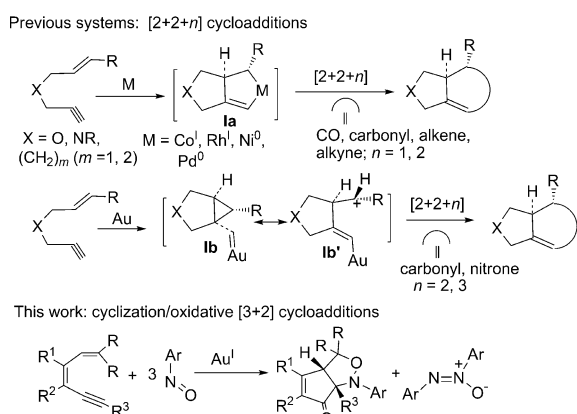


# Gold-Catalyzed Cyclization/Oxidative [3+2] Cycloadditions of 1,5-Enynes with Nitrosobenzenes without Additional Oxidants\*\*

Chun-Hao Chen, Yen-Ching Tsai, and Rai-Shung Liu\*

Metal-catalyzed [2+2+m] cycloadditions ( $m=1-3$ ) of 1, $n$ -enynes ( $n=5-7$ ) with small molecules are powerful tools for accessing complicated hetero- and carbocycles.<sup>[1,2]</sup> These reactions are appealing because their mechanisms can be altered by using different metal complexes. As shown in Scheme 1, low-valent metal species react with these enynes to

This oxidative cycloaddition was realized with the treatment of the 1,5-enyne **1a** (1 equiv) with nitrosobenzene (**2a**; 1.5 equiv) and [P(*t*Bu)<sub>2</sub>(*o*-biphenyl)AuCl]/AgNTf<sub>2</sub> (5 mol %) in 1,2-dichloroethane (DCE; 25 °C, 24 h) to give the oxidative cycloadduct **3a** in 21 % yield, together with the cycloisomerization product **4a** in 70 % yield (Table 1, entry 1).<sup>[7]</sup> The



**Scheme 1.** Metal-catalyzed cycloadditions on 1, $n$ -enynes.

form metalcycloalkene intermediates (**Ia**) initially,<sup>[3]</sup> whereas gold(I) catalysts generate the cyclopropyl gold carbene **Ib** which has a resonance structure, that is, the alkenylgold carbocation **Ib'**.<sup>[4]</sup> We sought a new catalytic [2+2+m] cycloaddition of 1, $n$ -enynes to generate an additional functionality on the resulting cycloadducts. Although catalytic cycloadditions of nitrosobenzenes have been intensively studied,<sup>[5,6]</sup> we are aware of no report on the cycloaddition of nitroso species with 1, $n$ -enynes ( $n=5-7$ ).<sup>[6]</sup> We report herein the gold-catalyzed cyclization/oxidative [3+2] cycloadditions of 1,5-enynes with nitrosobenzenes. Notably, nitrosobenzenes not only provide two-atom building units, but also lead to the alkyne oxidation. Such a reaction pattern is unprecedented in metal-catalyzed cycloadditions of 1, $n$ -enynes.

**Table 1:** Tests over various gold catalysts.

Entry <sup>[a]</sup>	Au	$n$	Solvent	$t$ [h]	Yield [%] <sup>[b]</sup>		
					<b>3a</b>	<b>4a</b>	<b>5a</b>
1	[LAuCl]/AgNTf <sub>2</sub>	1.5	DCE	24	21	70	18
2	[LAuCl]/AgSbF <sub>6</sub>	1.5	DCE	14	41	53	35
3	[LAuCl]/AgSbF <sub>6</sub>	4.0	DCE	4	82	6	57(75) <sup>[c]</sup>
4	[PPh <sub>3</sub> AuCl]/AgSbF <sub>6</sub>	4.0	DCE	4	77	8	(76) <sup>[c]</sup>
5	[IPrAuCl]/AgSbF <sub>6</sub>	4.0	DCE	5	72	16	(73) <sup>[c]</sup>
6	[LAuCl]/AgSbF <sub>6</sub>	4.0	CH <sub>2</sub> Cl <sub>2</sub>	3	85	6	(82) <sup>[c]</sup>
7	[LAuCl]/AgSbF <sub>6</sub>	4.0	CH <sub>3</sub> CN	24	–	87	–

