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Diversity in Gold- and Silver-Catalyzed Cycloisomerization of Epoxide−Alkyne Functionalities

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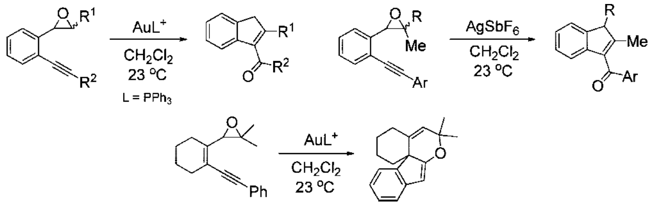
ABSTRACT



We report Au(I)- and Ag(I)-catalyzed cycloisomerizations of epoxide−alkyne functionalities in both aromatic and nonaromatic systems, leading to diversified carbocyclic and heterocyclic frameworks with high chemoselectivities. The use of such cycloisomerizations is reflected by a facile access to the cores of natural pallidol and gibberic acid.

One important advent in modern catalysis is the generation of reactive metal carbenoids and nonclassical carbocations in the cycloisomerzation of enynes catalyzed by electrophilic metals.[1,2] The use of this method is manifested by the diversity of carbo- and heterocyclic products as substrate structures and catalysts are modified.[1,2] Although there is growing interest on metal-mediated coupling reactions of epoxides with alkynes,[3] no precedent is reported for generation of metal carbenoids from such functionalities.[4,5] Herein, we report new Au(I)- and Ag(I)-catalyzed cycloisomerizations of epoxide−alkyne functionalities to give diversified carbocyclic and heterocyclic compounds selectively; Au(I) generates carbenoid species, whereas Ag(I) gives carbocation intermediates. The significance of this new catalysis is its easy construction of the central skeletons of naturally occurring pallidol,[6a] gibberic acid,[6b] and flavothebaone.[6c]

Table 1 shows the results for disubstituted epoxide **1a** (*E*/*Z* = 1.1)[7] using cationic Ag(I) and Au(I) catalysts after we

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(1) (a) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431. (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (e) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (f) Lipschutz, B. H.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 2793.

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(4) For generation of α-carbonyl gold carbenoids from Ph_2SO, see: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (b) Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838. (c) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156.

(5) For generation of α-carbonyl gold carbenoids from nitrone, see: Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040.

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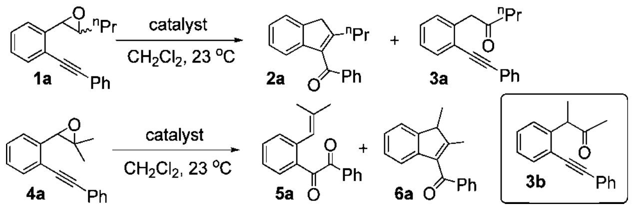
(7) The *E*/*Z* ratios of starting epoxides **1a**−**j**, **4e**,**g**, and **8b**,**g** are provided in the Supporting Information.

10.1021/ol802047g CCC: $40.75

Table 1. Catalyst Screening for Substituted Epoxides **1a** and **4a**

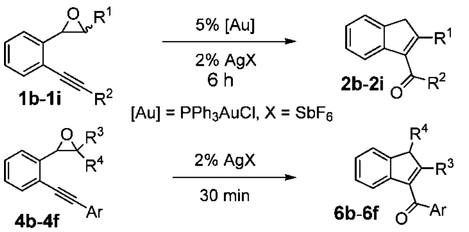


entry	substrate[a]	PPh_3AuCl mol %	AgX, mol % (X)	time (h)	product (yield, %)[b]
1	**1a**		5 (SbF_6)	6	**3a** (90)
2	**1a**	5	5 (SbF_6)	1	**2a** (35), **3a** (35)
3	**1a**	5	2 (SbF_6)	6	**2a** (78), **3a** (1)
4	**3a**	5	2 (SbF_6)	24	**3a** (95)
5	**4a**	5	2 (SbF_6)	24	**4a** (57), **5a** (41)
6	**4a**		2 (SbF_6)	0.5	**6a** (86)
7	**3b**		2 (SbF_6)	24	**3b** (94)

