

Gold-Catalyzed Formal [3 + 3] and [4 + 2] Cycloaddition Reactions of Nitrosobenzenes with Alkenylgold Carbenoids

Vinayak Vishnu Pagar,[†] Appaso Mahadev Jadhav,[†] and Rai-Shung Liu*[‡]

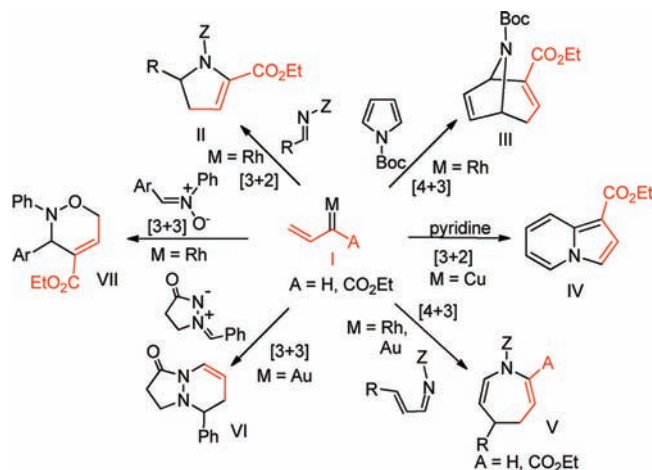
Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan 30013, ROC

S Supporting Information

ABSTRACT: We report two new formal cycloaddition reactions between nitrosobenzenes and alkenylgold carbenoids. We obtained quinoline oxides **3** in satisfactory yields from the gold-catalyzed [3 + 3]-cycloadditions between nitrosobenzenes and alkenyldiazo esters **1**. For propargyl esters **5**, its resulting gold carbenes react with nitrosobenzene to give alkenylimine **8**, followed by a [4 + 2]-cycloaddition with nitrosobenzene.

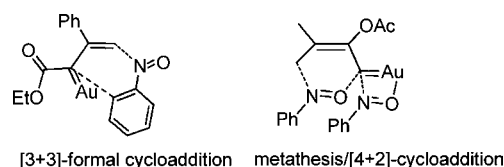
Nitrogen-containing frameworks are important skeletons in numerous naturally occurring compounds, especially in the alkaloid family.¹ Cycloaddition reactions of alkenylcarbenoids with nitrogen-based dipolarophiles are powerful tools to access nitrogen-containing heterocycles of medium sizes.² Scheme 1 summarizes various cycloadditions of alkenylmetal

Scheme 1. Metal-Catalyzed Cycloadditions for the Synthesis of Nitrogen-Containing Heterocycles



carbenoids (**I**) with imines, pyrroles, pyridines, alkenyl imines, azomethine imines, and nitrones, yielding diverse cycloadducts with high regioselectivities.^{3–8} Cycloaddition reactions on nitrosobenzenes are synthetically useful because the product skeletons incorporate both oxygen and nitrogen functionalities.^{9–11} Reported examples are much fewer than for alkenes, organic carbonyls, and imines; notable instances include [4 + 2] cycloadditions with dienes⁹ and [3 + 2]-cycloadditions with alkynes.¹⁰ In this work, we report two distinct [3 + 3] and [4 + 2] formal cycloadditions between nitrosobenzenes with alkenylgold carbenoids **I**, as depicted in Scheme 2. Although

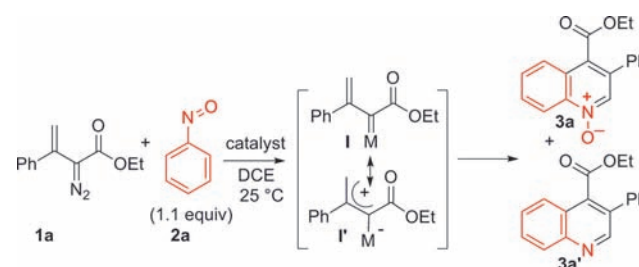
Scheme 2. Two New Formal Cycloaddition Reactions



the reactions of metal carbenoids with nitrosobenzenes were reported to give nitron species,¹² such a reaction route does not influence our new cycloadditions in most instances.