[a] [**1a**] = 0.3 M, 25 °C. [b] Yield of product isolated from silica gel column. [c] Yield determined by NMR spectroscopy. L = P(*t*Bu)<sub>2</sub>(*o*-biphenyl), IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, Tf = trifluoromethanesulfonyl.

yield of **3a** was increased to 41 % with [[P(*t*Bu)<sub>2</sub>(*o*-biphenyl)AuCl]/AgSbF<sub>6</sub> (5 mol %, entry 2). For the two above-mentioned entries, we also isolated 1,2-diphenyldiazene oxide (**5a**) which was identified upon comparison of its NMR spectra and mass data with those of an authentic sample.<sup>[8]</sup> The structure of **3a** was confirmed by an X-ray diffraction study to confirm a *cis*-fused ring system with the methyl group and its neighboring hydrogen atom *cis* to each other.<sup>[9]</sup> Accordingly, three equivalents **2a** are required to achieve the reaction. With an increased loading (4 equiv) of **2a**, the yield of **3a** was significantly increased to 82 % (entry 3). Other gold catalysts such as [PPh<sub>3</sub>AuCl]/AgSbF<sub>6</sub> and [IPrAuCl]/AgSbF<sub>6</sub> also produced the desired cycloadduct **3a** (entries 4 and 5). [[P(*t*Bu)<sub>2</sub>(*o*-biphenyl)AuCl]/AgSbF<sub>6</sub> in CH<sub>2</sub>Cl<sub>2</sub> gave **3a** with a yield of up to 85 % (entry 6), but afforded **4a** exclusively (87 %) with CH<sub>3</sub>CN as the solvent (entry 7). The yield of **5a** was almost the same as that for **3a** according to the NMR analysis of the crude reaction mixture (entries 3–6).

The oxidative cycloadditions of **2a** (4 equiv) with various 1,5-enynes (**1b–1i**) bearing a variety of alkynyl and phenyl substituents (R, X, and Y) is shown (Table 2). The reactions

[\*] C. H. Chen, Y. C. Tsai, Prof. Dr. R.-S. Liu  
Department of Chemistry, National Tsing Hua University  
Hsinchu (30013) Taiwan (China)  
E-mail: rslu@mx.nthu.edu.tw

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**Table 2:** Oxidative [3+2] cycloadditions using various enynes.

Entry <sup>[a]</sup>	Enyne	t [h]	Yield [%] <sup>[b]</sup>	
	X = Y = H			
1	R = <i>n</i> Bu ( <b>1b</b> )	10	73 ( <b>3b</b> )	6 ( <b>4b</b> )
2	R = <i>i</i> Pr ( <b>1c</b> )	7	77 ( <b>3c</b> )	5 ( <b>4c</b> )
3	R = cyclopropyl ( <b>1d</b> )	8	77 ( <b>3d</b> )	11 ( <b>4d</b> )
4	R = Ph ( <b>1e</b> )	36	81 ( <b>3e</b> )	10 ( <b>4e</b> )
	R = Me			
5	X = Cl, Y = H ( <b>1f</b> )	3	80 ( <b>3f</b> )	9 ( <b>4f</b> )
6	X = H, Y = Cl ( <b>1g</b> )	5	83 ( <b>3g</b> )	9 ( <b>4g</b> )
7	X = OMe, Y = H ( <b>1h</b> )	5	– ( <b>3h</b> )	80 ( <b>4h</b> )
8	X = H, Y = OMe ( <b>1i</b> )	4	78 ( <b>3i</b> )	8 ( <b>4i</b> )

[a] [1] = 0.30 M, L = P(*t*Bu)<sub>2</sub>(*o*-biphenyl). [b] Yield of product isolated from silica gel column.