[a] [Epoxides] = 0.1 M in dry CH_2Cl_2. [b] Yields were reported after elution from a silica column.

found poor activity for commonly used catalysts (5 mol %) including $PtCl_2$, $PtCl_2$/CO, $AuClPPh_3$, AuCl, $AuCl_3$, and AgOTf in CH_2Cl_2 (23 °C, 24−48 h).[8] $AgSbF_6$ was active in the rearrangement of epoxide **1a** to ketone **3a** in a 90% yield (entry 1). The use of $PPh_3AuCl/AgSbF_6$, each at 5 mol % loading, led to 3-1*H*-indenyl ketones **2a** (35%) and side product **3a** (35%, entries 2). The yield of desired ketone **2a** was improved up to 78% with $PPh_3AuCl/AgSbF_6$ (5/2 mol %, entry 3). Ketone **3a** was not the intermediate for 3-1*H*-indenyl ketone **2a** because it was recovered exclusively with this modified catalyst in CH_2Cl_2 (23 °C, 24 h, entry 4). The same reaction on trisubstituted epoxide **4a** gave diketone **5a** (41%) in addition to unreacted **4a** (57%); nevertheless, we improved the yield of 3-1*H*-indenyl ketone **6a** up to 86% with $AgSbF_6$ catalyst (2 mol %). Herein, formation of **6a** from epoxide **4a** does not involve ketone **3b** as a reaction intermediate according to the control experiment depicted in entry 7.

Table 2. Catalytic Cycloisomerization of Epoxide−Alkyne



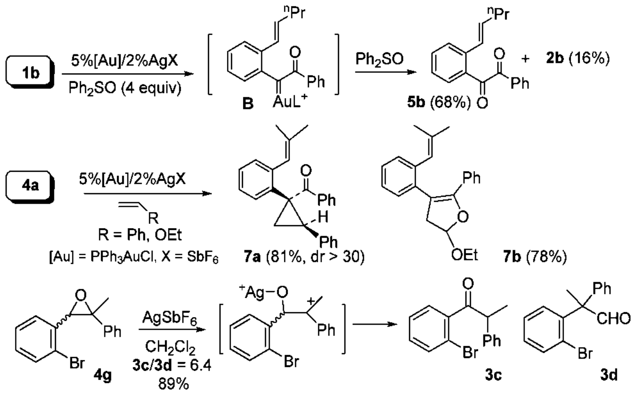
entry	epoxides[a,b]	ketones[c] (yield, %)
1	R^1 = Me, R^2 = Ph **(1b)**	**2b** (73)
2	R^1 = CH_2Ph, R^2 = Ph **(1c)**	**2c** (46)
3	R^1 = ${}^nPr$, R^2 = 4-$MeOC_6H_4$ **(1d)**	**2d** (80)
4	R^1 = ${}^nPr$, R^2 = 4-FC_6H_4 **(1e)**	**2e** (74)
5	R^1 = ${}^nPr$, R^2 = 2-thienyl **(1f)**	**2f** (60)
6	R^1 = ${}^nPr$, R^2 = ${}^nPr$ **(1 g)**	**2g** (76)
7	R^1 = ${}^nPr$, R^2 = Me **(1 h)**	**2h** (70)
8	R^1 = ${}^nPr$, R^2 = NMeTs **(1i)**	**2i** (81)
9	R^3 = R^4 = Me, Ar = 4-$MeOC_6H_4$ **(4b)**	**6b** (89)
10	R^3 = R^4 = Me, Ar = 4-FC_6H_4 **(4c)**	**6c** (81)
11	R^3 = R^4 = Me, Ar = 2-thienyl **(4d)**	**6d** (81)
12	R^3 = Me, R^4 = Ph, Ar = Ph **(4e)**	**6e** (78)
13	R^3, R^4 = $-(CH_2)_4-$, Ar = Ph **(4f)**	**6f** (71)

[a] [Epoxides] = 0.1 M, 23 °C, CH_2Cl_2. [b] The *E*/*Z* ratios of the epoxides are provided in the Supporting Information. [c] Yields were reported after elution from a silica column.