Shown in Table 1 is the generation of metal carbenoids from alkenyldiazoacetates **1a** over various metal catalysts.² We first

Table 1. Catalyst Screening for Formal [3 + 3]-Cycloadditions between Nitrosobenzenes and Alkenyldiazoacetates



entry	catalyst ^a (mol %)	time (h)	compounds (yields) ^b
1	Rh ₂ (OAc) ₄ (2.5)	1.5	3a (62%)
2	CuCl (5)	0.35	messy mixture
3	IPrCuCl/AgNTf ₂ (5)	0.8	3a (52%)
4	IPrCuCl/AgSbF ₆ (5)	0.5	3a (22%)
5	IPrAuCl/AgNTf ₂ (5)	0.5	3a (61%), 3a' (8%)
6	PPh ₃ AuCl/AgNTf ₂ (5)	2.1	3a (65%), 3a' (10%)
7	LAuCl/AgNTf ₂ (5)	2.0	3a (72%), 3a' (11%)
8	LAuCl/AgSbF ₆ (5)	2.0	3a (47%), 3a' (9%)
9	AgNTf ₂ (5)	0.15	messy mixture
10	HOTf (5)	0.5	messy mixture

^aL = P(*t*-Bu)₂(*o*-biphenyl), IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, [substrate] = 0.05 M. ^bProduct yields are reported after purification from silica column.

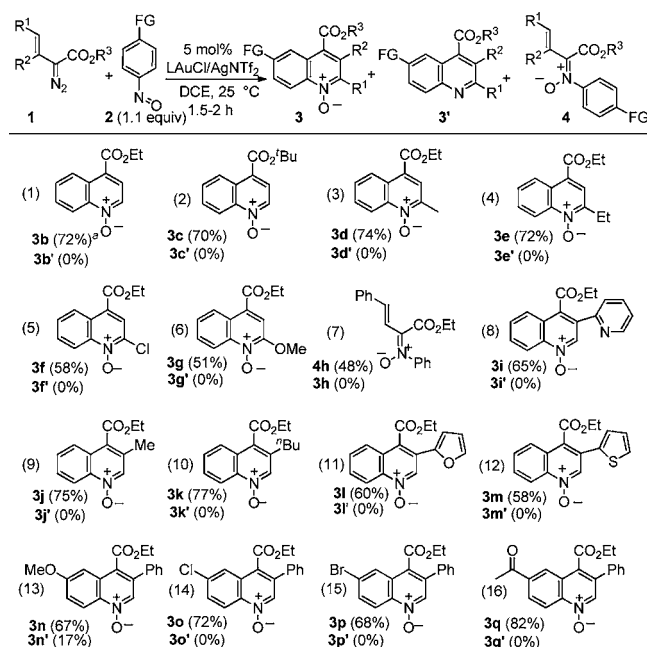
examined the reaction in the presence of Rh₂(OAc)₄ (2.5 mol %) and nitrosobenzene **2a** (1.1 equiv) in dichloroethane (DCE) at 25 °C for 1.5 h, during which starting **1a** was completely consumed

