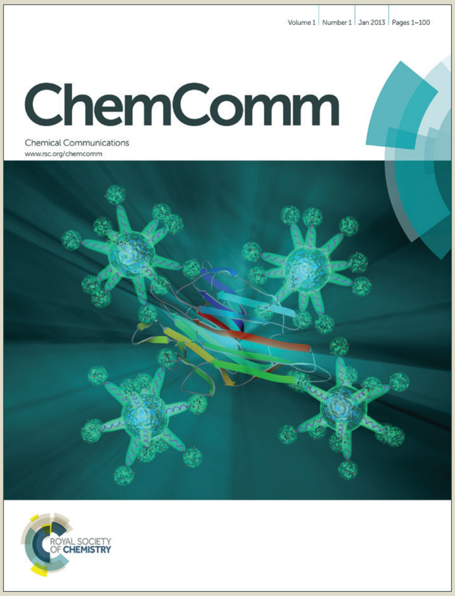
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name RSCPublishing

COMMUNICATION

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

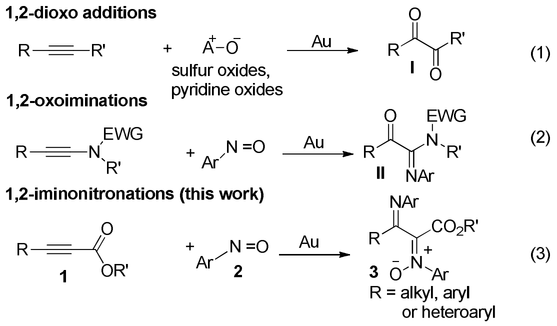
Gold-catalyzed 1,2-Iminonitronations of Electron-deficient Alkynes with Nitrosoarenes to Afford α-Imidoyl Nitrones

RahulKumar Rajmani Singh and Rai-Shung Liu*

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

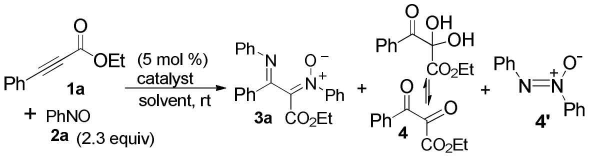
Although alkene and alkynes are two important unsaturated hydrocarbon motifs in organic synthesis; catalytic oxidations of alkynes[1] are much less explored than for alkenes.[2-3] One important advent in Au- and Pt-catalyzed reactions is the functionalization of electrophilically activated alkynes with diverse nucleophiles.[4] Pyridine *N*-oxides or sulfoxides allow gold-catalyzed 1,2-double oxidations of alkynes to afford 1,2-dicarbonyl products (**I**) efficiently [5](eq 1). Metal-catalyzed reactions of terminal alkynes with nitrosoarenes were reported to produce indole derivatives.[6] To implement 1,2-oxidative difunctionalizations of alkynes, we reported 1,2-oxoiminations of ynamides using nitrosoarenes to enable a reaction of metathesis type (eq 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 represents a special case of 1,2-dual imination reactions. The contrasting outcome in eq 2-3 is due to their distinct mechanisms involving non-carbene[7] 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 $LAuCl/AgNTf_2$ (L = $P(t\text{-}Bu)_2(o\text{-biphenyl})$), 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 proportion (entry 1). A switch of its silver source with $LAuCl/AgSbF_6$ (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 $PPh_3AuCl/AgNTf_2$, $IPrAuCl/AgNTf_2$ (IPr = 3-bis(diisopropylphenyl)imidazol-2-ylidene) and $AuCl_3$ were also active, affording desired **3a** in 63-71% yields with side product **4** in 9-22% yields. (entries 3-5). $AgNTf_2$ and $PtCl_2/CO$ were catalytically inactive to give initial **1a** with 65-71% recovery (entries 6-7). For $LAuCl/AgNTf_2$, other solvents including dichloromethane (DCM), nitromethane and toluene, yielded compound **3a** were in 75%, 63% and 27% yields respectively; their by product **4** was obtained in 13-28% yields (entries 8-10). Structural characterization of compound **3a** relies on x-ray diffraction study of its indole relative **3j** (Table 2 , entry 9).[8] Our control experiment indicates that α,β-dioxo ester **4** arises from the alkyne oxidation of initial **1a** rather than from the hydration of product **3a** (see eq 5).



