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C–H Insertion

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Gold-Catalyzed Oxidative Cyclizations of *cis*-3-En-1-ynes To Form Cyclopentenone Derivatives**

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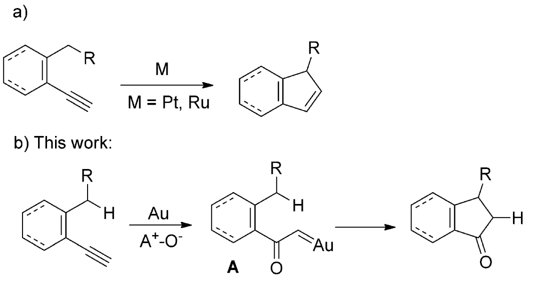
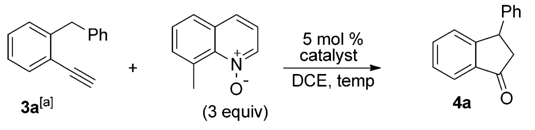
Cycloisomerizations of 1,*n*-enynes ($n = 5$, 6) catalyzed by transition metals are powerful tools for accessing complicated carbocycles.[1,2] Such reactions have been intensively studied for many transition metals having diverse reaction mechanisms. Metal-catalyzed oxidative cyclizations of 1,*n*-enynes ($n = 5$, 6) are synthetically appealing because the product skeletons incorporate oxy or oxo functionalities,[3,4] but there are fewer reported examples for enyne oxidative cyclizations than for their cycloisomerzation reactions.[1,2] Our group and the groups of others have reported the catalytic cycloisomerizations of *cis*-3-en-1-ynes to form cyclopentadiene derivatives using ruthenium or platinum catalysts, respectively (Scheme 1 a);[5] the corresponding oxidative cyclization remains undocumented. Herein, we report new gold-catalyzed oxidative cyclizations of *cis*-3-en-1-ynes to give cyclopentenone skeletons using 8-methylquinoline oxide (Scheme 1 b). Notably, the mechanistic transformation of this C–H activation is proven to proceed through a noncarbene route, thus excluding the intermediacy of the α-carbonyl carbene **A**.[6,7]



Scheme 1. a) Cycloisomerizations and b) oxidative cyclizations of 3-en-1-ynes.

The reaction of the *cis*-3-en-1-yne **3a** in the presence of various gold catalysts and 8-methylisoquinoline oxide[7] (3 equiv) as the oxidant were investigated (Table 1). The use of $[PPh_3AuCl]/AgNTf_2$ (5 mol %) resulted in the complete consumption of **3a** in hot 1,2-dichloroethane (DCE, 80 °C, 10 h), thus giving 3-phenylindanone (**4a**) in 42 % yield (entry 1). Catalytic efficiencies were improved with $[ClAuP(tBu)_2(o\text{-biphenyl})]/AgNTf_2$ and $[ClAuP(tBu)_2(o\text{-biphenyl})]/AgSbF_6$, both of which gave the desired **4a** in 70 % and 65 % yield, respectively (entries 2–3). We enhanced the yields of **4a** to 83 % and 77 % using $[IPrAuCl]/AgNTf_2$ and $[IPrAuCl]/AgSbF_6$, respectively (entries 4–5). At 25 °C with an extended reaction time (24 h), the conversion was complete for the $[IPrAuCl]/AgNTf_2$ catalyst to give compound **4a** in 80 % yield (entry 6). $AuCl_3$ gave **4a** in a low yield (26 %) together with unreacted **3a** in 60 % recovery (entry 7). $AgNTf_2$ was inactive in this oxidative cyclization and 72 % of **3a** was recovered (entry 8).

Table 1: Gold-catalyzed oxidative cyclization of *cis*-substituted 3-en-1-yne.