Table 2 summarizes the results for various di- and trisubstituted epoxides **1b**−**i** and **4b**−**f**, catalyzed by $PPh_3AuCl/AgSbF_6$ (5/2 mol %) and $AgSbF_6$ (2 mol %), respectively. This catalysis is applicable to epoxides **1b**−**c** bearing various R^1 substituents (R^1 = Me and CH_2Ph), giving cyclized ketones **2b**,**c** in 73% and 46% yields, respectively (entries 1 and 2). For epoxides **1d**−**i** comprising various alkynyl R^2 substituents (R^2 = 4-$MeOC_6H_4$, 4-FC_6H_4, 2-thienyl, 1-propyl, methyl, and NMeTs), the suitability of this catalysis is reflected by good yields (60−80%) of resulting cyclized ketones **2d**−**i**. A 1,2-methyl migration is extendible to epoxides **4b**−**d** bearing various arylalkynyl susbtituents (Ar = 4-$MeOC_6H_4$, 4-FC_6H_4, and 2-thienyl, entries 9−11), giving the resulting ketones **6b**−**d** in 81−89% yields. Treatment of epoxide **4e** with $AgSbF_6$ (5%) in CH_2Cl_2 (23 °C, 10 min) provided cyclized ketones **6e** in 78% yield, of which the phenyl group was 1,2-shifted to the neighboring indenyl C(1)-carbon (entries 12). The same silver-catalyzed cycloisomerization of epoxides **4f** provided desired ketone **6f** (72%) with a ring expansion.

The generation of diketone **5a** from epoxide **4a** (Table 1, entry 5) is likely formed from water oxidation of α-carbonyl Au(I)−benzylidene **B**.[9] To verify this intermediacy, as depicted in Scheme 1, epoxide **1b** was treated with $PPh_3AuCl/AgSbF_6$ (5/2 mol %) and Ph_2SO[4b] (4 equiv) in CH_2Cl_2 (23 °C, 48 h), giving a 68% yield of diketone **5b**. Treatment of epoxide **4a** with styrene or ethoxyethene (10 equiv) with the same Au(I)/Ag(I) catalyst delivered cyclopropane and acetal

Scheme 1



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(8) Screening of catalyst activity over commonly used catalysts is provided in Table S1, Supporting Information.

products **7a** and **7b** in 78−81% yields. With additional trapping experiments,[10] we confirmed the intermediacy of gold−carbenoids **B**, but we could not identify Ag(I)−-carbenoid species because the production of cyclized ketone **6a** from epoxide **2a** was unaffected by these reagents. The 1,2-phenyl shift in the Ag(I)-catalyzed transformation of epoxide **4e** into cyclized ketone **6e** (Table 2, entry 12) is unusual as we observed different 1,2-migration patterns for Ag(I)-catalyzed rearrangement of the model molecule **4g**, which gave ketone **3c** and **3d** in a 89% combined yields (**3c**/**3d** = 6.4) via expected tertiary cationic intermediate.