Received: October 24, 2011

Published: November 30, 2011

to give compound **3a** in 62% yield. Among various copper catalysts at 5 mol % loading (entries 2–4), $\text{IPrCuCl}/\text{AgNTf}_2$ showed the best performance to give desired **3a** in 52% yield. As shown in entries 5–7, gold catalysts (5 mol %) were efficient for this intermolecular cycloaddition with a 61% yield of desired **3a** for $\text{IPrAuCl}/\text{AgNTf}_2$, 65% yield for $\text{PPh}_3\text{AuCl}/\text{AgNTf}_2$, and 72% yield for $\text{ClAuP}(t\text{-Bu})_2(o\text{-biphenyl})/\text{AgNTf}_2$; we also obtained quinoline species **3a'** in small proportion (8–11%). An alteration of silver salt as in $\text{ClAuP}(t\text{-Bu})_2(o\text{-biphenyl})/\text{AgSbF}_6$ gave **3a** in diminished yield (47%) together with byproduct **3a'** in 9%. In control experiments, AgNTf_2 and HOTf gave products in a complicated mixture (entries 9 and 10). For compound **3a**, we confirmed its molecular structure through X-ray diffraction of its related compound **3b** (Table 2, entry 1).¹³ The better performance of

Table 2. Reaction Scopes with the [3 + 3] Formal Cycloaddition of Nitrosobenzenes with Alkenyldiazocarboxylates



^aL = $\text{P}(t\text{-Bu})_2(o\text{-biphenyl})$, [substrate] = 0.05 M. All product yields are reported after purification from silica column.

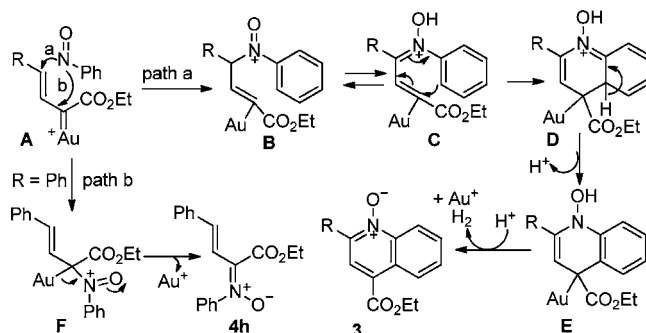
gold catalysts than copper and rhodium is attributed to a significant contribution of resonance structure **I'** (M = Au) that is visualized as a gold-stabilized allylic cation to facilitate an attack of nitrosobenzene.^{14,15}

Table 2 shows the generalization of this [3 + 3] formal cycloaddition using various alkenyldiazo esters and nitrosobenzenes. In a typical operation, starting diazo compound **1** was treated with nitrosobenzene **2** (1.1 equiv) and $\text{ClAuP}(t\text{-Bu})_2(o\text{-biphenyl})/\text{AgNTf}_2$ (5 mol %) in DCE (25 °C) for 1.5–2.0 h to attain a complete conversion. We obtained quinoline oxides **3** almost exclusively, except entry 7 that gave nitrone **4h** in 48% yield. Entries 1 and 2 show the compatibility of this cycloaddition with unsubstituted alkenyldiazo species **1** ($\text{R}^1 = \text{R}^2 = \text{H}$) bearing various esters ($\text{R}^3 = \text{Et}, t\text{-Bu}$), giving desired compounds **3b** and **3c** in 70–72% yields. We examined also the reactions of substrates containing varied C(3)-substituents ($\text{R}^1 = \text{Me}, \text{Et}, \text{Cl}, \text{OMe}$; entries 3–6), producing desired quinoline oxides **3d** and **3g** in 51–74% yields, whereas

the phenyl substrate (entry 7) gave nitrone **4h** in 48% yield. Alkenyldiazo species comprising various C(2)-substituents ($\text{R}^2 = 2\text{-pyridinyl}, \text{Me}, n\text{-Bu}, 2\text{-furanyl}, 2\text{-thienyl}$, entries 8–12) gave consistently quinoline oxides **3i–3m** in satisfactory yields (58–77%). We tested also the cycloaddition on both electron-deficient and -rich nitrosobenzenes (FG = OMe, Cl, Br, acetyl), which all proceeded well to give desired products **3n–3q** with yields exceeding 67% (entries 13–16).