3a[a]

4a

Entry	Catalyst[b]	*T* [°C]	*t* [h]	Yield [%][c]
1	$[PPh_3AuCl]/AgNTf_2$	80	10	42
2	$[LAuCl]/AgNTf_2$	80	3	70
3	$[LAuCl]/AgSbF_6$	80	3	65
4	$[IPrAuCl]/AgNTf_2$	80	2.5	83
5	$[IPrAuCl]/AgSbF_6$	80	3	77
6	$[IPrAuCl]/AgNTf_2$	25	24	80
7	$AuCl_3$	80	10	26[d]
8	$AgNTf_2$	80	10	no reaction[d]

[a] [**3a**] = 0.17 M. [b] L = $P(tBu)_2(o\text{-biphenyl})$. [c] Product yields are reported for products isolated from a silica gel column. [d] Starting **3a** was recovered in 60% in entry 7, and 72% in entry 8. IPr = 1,3-bis(diisopropyl phenyl)imidazol-2-ylidene), Tf = trifluoromethanesulfonyl.

We prepared various benzene-derived substrates (**3b**–**3p**) to examine the scope of this oxidative cyclization. In a typical operation, the starting substrate was treated with 8-methylquinoline oxide (3 equiv) and $[IPrAuCl]/AgNTf_2$ in hot DCE (80 °C) to give the corresponding indanone products **4b**–**4p** almost exclusively. We obtained satisfactory yields (84–86 %) of the indanones **4b**, **c** bearing an electron-deficient benzene (Table 2, entries 1–2), whereas a complex mixture of products was obtained for substrate **3d**, which has an electron-rich 4-methoxyphenyl group (entry 3). This oxidative cyclization worked well also with substrates **3e** and **3f**, thus giving the desired products in 68 and 78 % yields, respectively (entries 4 and 5). This new reaction is applicable to the substrates **3g**–**3l** bearing alkyl substituents, and the corresponding products **4g**–**4l** were obtained in 67–90 % yields (entries 6–11). The

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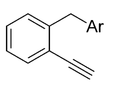
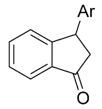
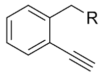
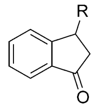
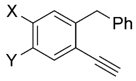
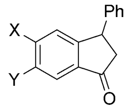
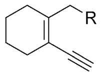
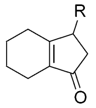
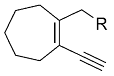
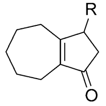
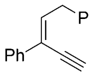
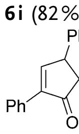
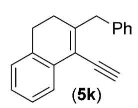
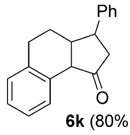
Table 2: Reaction scope for the synthesis of indanones.

Entry	3-En-1-ynes[a]	t [h]	Products[b]
			
1	Ar = 4-FC_6H_4 (**3b**)	3	**4b** (86%)
2	Ar = 4-ClC_6H_4 (**3c**)	2	**4c** (84%)
3	Ar = 4-$MeOC_6H_4$ (**3d**)	2	complex mixture
4	Ar = 2-thienyl (**3e**)	2.5	**4e** (68%)
5	Ar = 3-thienyl (**3f**)	3	**4f** (78%)
			
6	R = H (**3g**)	2.5	**4g** (83%)
7	R = benzyl (**3h**)	0.5	**4h** (85%)
8	R = CH_2Cl (**3i**)	2.5	**4i** (71%)
9	R = CH_2OTBS (**3j**)	2	**4j** (67%)
10	R = CH_2OMOM (**3k**)	1.5	**4k** (71%)
11	R = $CH_2CH{=}CH_2$ (**3l**)	0.5	**4l** (90%)
			
12	X = F, Y = H (**3m**)	6	**4m** (67%)
13	X = H, Y = F (**3n**)	7	**4n** (63%)
14	X = MeO, Y = H (**3o**)	6	**4o** (63%)
15	X = H, Y = OMe (**3p**)	12	**4p** (62%)

[a] [3-en-1-ynes] = 0.17 M, reactions performed at 80 °C. [b] Product yields are reported for products isolated from a silica gel column. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

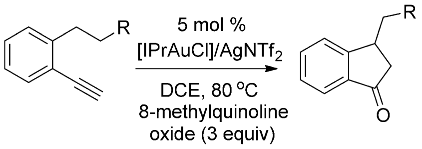
Table 3: Reaction scope for the synthesis of cyclopentenones.