were run with [(P(*t*Bu)<sub>2</sub>(*o*-biphenyl))AuCl]/AgSbF<sub>6</sub> (5 mol %) in CH<sub>2</sub>Cl<sub>2</sub> (25 °C, 0.3 M). We made no attempts to isolate **5a** for these reactions. Various internal alkynes (**1b–e**) were used in this reaction to give the desired compounds **3b–e** together with the indene derivatives **4b–e** in small quantities (entries 1–4). The reactions are sensitive to the substituents on the phenyl ring (**1f–i**); we obtained the desired cycloadducts **3f,g** and **3i** (entries 5, 6, and 8) in satisfactory yields, whereas **1h** gave only the cycloisomerization product **4h** in 80% yield (entry 7). This substituent effect provides insight into the mechanism.<sup>[10]</sup>

Table 3 shows our results on additional 1,5-enynes (**1j–p**). For the substrates **1j–l** bearing various trisubstituted alkenes including cyclopentylidene, cyclohexylidene, and 3-pentylidene groups (entries 1–3), the corresponding products **3j–l** were obtained in reasonable yields (72–82%). We also prepared the trisubstituted alkene **1m** with both *E* and *Z* configurations (entries 4 and 5), and their gold-catalyzed reactions resulted in the same cycloadduct **3m** with the methyl group *cis* to the neighboring hydrogen atom. Notably, this *cis*-configured product is 0.75 kcal mol<sup>−1</sup> higher in energy than the *trans*-configured isomer.<sup>[11]</sup> Similarly, both *trans*- and *cis*-styrene derivatives of **1n** (entries 6 and 7) gave the same cycloadduct **3n**, wherein the two adjacent hydrogen atoms are *cis* configured according to the <sup>1</sup>H NMR NOE spectra (see the Supporting Information). To our delight, the reactions also proceeded with the nonbenzoid substrates **1o** and **1p** (entries 8 and 9), thus delivering the products **3o** and **3p**, respectively.

Table 4 shows the reactions using different nitrosobenzenes (**2b–f**). The cycloadducts **6b–f** and 1,2-diphenyldiazene oxides **5b–f** were obtained in nearly the same proportions. The reactions worked efficiently not only for the electron-deficient nitrosobenzenes **2b–d** (entries 1–3), but also for the electron-rich analogues **2e,f** (entries 4 and 5). The reaction time of 4–8 hours for the nitroso species **2e,f** is attributed to their ability to coordinate to the gold catalyst. In all cases **4a** was produced in small proportions (0–11%).

**Table 3:** Oxidative cycloadditions on 1,5-enynes.

Entry <sup>[a]</sup>	Enyne	t [h]	Yield [%] <sup>[b]</sup>	
1	<b>1j</b> ( <i>n</i> = 1)	11	77 ( <b>3j</b> )	9 ( <b>4j</b> )
2	<b>1k</b> ( <i>n</i> = 2)	2.5	72 ( <b>3k</b> )	11 ( <b>4k</b> )
3	<b>1l</b>	5.5	82 ( <b>3l</b> )	8 ( <b>4l</b> ) <sup>[c]</sup>
4	<i>E</i> - <b>1m</b> (R <sup>1</sup> = Ph, R <sup>2</sup> = Me)	14	75 ( <b>3m</b> )	10 ( <b>4m</b> )
5	<i>Z</i> - <b>1m</b> (R <sup>1</sup> = Me, R <sup>2</sup> = Ph)	15	77 ( <b>3m</b> )	9 ( <b>4m</b> )
6	<i>E</i> - <b>1n</b> (R <sup>1</sup> = 4-MeOC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = H)	24	63 ( <b>3n</b> )	–
7	<i>Z</i> - <b>1n</b> (R <sup>1</sup> = H, R <sup>2</sup> = 4-MeOC <sub>6</sub> H <sub>4</sub> )	20	67 ( <b>3n</b> )	–
8	<b>1o</b> (R = Me)	14	85 ( <b>3o</b> )	–
9	<b>1p</b> (R = <i>n</i> Bu)	15	82 ( <b>3p</b> )	–

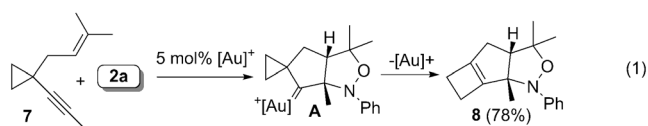
[a] [1] = 0.3 M, 5 mol % [(P(*t*Bu)<sub>2</sub>(*o*-biphenyl))Au]SbF<sub>6</sub>, CH<sub>2</sub>Cl<sub>2</sub>, **2a** (4 equiv), 25 °C. [b] Yield of product isolated from silica gel column. [c] *E/Z* = 2.5.