We prepared additional propiolate derivatives (**1b**–**1m**) to assess the scope of the reaction. The 1,2-iminonitronations of nitrosobenzene (2.3 equiv) with various ethyl propiolate derivatives (**1b**–**1m**) are shown in Table 2. In most cases, α,β -dioxo esters were also produced in minor proportions, but we did not isolated them. The reactions were run with $P(t\text{-}Bu)_2(o\text{-biphenyl})AuCl/AgNTf_2$ (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 variable *p*-phenyl substituents (4-XC$_6$H$_4$, 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 expanded 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 11-12). 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 products were obtained. Among these products, the molecular structure of species **3j** is elucidated by x-ray diffraction to characterize its structure.[8]

Table 1. Reactions over various catalysts.

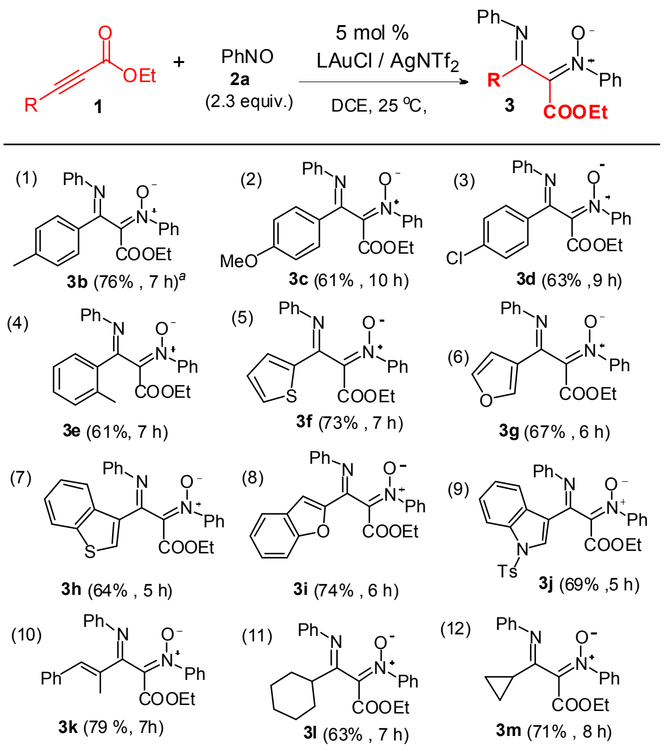


entry	catalyst	solvent^a	time (hour)	yield^b (%) 1a	3a	4
1	LAuCl/AgNTf$_2$	DCE	6	—	77	13^c
2	LAuCl/AgSbF$_6$	DCE	6	—	67	21
3	AuClPPh$_3$/AgNTf$_2$	DCE	6	—	64	19
4	IPrAuCl/AgNTf$_2$	DCE	10	—	71	9
5	AuCl$_3$	DCE	7	—	63	22
6	AgNTf$_2$	DCE	12	65	—	—
7.	PtCl$_2$/CO	DCE	12	71	—	—
8.	LAuCl/AgNTf$_2$	DCM	24	—	75	14
9.	LAuCl/AgNTf$_2$	CH$_3$NO$_2$	12	12	63	13
10	LAuCl/AgNTf$_2$	toluene	18	45	27	28

L = P(*t*-Bu)$_2$(*o*-biphenyl), IPr =,3-bis(diisopropylphenyl)imidazol-2-ylidene) ^{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.

We studied also 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/AgNTf$_2$ (5 mol %) in DCE (25 °C, 7-9 h). 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 electron-deficient phenyl analogues **2e** and 2f (XC$_6$H$_4$, X = Br and Cl, entries 4-5), the same reactions afforded α-imidoyl nitrones **5e-5f** in 73% and 69% yields, respectively.

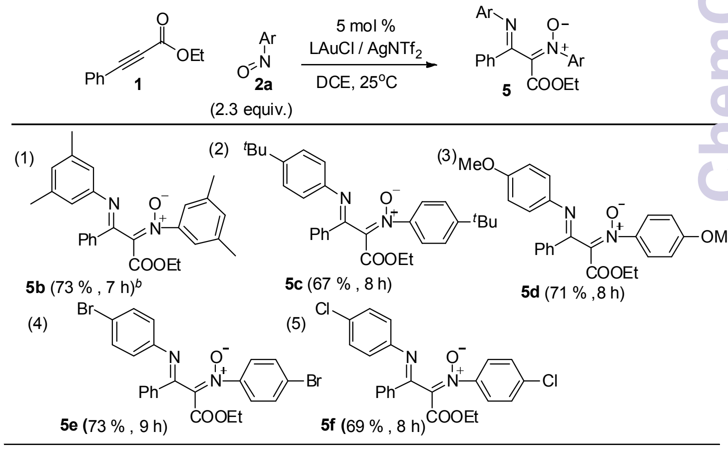
Table 2. Catalytic reactions with various alkynes^a