Entry	3-En-1-ynes[a]	t [h]	Products[b]
			
1	R = C_6H_5 (**5a**)	0.8	**6a** (88%)
2	R = CH_2Cl (**5b**)	0.5	**6b** (87%)
3	R = CH_2OTBS (**5c**)	2.0	**6c** (67%)
4	R = benzyl (**5d**)	0.5	**6d** (81%)
5	R = $CH_2CH{=}CH_2$ (**5e**)	0.5	**6e** (90%)
			
6	R = C_6H_5 (**5f**)	0.8	**6f** (85%)
7	R = CH_2Cl (**5g**)	0.5	**6g** (81%)
8	R = CH_2OTBS (**5h**)	2.0	**6h** (64%)
9	R = CH_2Ph (**5i**)	0.5	**6i** (82%)
10	 (**5j**)	0.5	 **6j** (82%)
11	 (**5k**)	0.4	 **6k** (80%)

[a] [3-En-1-ynes] = 0.17 M, reactions performed at 80 °C. [b] Product yields are reported for products isolated from a silica gel column.

reactions can also be extended to substrates **3m**–**3p** bearing a fluoro and methoxy group at either the C4- or C5-carbon atoms of the bridging benzenes, thus giving the expected indanone derivatives **4m**–**4p** in 62–67% yields (entries 12–15).

The scope of this oxidative cyclization is substantially expanded with its application to the nonbenzene-derived substrates **5a**–**5k**, as shown in Table 3. In most instances, the conversions were complete within a short period (0.4–0.8 h). The results demonstrate the efficient syntheses of the useful hexahydro-1*H*-inden-1-ones **6a**–**6e** (67–90%) from gold-catalyzed oxidative cyclizations of the 3-en-1-ynes **5a**–**5e** bearing a bridging cyclohexene (entries 1–5). To our delight, this new synthesis is additionally applicable to the synthesis of the bicyclo[5.3.0]decen-10-ones **6f**–**6i** (64-85%) using substrates **5f**–**5i** (entries 6–9). We tested the reactions on acyclic 3-en-1-yne **5j**, which gave desired cyclopentenone **6j** in 82% yield (entry 10). The reaction proceeded well with starting **5k**, bearing a bridging dihydronaphthalene, thus giving compound **6k** in 80% yield.

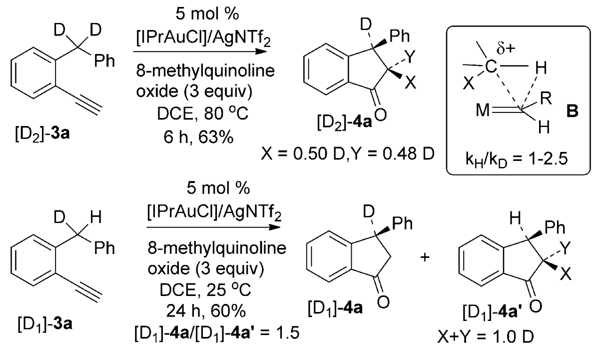


Substrates	Compounds (t [h], Yield [%])
1) R = 4-ClC_6H_4 (**3q**)	**4q** (0.5, 87)
2) R = 4-$MeOC_6H_4$ (**3r**)	**4r** (2, 77)
3) R = H (**3s**)	no reaction[a]

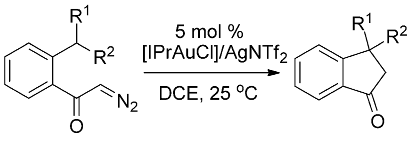
Scheme 2. The effects of substituents. [a] **3s** was recovered in 51% yield after 12 h.