**Table 4:** Oxidative Cycloadditions with Nitrosobenzenes.

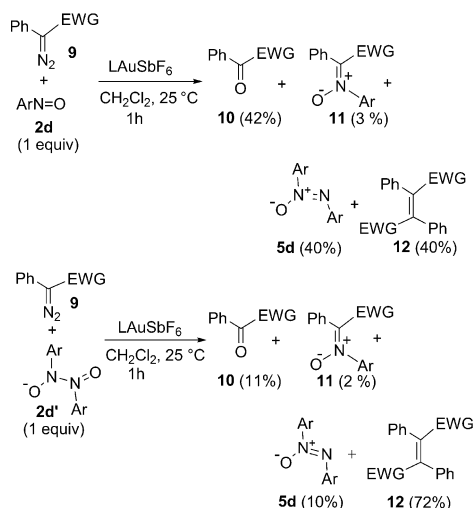
Entry	Nitroso compound <sup>[a]</sup>	t [h]	Yield [%] <sup>[b]</sup>		
			6	4a	5
1	X = NO <sub>2</sub> ( <b>2b</b> )	0.5	71 ( <b>6b</b> )	11	67 ( <b>5b</b> )
2	X = Cl ( <b>2c</b> )	1	77 ( <b>6c</b> )	6	71 ( <b>5c</b> )
3	X = Br ( <b>2d</b> )	0.5	79 ( <b>6d</b> )	5	75 ( <b>5d</b> )
4	X = <i>t</i> Bu ( <b>2e</b> )	4	80 ( <b>6e</b> )	7	76 ( <b>5e</b> )
5	X = OMe ( <b>2f</b> )	8	91 ( <b>6f</b> )	–	84 ( <b>5f</b> )

[a] [1a] = 0.3 M, nitroso (4 equiv), [(P(*t*Bu)<sub>2</sub>(*o*-biphenyl))Au]SbF<sub>6</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C. [b] Yield of product isolated from silica gel column.

Equation (1) shows relevant data to support the intermediacy of the gold carbenes **A**. We prepared the acyclic 1,5-enyne **7** which reacted with **2a** (4 equiv) and the gold catalyst (5 mol%) to deliver the tricyclic species **8** in 78% yield. Formation of this compound arose from a 1,2-cyclopropane migration to the neighboring gold carbene center in species **A**. Equation (1) represents the first formal [2+2+1] cycloaddition for the enyne/nitroso functionalities.



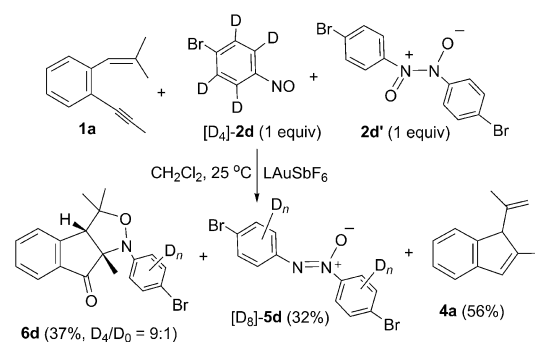
The nitrosobenzenes **2a–e** are in equilibrium with a dimeric species in solution.<sup>[12]</sup> Their respective reactivities toward the oxidation of gold carbenes should be addressed. We tested the gold-catalyzed oxidation of the diazocarbonyl species **9** with a nitroso species to compete with its catalytic diazo decomposition to the olefin **12** (Scheme 2). The treat-



**Scheme 2.** Oxidation of gold carbenes by mono- or dimeric nitroso species. EWG = CO<sub>2</sub>Et, Ar = 4-BrC<sub>6</sub>H<sub>4</sub>

ment of this diazo species with [[P(*t*Bu)<sub>2</sub>(*o*-biphenyl)]AuCl]/AgSbF<sub>6</sub> (5 mol%) and monomeric the nitroso species **2d** (1 equiv) gave the dicarbonyl compound **10** and 1,2-diphenyldiazene oxide **5d** in 42 and 40% yield, respectively. With **2d'** (1 equiv),<sup>[13]</sup> the desired **10** and **11** were obtained in 11 and 2% yields, respectively, together with the tetrasubstituted olefin **12** in large 72%. Accordingly, we postulate that **2d'** is a poor oxygen donor and the resulting **10** and **11** presumably arise from the slow release of the monomeric form **2d**.