Accordingly, we envisage that PPh_3Au^+ initially complexes the internal alkyne of species **1a** to induce a 7-*endo*-cyclization to yield seven-membered oxacyclic species **A**, of which the gold−enol moiety promotes cleavage of the ether ring to form Au(I)−carbene **B** (Scheme 2). This carbene species is also represented by its pentadienyl cationic resonance **B′** to induce an electrocyclization cyclization[11] to generate 1-indanyl cation **C**. A subsequent 1,2-hydride shift[12] of this intermediate gave 2-indanyl cation **C** that formed desired 3-1*H*-indenyl ketone **2a** after elimination of PPh_3Au^+. In the case of trisubstituted epoxide **4a**, PPh_3Au^+ species generates the corresponding intermediate **B″** with its methyl and PhCO groups at the inner positions to inhibit the cyclization. For silver catalysis, prior rearrangemnt of epoxide to ketone, followed by ketone−alkyne metathesis,[13] i.e., **6a** → **3b** → **6a**, is unlikely to occur under reaction conditions (see Table 1, entry 7, and Scheme 1), and we propose that the mechanism likely involves a 1,2-phenyl shift of intermediate **A′** to give oxonium species **E**, which ultimately gave desired ketone **6e** through a rearrangement of oxetane intermediate **F**.

Scheme 2

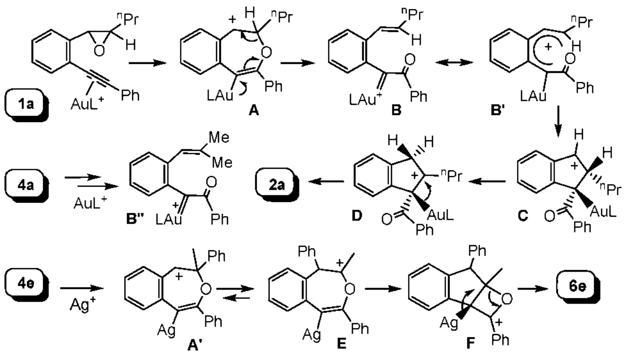
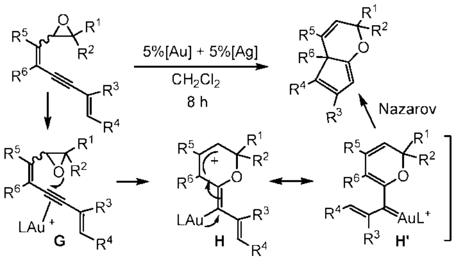
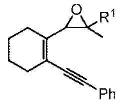
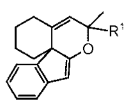
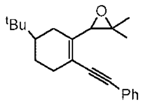
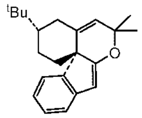
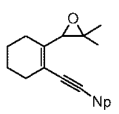
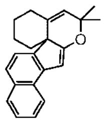
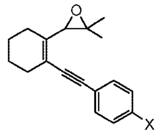
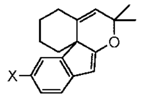


Table 3. Cycloisomerization of Nonaromatic Epoxides to Polycyclic 2*H*-Pyrans



entries	epoxides[a]	products[c]	yields
			
(1)	R^1 = Me (**8a**)	**9a**	86%
(2)	R^1 = Et (**8b**)[b]	**9b**	71%, dr = 1:1
(3)	 **8c**	 **9c**	77%, dr > 30
(4)	 **8d**	 **9d**	72%
			
(5)	X = F (**8e**)	**9e**	49%
(6)	X = Me (**8f**)	**9f**	78%

[a] [Epoxides] = 0.1 M, 23 °C, CH_2Cl_2. [b] The *E*/*Z* ratios of the epoxides are provided in the Supporting Information. [c] Yields were reported after elution from a silica column.

The diversity of this epoxide−alkyne cycloisomerization is also reflected by formation of complex 2*H*-pyran compounds **9a−f** from nonaromatic epoxides **8a−f** catalyzed by $PPh_3AuCl/AgSbF_6$ (5/5 mol %) in CH_2Cl_2 at 23 °C. Herein, the key intermediate **H** is formed by a 6-*exo-dig* attack of the epoxide at the alkyne of π-intermediate **G**, and its structure is best represented by its gold−carbenoid resonance form **H′**, which triggers a Nazarov-type cyclization[11] to give the observed products.

