Gold-Catalyzed Stereoselective Synthesis of Azacyclic Compounds through a Redox/[2 + 2 + 1] Cycloaddition Cascade of Nitroalkyne Substrates

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S *Supporting Information*

ABSTRACT: We report a new redox/cycloaddition cascade on readily available 1-alkynyl-2-nitrobenzenes that produces complex azacyclic compounds stereoselectively. The core structures of the resulting products are constructed through a formal $[2 + 2 + 1]$ cycloaddition among α-carbonyl carbenoids, nitroso species, and external alkenes.

Metal-catalyzed cycloadditions are powerful tools for generating complex molecular frameworks.[1] Metal carbenoids are valuable intermediates in organic reactions because of their potent reactivities in cycloadditions with alkenes.[2] In gold catalysis, the internal redox reactions on alkynes are among the most efficient methods for generating α-carbonyl carbenoids;[3,4] such approaches are safe and convenient because stable alkyne and organic oxides replace hazardous diazocarbonyl species. We envisage that the development of new redox/cycloaddition cascades on alkynes will represent a viable route toward products with molecular complexity, but existing examples are few.[5] Herein, we report such cascade reactions on cheap and readily available 1-alkynyl-2-nitrobenzenes using the protocol shown in Scheme 1. Notably, the core structures of the resulting cycloadducts are constructed through a formal $[2 + 2 + 1]$ cycloaddition among α-carbonyl carbenoids, nitroso species,[6] and external alkenes, as depicted by species **B**.

In a standard operation, 4 equiv of ethyl vinyl ether (**a**) mixed with PPh₃AuNTf₂ (5 mol %) in dichloroethane (DCE) at 25 °C was treated slowly with nitrobenzene **1** via a syringe pump for 0.5 h; this procedure circumvents the gold-catalyzed dimerization of starting **1** in the absence of olefin (eq 1).[7]
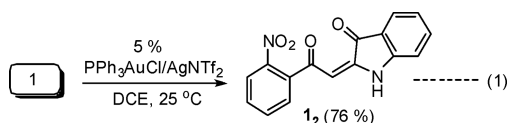
As shown in Table 1, the use of AuCl₃ and PtCl₂/CO gave a messy mixture of products, from which the desired cycloadduct **1a** was isolated in 8% yield in the Pt catalysis. In contrast, use of ClAuP(*t*-Bu)₂(*o*-biphenyl)/AgNTf₂ and IPrAuCl/AgNTf₂ [5 mol %; IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene] enabled complete conversion to give **1a** and **1a′** as a diastereomeric mixture (entries 3 and 4) that was separable on a silica column. The stereoselectivity was greatly enhanced with PPh₃AuCl/AgSbF₆ or PPh₃AuCl/AgNTf₂, giving cycloadduct **1a** in 85−89% yield with

epimer **1a′** in 2−5% yield (entries 5 and 6). AgNTf₂ alone gave an exclusive recovery of unreacted **1** (65%; entry 7). The structure of compound **1a** was determined with ¹H nuclear Overhauser effect (NOE) spectra and confirmed by an X-ray diffraction study of its relative **6a**.[8] Compound **1a** and its epimer **1a′** were not interconvertible in the presence of PPh₃AuSbF₆ or PPh₃AuNTf catalyst (5 mol %) under the reaction conditions (DCE, 25 °C, 2 h), although **1a** is more thermodynamically favorable than **1a′**.[9]

The scope of this catalysis is demonstrated by its applicability to diverse electron-rich alkenes and dienes **b**−**n** (4 equiv), as depicted in Table 2. The resulting azacyclic products **1b**−**1n** were obtained exclusively as single diastereomers from starting **1**, except in the case of **n** (entry 14), for which some of the epimer **1n′** (8%) was formed. The efficiency of this catalysis is reflected by the fact that the yields of products exceeded 68%. Entries 1−3 show the workability of various enol ethers **b**−**d** (R = trimethylsilyl, benzyl, *tert*-butyl) that delivered the corresponding products **1b**−**1d**. This catalysis is compatible with ethyl and phenyl vinyl sulfides **e** and **f**, which gave sulfur-containing compounds **1e** and **1f** in 92 and 76% yield, respectively (entries 4 and 5). Cyclic enol ethers **g** and **h** gave stereoselective formation of complex azacyclic products **1g** and **1h** in 79 and 83% yield, respectively (entries 6 and 7). The structures of azacycles **1g** and **1h** were determined by ¹H NOE spectra; the corresponding value J_{23} = 0 Hz is consistent with a dihedral angle of $\sim$90° expected for this geometry. For 2-substituted enol ether **i** with $Z/E = 1$ (entry 8), the gold catalysis gave compound **1i** with the same stereochemistry (J_{23} = 0 Hz). We obtained the same product in decreased yield (31%) using starting **i** with $Z/E = 1/3$ (entry 9), with a side product **1₂** (46%) from the dimerization of starting **1** (eq 1). The cis isomer of species **i** appeared to be more active than the trans form in this cycloaddition. The structures of **1g**, **1h**, and **1i** were confirmed by ¹H NOE spectra. The workability of this synthesis with aryl alkenes **j**−**m** to give the expected products **1j**−**1m** stereoselectively and efficiently (entries 10−13) further demonstrates its broad utility,. This reaction was extensible even to electron-rich diene **n**, which afforded azacyclic product **1n** in 68% yield (entry 14).