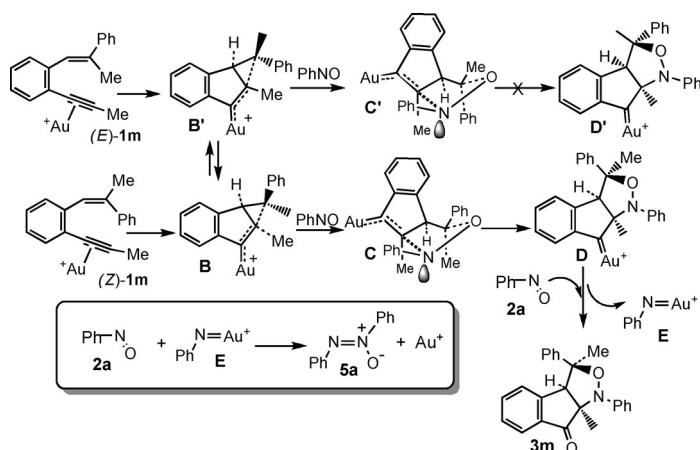
In a separate experiment, the treatment of **1a** with [D<sub>4</sub>]-**2d** (1 equiv), **2d'** (1 equiv), and [[P(*t*Bu)<sub>2</sub>(*o*-biphenyl)]Au]SbF<sub>6</sub> (5 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (25 °C) gave the desired [D<sub>4</sub>]-**6d** as a major component (D<sub>4</sub>/D<sub>0</sub> = 9:1; Scheme 3). <sup>1</sup>H NMR analysis of **5d**, using CDCl<sub>3</sub> as an internal standard, indicated



**Scheme 3.** Deuterium-labeling experiment.

a very small proton content (< 10%). The <sup>13</sup>C NMR spectrum resembled that of the fully deuterated sample [D<sub>8</sub>]-**5d** (see the Supporting Information). Its FAB mass spectra showed primarily the signal for [D<sub>8</sub>]-**5d**. Again, this deuterium-labeling experiment confirms that the monomeric form **2d** is actually the oxygen source for **6d**.

A plausible mechanism (Scheme 4) to account for the stereoselectivity of **3m** from either (*E*)-**1m** or (*Z*)-**1m** is shown. For (*Z*)-**1m**, the initially formed cyclopropyl carbene



**Scheme 4.** A plausible mechanism for gold-catalyzed oxidative cycloaddition.

**B** has a an alkenylgold carbocation resonance structure, which enables a [3+2] cycloaddition with nitrosobenzene to form the cyclic transition-state **C** by either a concerted or stepwise process.<sup>[13]</sup> This process is feasible because the alkenyl phenyl group lies at the less hindered equatorial position. This cycloaddition generates the gold carbene **D** with the observed stereochemistry. For (*E*)-**1m**, the nitroso cycloaddition might encounter difficulty because the corresponding cyclic transition-state **C'** has the phenyl group at the axial position. This proposed stereochemistry is analogous to that for the Sn(OTf)<sub>2</sub>-catalyzed [3+2] cycloaddition of substituted cyclopropane derivatives with aldehydes.<sup>[14,15]</sup> We postulate an equilibrium between **B** and **B'** because of their significant alkenylgold carbocation resonance structures.

According to our control experiments (Schemes 2 and 3), the subsequent oxidations of the resulting gold-carbenes **D** rely on the monomeric nitroso species **2a**.<sup>[16,17]</sup> This process is expected to generate **3m** and the gold nitrenes **E** simultaneously. We hypothesize that this nitrene species reacts further with nitrosobenzene to regenerate the gold catalyst and **5a**. Notably, **2a** is inactive toward the oxidation of species **B** (or **B'**), which is not a pure gold carbene because of their additional resonance structures.

