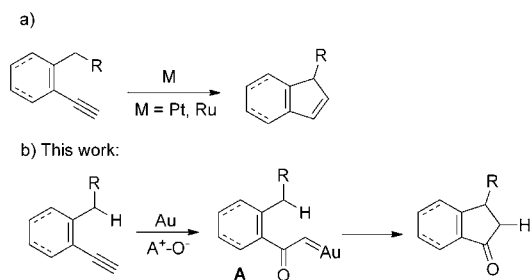


Gold-Catalyzed Oxidative Cyclizations of *cis*-3-En-1-yne To Form Cyclopentenone Derivatives**

Sabyasachi Bhunia, Satish Ghorpade, Deepak B. Huple, and Rai-Shung Liu*

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 cycloisomerization reactions.^[1,2] Our group and the groups of others have reported the catalytic cycloisomerizations of *cis*-3-en-1-yne to form cyclopentadiene derivatives using ruthenium or platinum catalysts, respectively (Scheme 1a),^[5] the corresponding oxidative cyclization



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

remains undocumented. Herein, we report new gold-catalyzed oxidative cyclizations of *cis*-3-en-1-yne to give cyclopentenone skeletons using 8-methylquinoline oxide (Scheme 1b). 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]

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 [PPh₃AuCl]/AgNTf₂ (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

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

Entry	Catalyst ^[b]	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[c]
1	[PPh ₃ AuCl]/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(*t*Bu)₂(*o*-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.

(entry 1). Catalytic efficiencies were improved with [ClAuP(*t*Bu)₂(*o*-biphenyl)]/AgNTf₂ and [ClAuP(*t*Bu)₂(*o*-biphenyl)]/AgSbF₆, 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]/AgNTf₂ and [IPrAuCl]/AgSbF₆, respectively (entries 4–5). At 25 °C with an extended reaction time (24 h), the conversion was complete for the [IPrAuCl]/AgNTf₂ catalyst to give compound **4a** in 80 % yield (entry 6). AuCl₃ gave **4a** in a low yield (26 %) together with unreacted **3a** in 60 % recovery (entry 7). AgNTf₂ was inactive in this oxidative cyclization and 72 % of **3a** was recovered (entry 8).

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]/AgNTf₂ 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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[**] We thank the National Science Council, Taiwan, for financial support of this work.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201108027>.

Table 2: Reaction scope for the synthesis of indanones.

Entry	3-En-1-yne ^[a]	t [h]	Products ^[b]
1	Ar = 4-FC ₆ H ₄ (3b)	3	4b (86%)
2	Ar = 4-ClC ₆ H ₄ (3c)	2	4c (84%)
3	Ar = 4-MeOC ₆ H 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 ₂ Cl (3i)	2.5	4i (71%)
9	R = CH ₂ OTBS (3j)	2	4j (67%)
10	R = CH ₂ OMOM (3k)	1.5	4k (71%)
11	R = CH ₂ CH=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-yne] = 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.

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).

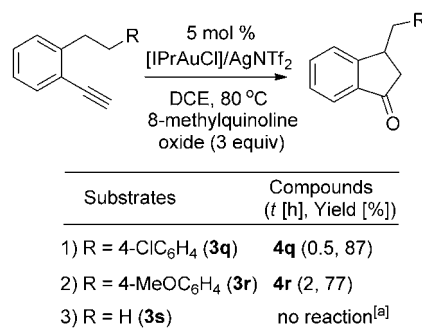
The scope of this oxidative cyclization is substantially expanded with its application to the nonbenzene-derived substrates **5a–5k**, as shown in Table 3. In most instances, the conversions were complete within a short period (0.4–0.8 h). The results demonstrate the efficient syntheses of the useful hexahydro-1*H*-inden-1-ones **6a–6e** (67–90%) from gold-catalyzed oxidative cyclizations of the 3-en-1-yne **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.

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

Table 3: Reaction scope for the synthesis of cyclopentenones.