Table 3 shows the applicability of this catalysis with nitrobenzenes **2**−**9** bearing various substituents on their phenyl groups. For substrates **2**−**5** having electron-withdrawing groups at C4, the reactions with ethyl vinyl ether **a** proceeded smoothly to give the desired compounds **2a**−**5a** in 68−84% yield.

Scheme 1. Gold-Catalyzed Redox/Cycloaddition Cascade
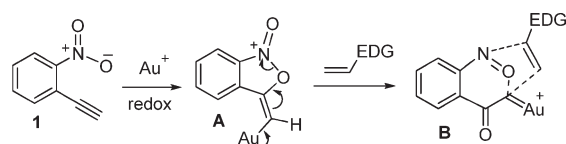
Table 1. Catalyst Screening for the Reaction of 1 and Enol Ether a
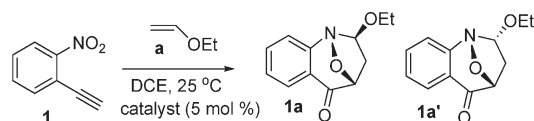
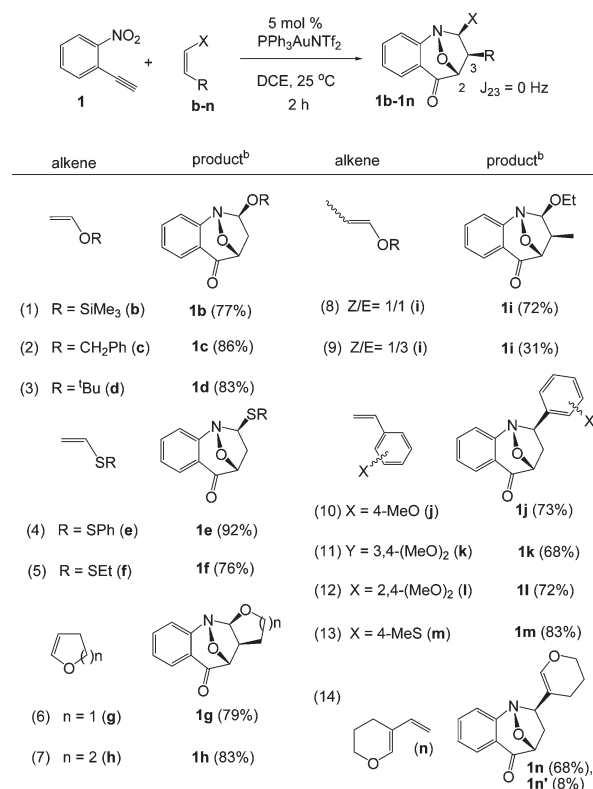| entry	catalyst[a]	time (h)	products[b]
1	AuCl$_3$	2	complicated mixture
2	PtCl$_2$/CO	2	1a (8%)
3	LAuCl/AgNTf$_2$	2	1a (65%), 1a′ (35%)
4	IPrAuCl/AgNTf$_2$	2	1a (54%), 1a′ (39%)
5	PPh$_3$AuCl/AgSbF$_6$	2	1a (85%), 1a′ (5%)
6	PPh$_3$AuCl/AgNTf$_2$	2	1a (89%), 1a′ (2%)
7	AgNTf$_2$	12	1 (65%)

[a] L = P(t-Bu)$_2$(o-biphenyl). The reaction was performed using [substrate] = 0.05 M and 4 equiv of enol ether a. [b] Reported product yields were obtained after separation on a silica column.