An understanding the effects of the C–H acidity is discussed (Scheme 2). We found that the transformation of **3q**, bearing a 4-chlorophenyl substituent, proceeded more rapidly and efficiently than its 4-methoxyphenyl analogue **3r** in the formation of the corresponding cyclized products **4q** and **4r**. We observed no desired product for the substrate, even after a longer reaction time (12 h); 51% of **3s** was recovered. The presence of an electron-withdrawing substituent as in substrates **3h**–**3l** (Table 2, entries 7–11) is clearly indispensable for this oxidative cyclization, thus reflecting the importance of the C–H acidity.

We also prepared [D_2]-**3a**, which was deuterated 100% at the methylene position, and the gold-catalyzed reactions provided a 63% yield of the indanone [D_2]-**4a** having a 50% and 48% deuterium content for the methylene positions, which is indicative of a 1,2-hydrogen shift. As shown in Scheme 3, we studied the kinetic isotope effect using the monodeuterated sample [D_1]-**3a** and the corresponding indanone **4a** has different deuterium distributions with [D_1]-**4a**/[D_1]-**4a′** having a $k_H/k_d = 1.5$. Although a three-centered



Scheme 3. Deuterium-labeling experiments.



substrates	Compounds (t [h], Yield [%])
1) $R^1 = R^2 = H$ (**7b**)	(12, complex mixture)
2) $R^1 = H$, $R^2 = Me$ (**7c**)	**4s** (12, 37)
3) $R^1 = R^2 = Me$ (**7d**)	**4t** (0.4, 67)

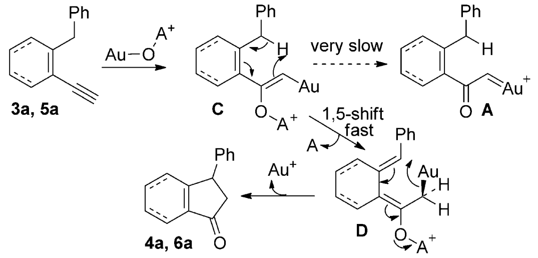
Scheme 5. The nature of C–H insertion.

concerted mechanism (**B**) is well accepted for most metal–carbene species that give a $k_H/k_d = 1$–2.5, such reactions are assisted by an electron-donating group (X = EDG) because of the positive character that develops on the reacting carbon atom.[8,9] This model, however, is incompatible with our observation that an electron-withdrawing group enhances the C–H activation.

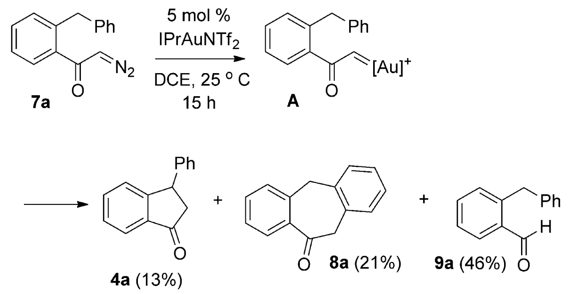
We assessed the role of the α-carbonyl carbenoid **A** using the authentic diazocarbonyl species **7a**.[8d] Treatment of **7a** with [IPrAu]/AgNTf$_2$ (5 mol %) in DCE at 25 °C for 15 hours led to its complete consumption, but the desired **4a** was delivered in low yield (13 %) together with the arylation product **8a** (21 %) and aldehyde **9a** (46 %).[10,11] This information reveals that the α-carbonyl carbeniod **A** was actually generated from the diazocarbonyl species **7a**, but it lacks chemoselectivity toward the C–H bond insertion.

