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

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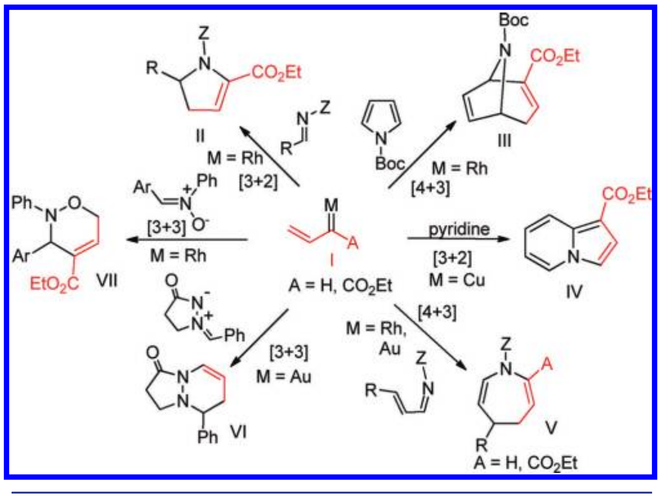
Supporting Information

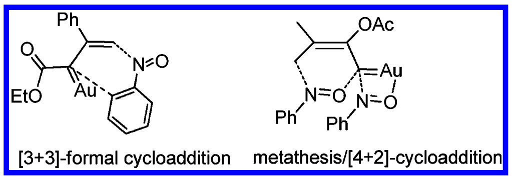
ABSTRACT: We report two new formal cycloaddition reactions between nitrosobenzenes and alkenylgold carbenoids. We obtained quinoline oxides **3** in satisfactory yields from the gold-catalyzed [3 + 3]-cycloadditions between nitrosobenzenes and alkenyldiazo esters **1**. For propargyl esters **5**, its 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 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 dienes[9] 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 the reactions of metal carbenoids with nitrosobenzenes were reported to give nitrone species,[12] such a reaction route does not influence our new cycloadditions in most instances.

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

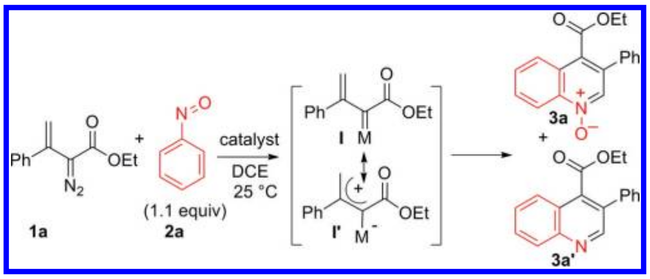


Scheme 2. Two New Formal Cycloaddition Reactions



Shown in Table 1 is the generation of metal carbenoids from alkenyldiazoacetates **1a** over various metal catalysts.[2] We first examined the reaction in the presence of $Rh_2(OAc)_4$ (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

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



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	$PPh_3AuCl/AgNTf_2$ (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

[a] L = P(*t*-Bu)$_2$(*o*-biphenyl), IPr=1,3-bis(diisopropylphenyl)imidazol-2-ylidene), [substrate] = 0.05 M. [b] Product yields are reported after purification from silica column.