Substrate 6 bearing a methyl group was also suitable for this catalysis, giving the desired product 6a in 67% yield; its structure was confirmed by X-ray diffraction.[8] Similar products 7a−9a were also obtained in good yields (73−82%) from substrates 7−9 bearing fluoro, chloro, and methyl groups, respectively, at the phenyl C5 carbon (entries 6−8).[10]

Scheme 2 presents data to assist an understanding of the reaction mechanism. Treatment of nitrobenzene 1 with styrene and the gold catalyst (5 mol %) delivered deoxygenated cyclopropane 10 in 23% yield, with dimerization product 1$_2$. Formation of compound 10 apparently proceeded through the intermediacies of α-carbonyl carbenoid B and species C and D. Using a chiral gold complex to probe the reaction mechanism, we obtained the resulting product (−)-1g with 73.1% ee. Such a chirality induction provides evidence for the participation of a gold fragment to generate new stereogenic centers; 1,3-dipolar cycloaddition on metal-free nitrone E is thus excluded[11]

The isolation of the cyclopropane compound 10 asserts the intermediacy of α-carbonyl carbenoids B. A formal [2 + 2 + 1] cycloaddition, as depicted in Scheme 1, provides a suitable formula for these products, but such a three-component cycloaddition probably begins from an initial intramolecular cyclization of gold carbenoid B to form ketonyl oxonium F, as depicted in Scheme 3. We envisage that the keto−enol tautomerism of species F generates enol G, which is also characterized by the resonance structure G′. A subsequent [3 + 2] cycloaddition of species G′ with enol ether in a concerted exo-addition mode would give the observed products 1a−1i. This proposed mechanism rationalizes not only the product stereoselectivity but also the observations in the control experiments. We performed theoretical calculations (B3LYP/LANL2DZ) to examine the

Table 2. Cycoadditions of Compound 1 with Various Alkenes[a]

	alkene	product[b]		alkene	product[b]
(1)	R = SiMe$_3$ (b)	1b (77%)	(8)	Z/E= 1/1 (i)	1i (72%)
(2)	R = CH$_2$Ph (c)	1c (86%)	(9)	Z/E= 1/3 (i)	1i (31%)
(3)	R = ^{t}Bu (d)	1d (83%)	(10)	X = 4-MeO (j)	1j (73%)
(4)	R = SPh (e)	1e (92%)	(11)	Y = 3,4-(MeO)$_2$ (k)	1k (68%)
(5)	R = SEt (f)	1f (76%)	(12)	X = 2,4-(MeO)$_2$ (l)	1l (72%)
(6)	n = 1 (g)	1g (79%)	(13)	X = 4-MeS (m)	1m (83%)
(7)	n = 2 (h)	1h (83%)	(14)	(n)	1n (68%), 1n′ (8%)

[a] Using [substrate] = 0.05 M and 4 equiv of alkene. [b] Reported product yields were obtained after separation on a silica column.

**Table 3. Cycloadditions with Various Nitrobenzenes**
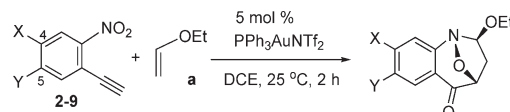
entry	nitrobenzene[a]	product (yield[b])
1	X = F, Y = H (2)	2a (68%)
2	X = Cl, Y = H (3)	3a (80%)
3	X = Br, Y = H (4)	4a (80%)
4	X = CF$_3$, Y = H (5)	5a (84%)
5	X = Me, Y = H (6)	6a (67%)
6	X = H, Y = F (7)	7a (73%)
7	X = H, Y = Cl (8)	8a (82%)
8	X = H, Y = Me (9)	9a (77%)

[a] Using [substrate] = 0.05 M and 4 equiv of enol ether a. [b] Reported product yields were obtained after separation on a silica column.

feasibility of this hypothetical cycloaddition using ethyl vinyl ether a and PH$_3$Au$^+$ catalyst. This reaction pathway appears to be very facile and highly exothermic, with E_a = 0.5 kcal/mol and ΔH = −32.3 kcal/mol.[12] Although the Au-catalyzed cycloaddition of nitrone E with enol may rationalize the asymmetric induction, as depicted in Scheme 2, this route fails to explain the stereoselectivity of products.

In summary, we have reported a new redox/cycloaddition cascade on readily available 1-alkynyl-2-nitrobenzenes[13,14] that