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

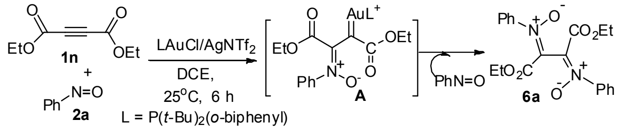
We tested the reaction on highly electron-deficient diethyl but-2-ynedioate (**1n**) to examine the reaction chemoselectivity (eq 4). The HRMS, ^{1}H and ^{13}C-NMR data support the structure of a bis-nitrone species **6a** with a plane of symmetry; this proposed structure was confirmed by x-ray diffraction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

Table 3. Catalytic reactions with various nitrosoarenes^a



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

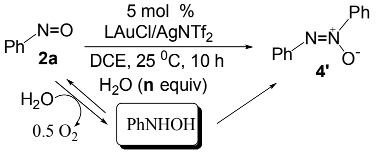
We postulate that the two ester groups stabilize their own conjugated nitrones, thus forming bis-nitrone groups safely. Formation of compound **6a** confirms the intermediacy of species **A**, in which gold carbene is replaced with nitrosobenzene to form a second nitrone functionality. Such a carbene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



(4)

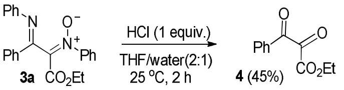
Diazene oxide **4'** represents a reducing form of nitrosobenzene **2a** and its detection in the system (Table 1, entry 1) urges us to perform additional experiments as depicted in Scheme 1. Treatment of nitrosobenzene **2a** with gold catalyst (5 mol %) in DCE delivered diazene oxide **4'** in 3% yield, 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 that 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]

Scheme 1. Formation of diazene oxide



n	2a	4'
0	94 %	3 %
2	89%	5.5 %

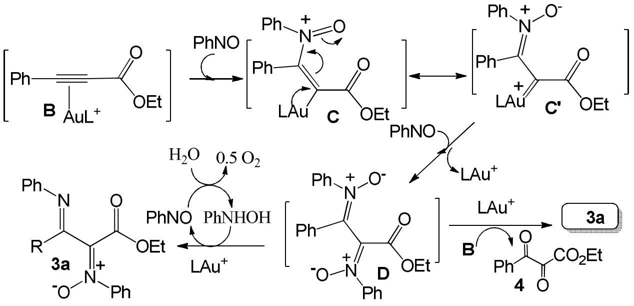
α-Imidoyl nitrone **3a** is robust toward the hydration with P(t-Bu)$_2$ (o-biphenyl)AuCl/AgNTf$_2$ in wet DCE. Hence, formation of ester **4** from propiolate **1a** in Table 1 (entry 1) is unlikely caused by the hydration of α-imidoyl nitrone **3a.** Shown in eq 5 is the successful hydration of species **3a** with HCl (1 equiv) in THF/water (2:1) to yield α,β-dioxo ester **4** in 45% yield.



(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 eq 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.

Scheme 2. A plausible reaction mechanism



In summary, we report gold-catalyzed 1,2-iminonitronations of propiolate derivatives with nitrosoarenes, giving α-imidoyl nitrones efficiently. The new reactions are applicable to diverse propiolate derivatives and nitrosoarenes. This outcome is distinct from the gold 1,2-oxoimination reactions of ynamides (eq 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 investigations.

Notes and references

1 Reviews for gold-catalyzed oxidations of alkynes, see: (*a*) L. Zhang. *Acc. Chem. Res.*, 2014, **47**, 877; (*b*) J. Xiao, X. Li, *Angew. Chem. Int. Ed.*, 2011, **50**, 7226.

2 For wacker oxidations, epoxidations and aziridination of alkenes, see selected reviews: (*a*) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.*, 2011, **111**, 2981; (*b*) Y. Zhu, Q. Wang, R. G. Cornwall, Y. Shi, *Chem. Rev.*, 2014, **114**, 8199; (*c*) L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.*, 2014, **114**, 7881; (*d*) J. B. Sweeney, *Chem Soc Rev*., 2002, **31**, 247; (*e*) T. Ibuka, *Chem. Soc. Rev.*, 1998, **27**, 145.