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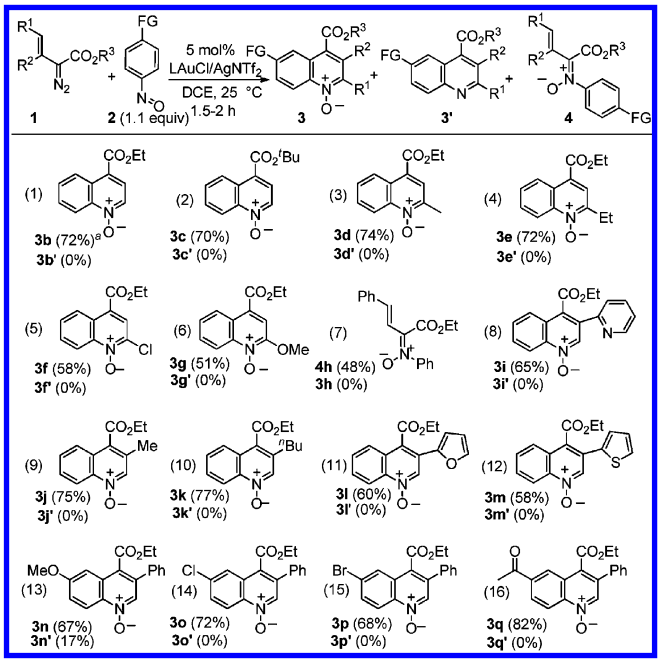
to give compound **3a** in 62% yield. Among various copper catalysts at 5 mol % loading (entries 2–4), IPrCuCl/AgNTf$_2$ showed the best performance to give desired **3a** in 52% yield. As shown in entries 5–7, gold catalysts (5 mol %) were efficient for this intermolecular cycloaddition with a 61% yield of desired **3a** for IPrAuCl/AgNTf$_2$, 65% yield for PPh$_3$AuCl/AgNTf$_2$, and 72% yield for ClAuP(*t*-Bu)$_2$(*o*-biphenyl)/AgNTf$_2$; we also obtained quinoline species **3a′** in small proportion (8–11%). An alteration of silver salt as in ClAuP(*t*-Bu)$_2$(*o*-biphenyl)/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 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. Reaction Scopes with the [3 + 3] Formal Cycloaddition of Nitrosobenzenes with Alkenyldiazocarboxylates

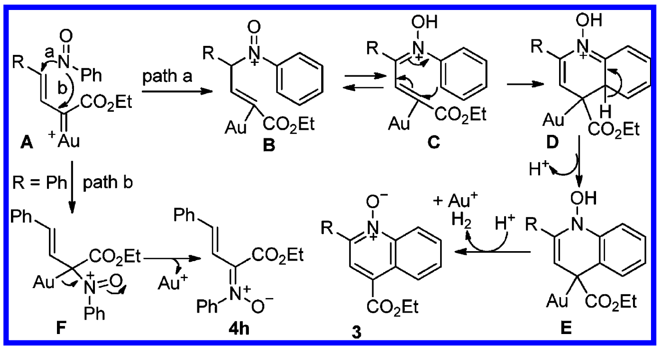


^{a}L = P(*t*-Bu)$_2$(*o*-biphenyl), [substrate] = 0.05 M. All product yields are reported after purification from silica column.

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 ClAuP(*t*-Bu)$_2$(*o*-biphenyl)/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** (R^1 = R^2 = H) bearing various esters (R^3 = Et, *t*-Bu), giving desired compounds **3b** and **3c** in 70–72% yields. We examined also the reactions of substrates containing varied C(3)-substituents (R^1 = Me, Et, Cl, 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 (R^2 = 2-pyridinyl, Me, *n*-Bu, 2-furanyl, 2-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).

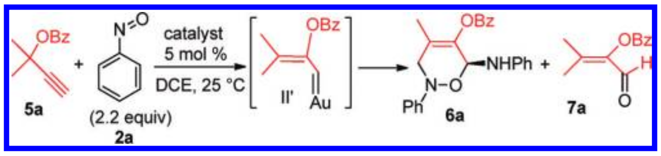
We propose a plausible mechanism in Scheme 3. The success of this formal cycloaddition relies on an attack of nitrosobenzene at the C(3)-carbon of carbenoids **A** (path a) bearing a small R substituent. The resulting species **B** attains an oxime/nitroso tautomeric equilibrium[17] to generate gold-containing alkenyl iminium **C** that undergoes a 6-*π* electrocyclization 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 (R = 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.

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



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 PPh$_3$AuCl/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 ClAu(*t*-Bu)$_2$P(*o*-biphenyl/AgNTf$_2$ and IPrAuCl/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 ClAu(*t*-Bu)$_2$P(*o*-biphenyl)/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). IPrCuCl/AgNTf$_2$ and Rh$_2$(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.