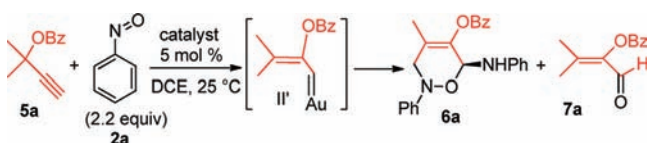
We propose a plausible mechanism in Scheme 3. The success of this formal cycloaddition relies on an attack of nitrosobenzene

Scheme 3. Proposed Mechanisms for the Formal [3 + 3] Cycloaddition



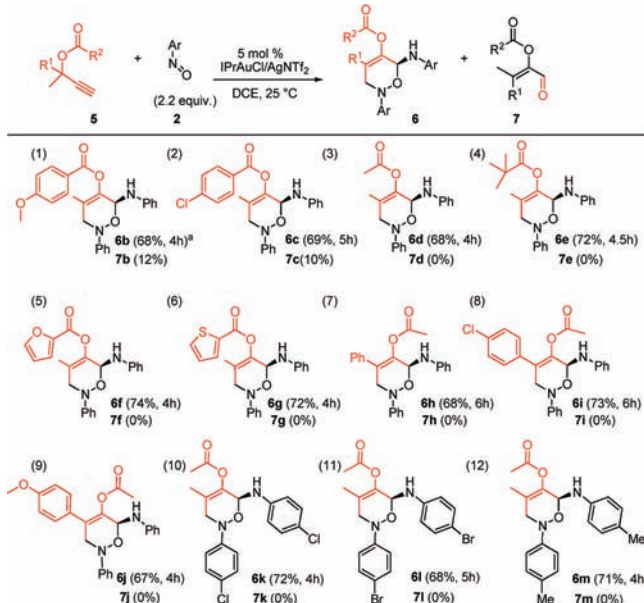
at the C(3)-carbon of carbenoids **A** (path a) bearing a small R substituent. The resulting species **B** attains an oxime/nitroso tautomeric equilibrium¹⁷ to generate gold-containing alkenyl iminium **C** that undergoes a 6- π electrocycloaddition to form a cyclized species **D**. A further loss of the proton of species **D** gives **N**-hydroxy dihydroquinoline **E**, further delivering observed product **3** after an oxidative aromatization or dehydrogenation. In the case of diazo substrate **1h**, its bulky phenyl substituent ($\text{R} = \text{Ph}$) exerts steric hindrance to impede the attack at the C(3)-carbon; the attack at the carbene carbon (path b) is expected to give nitrone product **4h**.¹² Applicable diazo substrates and nitrosobenzenes over a wide range highlight the utility of this [3 + 3] formal cycloaddition reaction.

We sought a distinct cycloaddition via an attack of nitrosobenzene at the carbene carbon of carbenoids (**II'**), generated in situ from the rearrangement of propargyl benzoate **5a** (Table 3).^{6b,7,15} This task is challenging because nitrone formation is known to be a competitive process.¹² As shown in Table 3, the reaction of starting substrate **5a** with nitrosobenzene (2.2 equiv) and $\text{PPh}_3\text{AuCl}/\text{AgNTf}_2$ in DCE (25 °C, 3 h) gave 3,6-dihydro-2H-[1,2]-oxazine **6a** and 2-en-1-al **7a** in 30% and 18% yields, respectively. To our pleasure, the use of $\text{ClAu}(t\text{-Bu})_2\text{P}(o\text{-biphenyl})/\text{AgNTf}_2$ and $\text{IPrAuCl}/\text{AgNTf}_2$ increased further the yields of oxazine **6a** to 68% and 74% yields together with 2-en-1-al **7a** in 12–18% yields (entries 2 and 3). Other silver salts, such as $\text{ClAu}(t\text{-Bu})_2\text{P}(o\text{-biphenyl})/\text{AgSbF}_6$, led to a diminished yield (60%) of oxazine **6a** together with 2-en-1-al **7a** in small proportion (15%, entry 4). AuCl_3 gave a complicated product mixture (entry 5). $\text{IPrCuCl}/\text{AgNTf}_2$ and $\text{Rh}_2(\text{OAc})_4$ were inactive to recover unreacted **5a** in 65–71% yields (entries 6 and 7). We have performed the X-ray diffraction study of compound **6a** to determine its molecular structure.¹³ Notably, side product 2-en-1-al (**7**) was completely absent for many other substrates upon the generalization of the reaction scope (see Table 4). This information indicates that compounds **6a** and **7a** are not produced concurrently from the disproportionation of one nitrosobenzene molecule.