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Scheme 2. Experiments To Elucidate the Mechanism
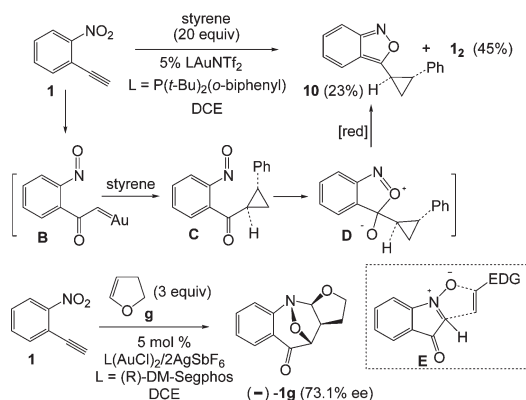
Scheme 3. Proposed Mechanism for Azacycles 1a—1i
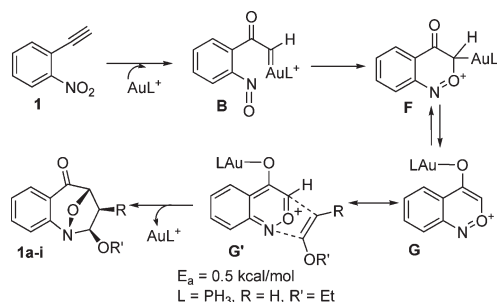
produces complex azacyclic compounds with high stereoselection. Such a cascade reaction is mechanistically interesting in that the central cores of the products are constructed through a formal $[2 + 2 + 1]$ cycloaddition among α-carbonyl carbenoids, nitroso species, and external alkenes. The utility of this catalysis includes diverse electron-rich alkenes and various substituents on the phenyl groups. The enantioselective synthesis of these azacyclic compounds is currently under investigation.

■ ASSOCIATED CONTENT

ⓢ Supporting Information. Experimental and computational procedures, characterization data for new compounds, and X-ray crystallographic data for compound **6a** and a relative of **1₂** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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(2) For selected examples, see: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244. (b) Shapiro, N. D.; Shi, Y.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 11654. (c) Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598. (d) Li, C. W.; Lin, G.-Y.; Lin, R.-S. *Chem.—Eur. J.* **2010**, *16*, 5803. (e) Davies, H. M. L.; Xiang, B.; Kong, N.; Stafford, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 7461. (f) Davies, H. M. L.; Hu, B.; Saikali, E.; Bruzinski, P. R. *J. Org. Chem.* **1994**, *59*, 4535–4541.

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(4) α-Carbonyl carbenoids are generated from nitrogen-based oxides. See: (a) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225–1228. (b) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (c) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040. (d) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258.

(5) One example was reported for this redox/cycloaddition cascade on substrates tethered with nitrone/alkyne/alkene functionalities, whereas our new system employs external alkenes (see ref 4c).

(6) For selected examples of cycloaddition reactions of nitrosobenzenes, see: (a) Benbow, J. F.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 12305. (b) McClure, K.; Benbow, J. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 8185. (c) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 4128. (d) Wang, T.; Huang, X.-L.; Ye, S. *Org. Biomol. Chem.* **2010**, *8*, 5007.

(7) Structural characterization of the dimerization product **1₂** relied on an X-ray diffraction study of its analogue; the X-ray data and a mechanism of formation of species **1₂** are presented in the Supporting Information.

(8) X-ray crystallographic data for compound **6a** appear in the Supporting Information.

(9) In the presence of PPh₃AuNTf₂, we observed a gradual change of species **1a** to a mixture in which **1a**/**1a′** = 6:1 after 24 h in DCE at 25 °C. Under the same conditions, its epimer **1a′** gave a composition **1a**/**1a′** = 2:1. A complete equilibrium requires a much longer time.

(10) Substrates bearing methoxy groups at the phenyl C4 or C5 atoms are incompatible with this catalysis because they tend either to stabilize the nitro group or to reduce the alkyne electrophilicity.

(11) Nitrone **E** may be generated from α-carbonyl carbenoid **B**, and its role is inferred from the mechanism of formation of the dimerization product **1₂**.[7] We envisage that the resulting cycloadduct **H** is somewhat strained and subject to gold-catalyzed rearrangement to the observed azacyclic product through intermediates **I** and **J**. Nevertheless, this mechanism is expected to give a mixture of isomeric products **1a** and **1a′** because of free rotation around the C3—C4 bond in intermediates **I** and **J**.
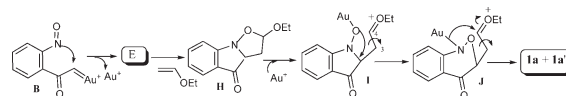
(12) See the Supporting Information for the details of the calculation procedures and the energy profiles of a concerted $[3 + 2]$ cycloaddition pathway.

(13) We also examined this reaction with internal alkyne **11**, but its gold catalysis gave benzo[*c*]isoxazole **12** in 76% yield. This transformation was previously reported by Yamamoto et al.,[14] but we have revised their mechanism involving gold α-carbonyl carbenoids as depicted below:
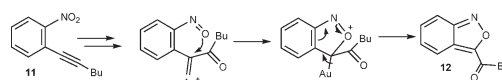
This reaction outcome also supports our hypothetical mechanism involving gold α-carbonyl carbenoids **B**.

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