a plane of symmetry; this proposed structure was confirmed by the X-ray diffraction study.⁸

We postulate that the two ester groups stabilize their own conjugated nitrones, thus forming bis-nitrone groups safely. Formation of compound **6a** confirms the intermediacy of species **A**, in which gold carbene is replaced with nitrosobenzene to form a second nitrone functionality. Such a carbene reaction has analogous precedents in literature,⁹ further manifesting the diversity of the carbene/nitrosoarene reactions.^{10–12}



Table 3 Catalytic reactions with various nitrosoarenes^a







Scheme 1 Formation of diazene oxide.

Diazene oxide 4' represents the reducing form of nitrosobenzene 2a and its detection in the system (Table 1, entry 1) urges us to perform additional experiments as depicted in Scheme 1. Treatment of nitrosobenzene 2a with a gold catalyst (5 mol%) in DCE delivered diazene oxide 4' in 3% yield, but additional water (2 equiv.) increased the yield of species 4' to 5.5%. We believe that water can facilitate the formation of diazene oxide 4', presumably *via N*-hydroxyaniline, which is unstable in solution to form diazene oxide 4'.¹³ Literature has documented a fast equilibrium between nitrosobenzene and *N*-hydroxyaniline in HCl/water/acetone.¹⁴

 α -Imidoyl nitrone **3a** is robust toward the hydration with P(*t*-Bu)₂ (*o*-biphenyl)AuCl/AgNTf₂ in wet DCE. Hence, formation of ester **4** from propiolate **1a** in Table 1 (entry 1) is unlikely caused by the hydration of α -imidoyl nitrone **3a**. Shown in eqn (5) is the successful hydration of species **3a** with HCl (1 equiv.) in THF/water (2:1) to yield α , β -dioxo ester **4** in 45% yield.

$$\begin{array}{c} \Pr & \mathsf{N} & \mathsf{O}^- & \mathsf{HCl}(1 \text{ equiv.}) \\ \Pr & \mathsf{N}^+_{\mathsf{Ph}} & \mathsf{THF/water(2:1)} & \mathsf{Ph} & \mathsf{O} \\ \mathbf{3a} & \mathsf{CO}_{\mathsf{PE}} & \mathsf{25}^{\,\mathsf{PC}}, \mathsf{2.h} & \mathsf{4}(45\%) & \mathsf{CO}_{2}\mathsf{Et} \end{array}$$
(5)

Scheme 2 presents a plausible mechanism for 1,2-iminonitronation reactions. A coordination of LAu^+ with ethyl propiolate **1a** induces an attack of nitrosobenzene to give intermediate **C** that also possesses gold carbene resonance **C'**. We postulate an initial formation of bis-nitrone species **D** in accord with the result in eqn (4). The ester group of bis-nitrone **D** will decrease the oxygen negative charge of the conjugated nitrone, and the other nitrone group becomes an active oxygen donor. We speculate that *N*-hydroxyaniline might serve as a reducing species to react with bis-nitrone **D** to give α -imidoyl nitrone **3a**. Alternatively, bis-nitrone species **D** might serve as an oxidant to oxidize propiolate **3** to give α -imidoyl nitrone **3a**, but this route is less important because the resulting α,β -dioxo ester **4** was obtained in low yield.

In summary, we report gold-catalyzed 1,2-iminonitronation of propiolate derivatives with nitrosoarenes, giving α -imidoyl nitrones efficiently. This new reaction is applicable to diverse



Scheme 2 A plausible reaction mechanism.

propiolate derivatives and nitrosoarenes. This outcome is distinct from the gold 1,2-oxoimination reactions of ynamides (eqn (2)) using the same oxidant, further reflecting the diversity of gold catalysis. Further development of this new catalytic reaction to access 1,2-difunctionalized compounds is under current investigation.

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