Table 3. Gold-Catalyzed Metathesis/Cycloaddition Cascades of Propargyl Esters

entry	catalyst ^a (mol %)	time (h)	compounds (yields) ^b
1	PPh ₃ AuCl/AgNTf ₂ (5)	3	6a (30%), 7a (18%)
2	LAuCl/AgNTf ₂ (5)	6	6a (68%), 7a (16%)
3	IPrAuCl/AgNTf ₂ (5)	6	6a (74%), 7a (12%)
4	IPrAuCl/AgSbF ₆ (5)	8	6a (60%), 7a (15%)
5	AuCl ₃ (5)	1.5	complicated mixture
6	IPrCuCl/AgNTf ₂ (5)	10	5a (65%)
7	Rh ₂ (OAc) ₄ (2.5)	12	5a (71%)

^aL = P(*t*-Bu)₂(*o*-biphenyl), IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, DCE = dichloroethane, [substrate] = 0.05 M. ^bProduct yields are reported after purification from silica column.

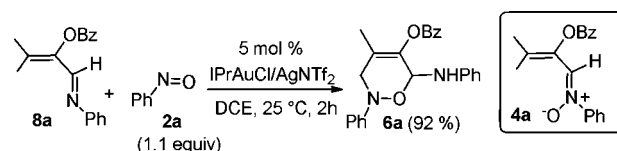
Table 4. Reaction Scopes for the Reactions of Nitrosobenzenes with Propargyl Esters

^aIPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, [substrate] = 0.05 M. All Product yields are reported after purification from silica column.

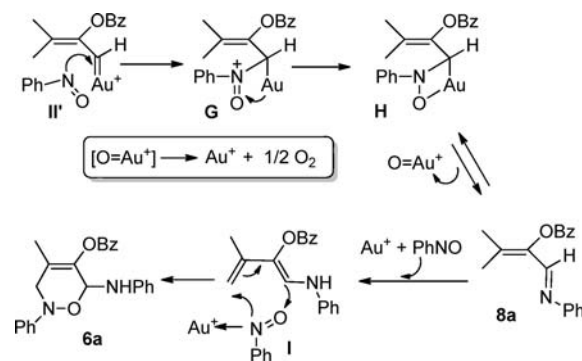
We prepared also various propargyl esters **5a–5i** to test their reactions with various nitrosobenzene; the results are shown in Table 4. In a typical operation, a propargyl ester was treated with nitrosobenzene (2.2 equiv) and IPrAuCl/AgNTf₂ (5 mol %) in DCE (25 °C) for 4–6 h before the workup. Notably, side products **7b** and **7c** were obtained in small proportions only from substrates **5b** and **5c** (entries 1 and 2). Entries 1–6 show the applicability of this reaction to several substrates bearing variable ester groups (R² = 4-methoxyphenyl, 4-chlorophenyl, methyl, *t*-butyl, 2-furanyl, 2-thienyl); their corresponding products **6b–6g** were obtained in 68–74% yields. This catalytic reaction works well for substrates bearing different R¹ substituents (R¹ = phenyl, 4-chlorophenyl, 4-methoxyphenyl), giving desired products **6h–6j** in 67–73% yields (entries 7–9). We examined the reactions between propargyl ester **5a** and various nitrosobenzenes (Ar = 4-chlorophenyl, 4-bromophenyl,

4-methylphenyl); their resulting products **6k–6m** (entries 10–12) were produced in 68–72% yields. In contrast, electron-rich nitrosobenzene (Ar = 4-methoxyphenyl) gave product in a complicated mixture under the same condition.