Entry	3-En-1-yne ^[a]	t [h]	Products ^[b]
1	R = C ₆ H ₅ (5a)	0.8	6a (88%)
2	R = CH ₂ Cl (5b)	0.5	6b (87%)
3	R = CH ₂ OTBS (5c)	2.0	6c (67%)
4	R = benzyl (5d)	0.5	6d (81%)
5	R = CH ₂ CH=CH ₂ (5e)	0.5	6e (90%)
6	R = C ₆ H ₅ (5f)	0.8	6f (85%)
7	R = CH ₂ Cl (5g)	0.5	6g (81%)
8	R = CH ₂ OTBS (5h)	2.0	6h (64%)
9	R = CH ₂ Ph (5i)	0.5	6i (82%)
10		0.5	6j (82%)
11		0.4	6k (80%)

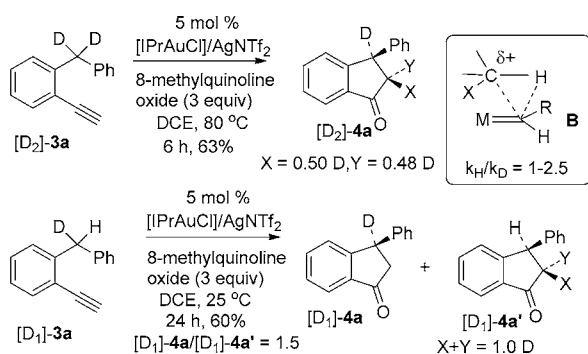
[a] [3-En-1-yne] = 0.17 M, reactions performed at 80 °C. [b] Product yields are reported for products isolated from a silica gel column.



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

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 [D₂]-**3a**, which was deuterated 100% at the methylene position, and the gold-catalyzed reactions provided a 63% yield of the indanone [D₂]-**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 [D₁]-**3a** and the corresponding indanone **4a** has different deuterium distributions with [D₁]-**4a**/[D₁]-**4a'** having a *k_H*/*k_D* = 1.5. Although a three-centered



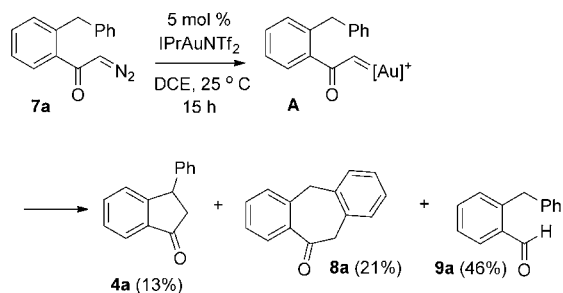
Scheme 3. Deuterium-labeling experiments.

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.

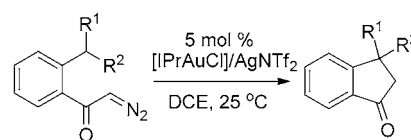
We assessed the role of the α -carbonyl carbenoid **A** using the authentic diazocarbonyl species **7a**.^[8d] Treatment of **7a** with [IPrAu]/AgNTf₂ (5 mol %) in DCE at 25 °C for 15 hours led to its complete consumption, but the desired **4a** was delivered in low yield (13%) together with the arylation product **8a** (21%) and aldehyde **9a** (46%).^[10,11] This information reveals that the α -carbonyl carbenoid **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 carbenoid **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 carbenoid **A** seems to follow a concerted mechanism (**B**; Scheme 3),^[9] thus showing the reactivity order: *tert*-C-H > *sec*-CH > CH₃. This trend is opposite to that of our oxidation system which has the order: CH₃ > *sec*-CH and *tert*-C-H.^[12]

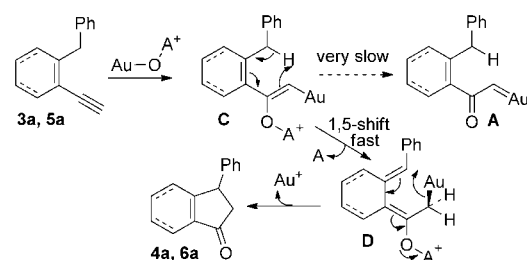
A plausible mechanism to rationalize the formation of indanone (**4a**) and cyclohexenone (**6a**) products is proposed (Scheme 6). The intermediacy of the α -carbonyl carbenoid **A** is excluded because it behaves very differently for the C-H activation according to our control experiment (Schemes 4



Scheme 4. The reaction using diazocarbonyl.



Scheme 5. The nature of C-H insertion.



Scheme 6. A plausible reaction mechanism.

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]

In summary, we report the first successful catalytic oxidative cyclization of *cis*-substituted 3-en-1-yne 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.

Received: November 15, 2011

Revised: December 21, 2011

Published online: February 1, 2012

Keywords: C-H insertion · cyclizations · gold · heterocycles · synthetic methods

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