We also studied the C–H insertion reactions of the α-carbonyl carbeniod **A** using the diazocarbonyl species **7b–d** (Scheme 5). We obtained no C–H insertion product for the methyl derivative **7b**, but the desired indanones **4s** and **4t** were isolated (37 and 67 % yield, respectively) from the **7c** and **7d**, respectively. The C–H insertion of the carbeniod **A** seems to follow a concerted mechanism (**B**; Scheme 3),[9] thus showing the reactivity order: *tert*-C-H > *sec*-CH > CH$_3$. This trend is opposite to that of our oxidation system which has the order: CH$_3$ ≫ *sec*-CH and *tert*-C-H.[12]

A plausible mechanism to rationalize the formation of indanone (**4a**) and cyclohexenone (**6a**) products is proposed (Scheme 6). The intermediacy of the α-carbonyl carbenoid **A** is excluded because it behaves very differently for the C–H activation according to our control experiment (Schemes 4 and 5). We envisage that the initially formed gold-containing enol ether **C** has a high barrier to overcome for the formation of the hypothetical carbenoid **A**. Instead, this species undergoes a rapid 1,5-hydrogen shift[13] to form the species **D**. We propose that such a shift has a proton character because it is captured by the electron-rich gold/alkenyl moiety. A subsequent cyclization of **D** is expected to give the observed product (**4a** or **6a**). This proposed mechanism explains the observation that an acidic C–H bond accelerates this oxidative cyclization. The nonbenzene-derived substrate **5a** is more active than its benzene-derived analogue **3a** because the 1,5-hydrogen shift of the former avoids dearomatization.[14]



Scheme 6. A plausible reaction mechanism.



Scheme 4. The reaction using diazocarbonyl.

In summary, we report the first successful catalytic oxidative cyclization of *cis*-substituted 3-en-1-ynes using a suitable gold complex and 8-methylquinoline oxide. The value of such reactions is reflected by their applicability to a broad range of benzene- and nonbenzene-derived substrates, thus giving various indanone and cyclopentenone derivatives, respectively. Similar products are not attainable efficiently using diazocarbonyl reagents because the gold carbenoid was proven to be unviable for the same C–H bonds. Accordingly, we hypothesize a 1,5-hydrogen shift of initially formed gold-containing enol ether **C** as the key step.

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[9] a) M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919; b) M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, M. P. Boone, V. Bagheri, M. Pearson, *J. Am. Chem. Soc.* **1993**, *115*, 958; c) D. F. Taber, E. H. Petty, K. Raman, *J. Am. Chem. Soc.* **1985**, *107*, 196.

[10] We are unsure about the mechanism for aldehyde **9a.** A tentative mechanism is proposed in the Supporting Information.

[11] Organic oxide and base may affect product distribution in Scheme 4. In the presence of 8-methylquinoline oxide (3 equiv), the reaction of dazocarbonyl species **7a** (1 equiv) and IPrAuNTf$_2$ (5 mol%) in DCE (25 °C, 25 h) only gave a 86% recovery of starting **7a**. The presence of 8-methylquinoline (1 equiv) retarded the reaction of diazocarbonyl species **7a** with IPrAuNTf$_2$ in DCE (25 °C, 35 h), giving desired **4a** (7%), arylation product **8a** (10%), aldehyde (19%) and unreacted **7a** (50%); the product distribution is analogous to that in Scheme 4.

[12] 2-Isopropyl-1-ethynylbenzene (**3t**) is inactive in this gold-catalyzed oxidative cyclization; its spectroscopic data is provided in the Supporting Information.

[13] A 1,5-hydrogen shift is a common process for *cis*-substituted dienes. See: a) M. J. Robins, Z. O. Guo, M. C. Samano, S. F. Wnuk, *J. Am. Chem. Soc.* **1999**, *121*, 1425; b) R. A. S. Chandraratna, A. L. Bayerque, W. A. Okamura, *J. Am. Chem. Soc.* **1983**, *105*, 3588; c) I. V. Alabugin, M. Maroharan, B. Breiner, F. D. Lewis, *J. Am. Chem. Soc.* **2003**, *125*, 9329; d) A. Kless, M. Nendel, S. Willsey, K. N. Houk, *J. Am. Chem. Soc.* **1999**, *121*, 4524.

[14] A 1,5-hydrogen shift may occur with 2-alkyl-1-alkenylbenzene with a dearomatization process; see Ref. [6a,b,d].