Structural analysis of oxazine **6a** leads us to postulate that it might be produced from an unprecedented gold-catalyzed cycloaddition of nitrosobenzene **2a** with alkenyl imine **8a** (Scheme 4). To verify this hypothesis, we prepared authentic

Scheme 4. Control Experiment to Clarify the [4 + 2] Cycloaddition

sample **8a** that reacted with nitrosobenzene **2a** (1.1 equiv) in DCE (25 °C, 2 h) to give desired oxazine **6a** in 92% yield in the presence of IPrAuCl/AgNTf₂ (5 mol %). In the absence of the gold catalyst, this mixture failed to give tractable amount of desired product **6a** at 25 °C in DCE (12 h) but gave **6a** in 63% yield at elevated temperatures (DCE, 80 °C, 12 h). We observed no reaction among nitron **4a**, nitrosobenzene **2a** (1.1 equiv), and the same gold catalyst. Alkenyl imine **8a**, rather than nitron **4a**, is truly the reaction intermediate.

Scheme 5. A Proposed Mechanism for the Metathesis/Cycloaddition Cascades

Shown in Scheme 5 is a plausible mechanism to rationalize the formation of oxazine **6a**. We envisage that nitrosobenzene initially attacks at the C(1)-carbene carbon to generate nitrosonium species **G** that subsequently forms gold-containing oxazetidine **H** via a unprecedented metathesis pathway.¹⁶ For species **H**, a subsequent loss of [Au=O]⁺ fragment gave alkenyl imine **8a** that underwent a hypothetical tautomerization to establish an equilibrium¹⁷ with 1-aminodiene **I**. The analogues of aminoalkyne **I** bearing a sec-amino group were documented.⁷ We envisage that gold-coordinate nitrosobenzene is highly electrophilic and becomes attacked by 1-aminodiene **I** to give observed oxazine **6a** ultimately.

To balance the oxygen mass, we propose the generation of [Au=O]⁺ in the catalytic circle, which presumably undergoes a disproportionation to regenerate cationic gold catalyst and oxygen. To test its occurrence, we added isopropanol (0.95 equiv) to a reaction system containing propargyl ester **5a**, nitrosobenzene **2a** (2.2 equiv), and IPrAuCl/AgNTf₂ (5 mol %) in CD₂Cl₂. At the end of reaction (25 °C, 4 h), this CD₂Cl₂ solution shows a

complete disappearance of isopropanol and ester **5a**, whereas acetone and oxazine **6a** were observed in the NMR spectra. We hypothesize that $[\text{Au}=\text{O}]^+$ oxidizes isopropanol to form acetone.

Before this work, the participation of nitrosobenzenes in metal-catalyzed cycloaddition reactions had few precedents.^{9,10} We report two new formal cycloadditions between nitrosobenzenes and alkenylgold carbenoids. We obtained [3 + 3] cycloaddition products using alkenyldiazo esters **1**, nitrosobenzenes, and suitable gold catalyst under ambient conditions. For propargyl esters **5**, its resulting gold carbenes initially react with nitrosobenzenes to give alkenyl imine **8a**, followed by a [4 + 2] cycloaddition with nitrosobenzene. The utility of these two reactions is manifested by a wide scope of substrates and nitrosobenzenes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data of new compounds, X-ray crystallographic data of compounds **3b** and **6a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

rslu@mx.nthu.edu.tw

Author Contributions

[†]These authors contributed equally.

■ ACKNOWLEDGMENTS

The authors thank the National Science Council and the Ministry of Education, Taiwan, for supporting this work.