3 For catalytic dihydroxylation and diammination reactions, see selected reviews: (*a*) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev*., 1994, **94**, 2483; (*b*) D. Lucet, T. L. Gall, C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2580; (*c*) P. N. Becker, R. G. Bergman, *Organometallics*, 1983, **7**, 789.

4 Reviews for gold catalysis: (*a*) A. Fürstner, *Chem. Soc. Rev.,* 2009, **38**, 3208; (*b*) N. T. Patil, Y. Yamamoto, *Chem. Rev.,* 2008, **108**, 3395; (*c*) A. Das, S. M. A. Abu, R.-S. Liu, *Org. Biomol. Chem.*, 2010, **8**, 960; (*d)* A. Arcadi, *Chem. Rev.,* 2008, **108**, 3266; (*e*) E. Jimenez-Nunez, A. M. Echavarren, *Chem. Rev.,* 2008, **108**, 3326; (*f*) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (*g*) A. S. K. Hashmi, *Chem. Rev.,* 2007, **107**, 3180.

5 (*a*) S. Shi, T. Wang, V. Weingand, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.,* 2014, **53**, 1148; (*b*) S. Shi, T. Wang, W. Yang, M. Rudolph, A. S. K. Hashmi, *Chem. Eur. J.,* 2013, **19**, 6576; (*c*) C.-F. Xu, M. Xu, Y.-X. Jia, C.-Y. Li, *Org. Lett.*, 2011, **13**, 1556.

6 (*a*) A. Penoni, G. Palmisano, Y. –L. Zhao, K. N. Houk, J. Volkman, K. M. Nicholas, *J. Am. Chem. Soc.,* 2009, **131**, 653*;* (*b*) S. Murru, A. A. Gallo, R. S. Srivastava, *ACS Catl*., 2011, **1**, 29; (*c*) A. Penoni, K. M. Nicholas, *Chem. commun.,* 2002, 484; (*d*) F. Ragaini, A. Rapetti, E. Visentin, M. Monzani, A. Caselli, S. Cenini , *J.Org. Chem.,* 2006, **71,** 3748.

7 A. Mukherjee, R. B. Dateer, R. Chaudhuri, S. Bhunia, S. N. Karad, R.-S. Liu, *J. Am. Chem. Soc*., 2011, **133**, 15372.

8 Crystallographic data of compounds **3j** and **6**a were deposited at Cambridge Crystallographic Data Center with CCDC 1020243 (**3j**) and CCDC 1022207 (**6a**).

9 For the reaction of gold-carbene with nitrosoarenes to form nitrone species, see selected examples: (*a*) Z.-J. Xu, D. Zhu, X. Zeng, F. Wang, B. Tan, Y. Hou, Y. Ly, G. Zhong, *Chem. Commun.,* 2010, **46**, 2504; (*b*) N. Asao, K. Sato, Y. Yamamoto, *Tetrahedron Lett.,* 2003, **44**, 5675; (*c*) C. V. Ramana, P. Patel, K. Vanka, B. Miao, A. Degterev, *Eur. J. Org. Chem.,* 2010, 5955.

10 Nitrosoarenes can react with gold carbene to form reactive dipole species to undergo [3+2]-cycloaddition with alkenes. See A. M. Jadhav, S. Bhunia, H.-Y. Liao, R.-S. Liu, *J. Am. Chem. Soc.,* 2011, **133**, 1769.

11 Nitrosobenzene can serve as an oxygen donor to oxidize a gold carbene to give a carbonyl product in a catalytic process, see: C.-H. Chen, Y.-C.Tsai, R.-S. Liu, *Angew, Chem. Int. Ed.,* 2013*,* **52***,* 4599.

12 For a similar deoxygenation process in the reaction of gold carbene with nitrones, see V. V. Pagar, A. M. Jadhav, R.-S. Liu, *J. Am. Chem. Soc.,* 2011, **133**, 20728.

13 In our previous work,[13a] we reported that *N*-hydroxyaniline alone in CD_2Cl_2 under N_2 will generate diazene oxide **4** in 7.5% yield whereas unreacted *N*-hydroxyaniline was present as the only remaining species. See related work (*a*) J.-M. Chen, C.-J. Chang, Y.-J. Ke, R.-S. Liu, *J. Org.Chem.,* 2014, **79**, 4306; (b) Y. Wang, L. Ye, L. Zhang, *Chem. Commun.,* 2011, **47**, 7815.

14 A small redox potential 0.5-0.6 V rationalizes an facile interconversion between *N*-nitrosobenzene and *N*-hydroxyaniline. See R. E. Lutz. M. R. Lytton, *J. Org. Chem.,* 1937, **2**, 68.