Before this work, transition-metal catalyzed cycloadditions of 1,*n*-enynes (*n* = 5–7) were strictly restricted to the [2+2+*m*] cycloaddition (*m* = 1–3) modes. In this work, we achieved a cyclization/oxidative [3+2] cycloaddition of 1,5-enynes and nitrosobenzene with high stereocontrol. These oxidative cycloadditions are applicable a variety of 1,5-enynes and nitrosobenzenes. According to our control experiments, monomeric nitrosobenzenes not only react with the cyclopropyl gold-carbene intermediates, but also lead to the oxidation of the key gold carbene intermediates.<sup>[18]</sup> This novel enyne oxidative cycloaddition highlights the use of gold catalysis.

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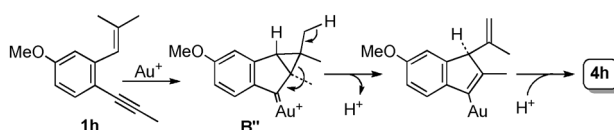
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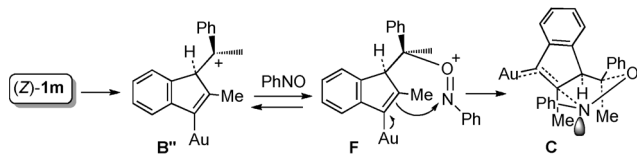
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- [9] CCDC 908146 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- [10] For the 1,5-enyne **1h** (Table 2, entry 7), the methoxy substituent stabilizes the resonance structure of the cyclopropyl gold carbene **B''** which tends to lose one proton to give the cycloisomerization product **4h**.



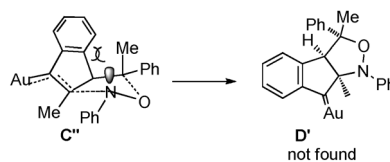
- [11] The energy differences between **3m** and its diastereomer was calculated using the B3LYP/6-311++G\*\* level of theory. <sup>1</sup>H NOE spectra of compounds **3m** and **3n** are provided in the Supporting Information.
- [12] a) S. Sigeeki, T. Takashi, Y. Nishiyama, Y. Ishii, *J. Org. Chem.* **1993**, *58*, 3633–3638; b) I. Halasz, I. Biljan, P. Novak, M. Ernest, H. Vancik, J. Plavec, G. Mali, V. Smrecki, *J. Mol. Struct.* **2009**, *918*, 19–25.
- [13] We do not exclude the possibility that cyclic the transition-state **C** is derived from the benzylic cation **B''** through a prior coordination of the nitroso species to its cationic center to form

**F**. A subsequent addition of the alkenylgold bond of **F** to the coordinated nitrosobenzene also forms **C**. This process rationalizes well the nonstereospecificity of the cycloaddition.



- [14] a) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650; b) P. D. Pohlhaus, J. S. Johnson, *J. Org. Chem.* **2005**, *70*, 1057–1059; c) M. J. Campbell, J. S. Johnson, A. T. Parsons, P. D. Pohlhaus, S. D. Sanders, *J. Org. Chem.* **2010**, *75*, 6317–6325; d) P. D. Pohlhaus, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015; e) M. J. Campbell, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, *131*, 10370–10371.

- [15] An alternative cyclic transition state **C''** is unlikely to occur because the axial methyl group exerts steric interaction with the bulky indene ring.



- [16] Nitrosobenzene was reported to undergo a nitrogen attack on the less hindered gold carbenes (see Ref. [6b]), but this process is likely impeded by steric hindrance for **D** in our system. Attack of the oxygen atom of nitrosobenzene on the gold carbene is also documented in a nonoxidation process (see Ref. [6a]).

- [17] We preclude the possibility that water and oxygen are the oxygen sources for the oxidation of **D** since we failed to obtain positive evidence using either  $\text{H}_2\text{O}^{18}$  or  $\text{O}_2^{18}$ .

- [18] We have performed additional experiments using a mixture of **2d'** ( $m$  equiv) and **m2d** ( $n$  equiv), thus amounting to three  $\text{ArNO}$  molecules ( $2m+n=3$ ). Oxidative cycloadduct **6d** was obtained in decreased yields with increasing proportions of **2d'** ( $m=1.5, n=0; m=1, n=1; m=0, n=3$ ). See Table S1 in the Supporting Information.