■ REFERENCES

- (1) Selected reviews: (a) Casiraghi, G.; Zanardi, F. *Chem. Rev.* **2000**, *100*, 1929. (b) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Bird, C. W., Ed.; Pergamon: Oxford, U.K., 1995; Vol. 2, p 121. (c) Sundberg, R. J. *Indoles*; Academic Press: London, U.K., 1996. (d) Lounasmaa, M.; Tamminen, T. In *The Tropane Alkaloids in Alkaloids*; Academic Press: New York, 1993; Vol. 44, p 1. (e) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (f) Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630. (g) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. (h) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650.
- (2) (a) Doyle, M. P.; McKervy, M. A.; Ye, T. *Modern Catalytic Method for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (c) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675.
- (3) Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. *J. Am. Chem. Soc.* **2003**, *125*, 4692.
- (4) Reddy, R. P.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10312.
- (5) Barluenga, J.; Lonzi, G.; Riesgo, L.; López, L. A.; Tomas, M. *J. Am. Chem. Soc.* **2010**, *132*, 13200.
- (6) (a) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 3741. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244.
- (7) Shapiro, N. D.; Shi, Y.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 11654.
- (8) Wang, X.; Xu, X.; Zavalij, P.; Doyle, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 16402.
- (9) Selected examples: (a) Yamamoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7082. (b) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 4128. (c) Nitsch, H.; Kresze, G. *Angew. Chem., Int. Ed.* **1976**, *15*, 760. (d) Jana, C. K.; Studer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6542. (e) Kumarn, S.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Lett.* **2005**, *7*, 4189. (f) Li, F.; Yang, B.; Miller, M. J.; Zajicek, J.; Noll, B. C.; Mollmann, U.; Dahse, H. M.; Miller, P. A. *Org. Lett.* **2007**, *9*, 2923.

- (10) (a) Penoni, A.; Palmisano, G.; Zhao, Y.-L.; Houk, K. N.; Volkman, J.; Nicholas, K. M. *J. Am. Chem. Soc.* **2009**, *131*, 653. (b) Murru, S.; Gallo, A. A.; Srivastava, R. S. *ACS Catal.* **2011**, *1*, 29. (c) Penoni, A.; Nicholas, K. M. *Chem. Commun.* **2002**, 484. (d) Ragaini, F.; Rapetti, A.; Visentin, E.; Monzani, M.; Caselli, A.; Cenini, S. *J. Org. Chem.* **2006**, *71*, 3748.
- (11) We recently reported gold-catalyzed stereoselective synthesis of azacyclic compounds from nitroalkyne substrates through a hypothetical [2 + 2 + 1] cycloaddition among nitrosobenzene, its tethered carbenes and external alkenes; see Jadhav, A. M.; Bhunia, S.; Liao, H. Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 1769.
- (12) (a) Druellinger, M. L. *J. Heterocycl. Chem.* **1976**, *13*, 1001. (b) Xu, Z.-J.; Zhu, D.; Zeng, X.; Wang, F.; Tan, B.; Hou, Y.; Ly, Y.; Zhong, G. *Chem. Commun.* **2010**, *46*, 2504.
- (13) X-ray crystallographic data of compounds **3b** and **6a** are provided in Supporting Information.
- (14) (a) Hashmi, A. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754. (b) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488. (c) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A. III; Toste, F. D. *Nat. Chem.* **2009**, *1*, 483. (d) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510. (e) Jiménez-Núñez, E.; Clavarié, C. K.; Bour, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030.
- (15) For the use of alkenylgold carbenoids to construct medium-sized carbocyclic rings, see: (a) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736. (b) Garayalde, D.; Kruger, K.; Nevado, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 911.
- (16) This metathesis pathway is distinct from the nitroso/alkyne metathesis reported by us recently, see: Mukherjee, A.; Dateer, R. B.; Chaudhuri, R.; Bhunia, S.; Karad, S. N.; Liu, R. S. *J. Am. Chem. Soc.* **2011**, *133*, 15372.
- (17) Raczynska, E. J.; Kosińska, W.; Osmialowski, B.; Gawinecki, R. *Chem. Rev.* **2005**, *105*, 3561.