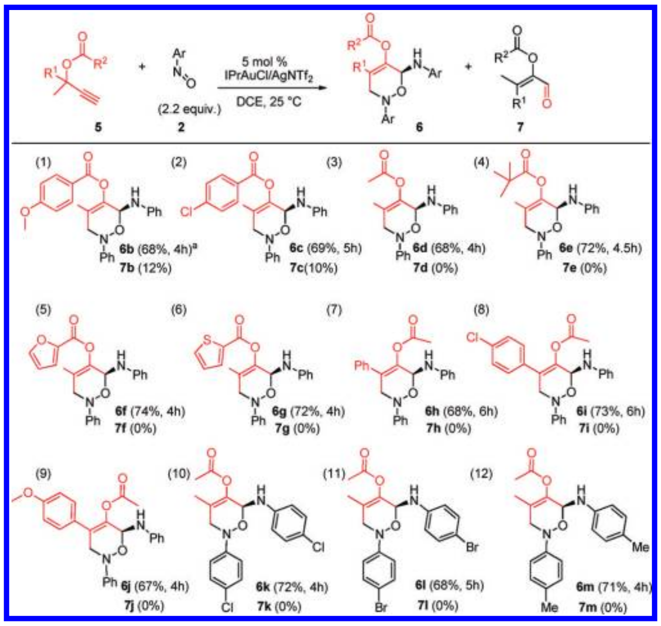
Table 3. Gold-Catalyzed Metathesis/Cycloaddition Cascades of Propargyl Esters



entry	catalyst[a] (mol %)	time (h)	compounds (yields)[b]
1	$PPh_3AuCl/AgNTf_2$ (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%)

[a] L = P(*t*-Bu)$_2$(*o*-biphenyl), IPr = 1,3-bis(diisopropylphenyl)imidazol-2- ylidene), DCE = dichloroethane, [substrate] = 0.05 M. [b] Product yields are reported after purification from silica column.

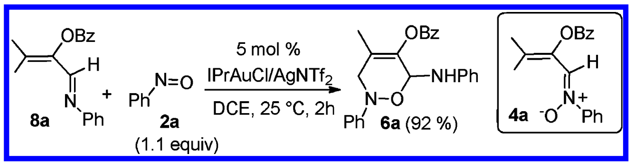
Table 4. Reaction Scopes for the Reactions of Nitrosobenzenes with Propargyl Esters



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

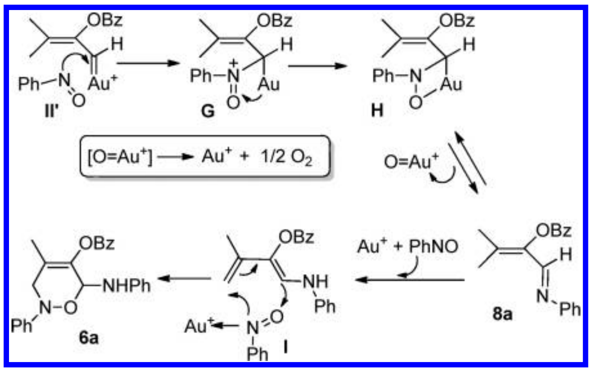
We prepared also various propargyl esters **5a–5i** to test their reactions with various nitrosobenzene; the results are shown in Table 4. In a typical operation, a propargyl ester was treated with nitrosobenzene (2.2 equiv) and $IPrAuCl/AgNTf_2$ (5 mol %) in DCE (25 °C) for 4–6 h before the workup. 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 (R^2 = 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 R^1 substituents (R^1 = 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.

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



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 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 $IPrAuCl/AgNTf_2$ (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 nitrone **4a**, nitrosobenzene **2a** (1.1 equiv), and the same gold catalyst. Alkenyl imine **8a**, rather than nitrone **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 hypothetic tautomerization to establish an equilibrium[17] 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 $IPrAuCl/AgNTf_2$ (5 mol %) in CD_2Cl_2. At the end of reaction (25 °C, 4 h), this CD_2Cl_2 solution shows a complete disappearance of isopropanol and ester **5a**, whereas acetone and oxazine **6a** were observed in the NMR spectra. We hypothesize that $[Au{=}O]^+$ 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.

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■ ACKNOWLEDGMENTS

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