Table 3 shows the applicability of this cycloisomerization to trisubstituted epoxides **8a−f** with varied epoxide R^2 and aryl groups; the products yields were generally high (>71%) except for fluorophenyl derivative **9f** (49% yield). The carbenoid character of species **H′** was verified by a trapping experiment with Ph_2SO oxidation.[4b,10]

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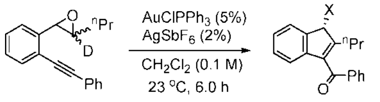
(9) Taduri, B. P.; Sohel, S. M. A.; Cheng, H.-M.; Liu, R.-S. *Chem. Commun.* **2007**, 2530.

(10) Additional trapping experiments to verify gold−carbenoids **B** and **H′** are depicted in Scheme S1, Supporting Information.

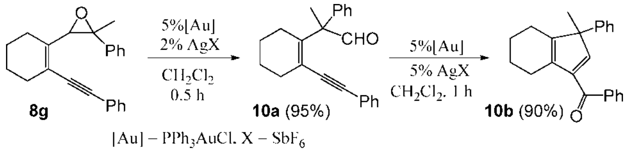
(11) (a) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (b) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019.

(12) We prepared deuterium labeled **d$_1$-1a**, and its cycloisomerization provided highly deuterated ketone **d$_1$-2a** (97%), clearly indicative of 1,2-hydride shift. NMR spectra data of **d$_1$-1a** and **d$_1$-2a** are provided in the Supporting Information.

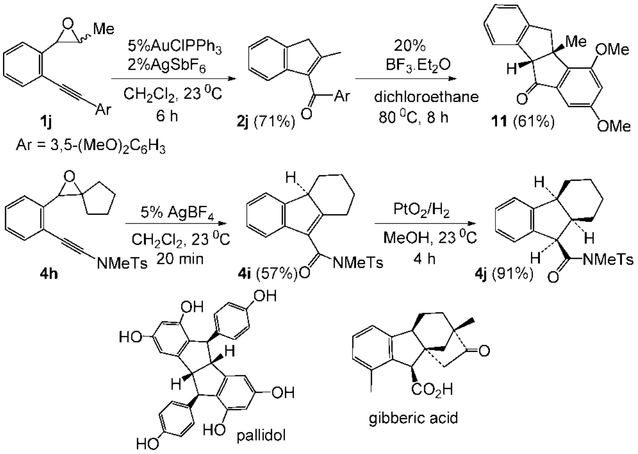


(13) (a) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493. (b) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259. (c) Jin, T.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 3137.

Scheme 3



Scheme 4



Scheme 3 provides additional diversified cycloisomerization of epoxide **8g**, which was initiated by an epoxy rearrangement. Treatment of epoxide **8g** with AgSbF$_6$ (5 mol %) and PPh$_3$AuCl/AgSbF$_6$ (5/2%) in CH$_2$Cl$_2$ (23 °C) for a brief time (1.0 and 0.5 h), respectively, gave aldehyde **10a** in 95% yield. A subsequent oxo-alkyne metathesis[13,14] of compounds **10a** with PPh$_3$AuCl/AgSbF$_6$ (5/5 mol %) furnished distinct 3-1*H*-indenyl ketone **10b** efficiently.

Scheme 4 shows the value of these new cyclizations for a rapid construction of the central cores of natural pallidol and gibberic acid, as represented by ketones **11** and **4j**, respectively. Treatment of epoxide **1j** with PPh$_3$AuCl(5%)/AgSbF$_6$(2%) provided desired ketone **2j** (71%), which underwent BF$_3$-catalyzed Nazarov cyclization to give tetracyclic ketone **11** (61%). Treatment of epoxide **4h** with AgBF$_4$ (5%) led to ring expansion to give tricyclic ketone **4i** (57%), which was treated by PtO$_2$/H$_2$ in CH$_3$OH (23 °C, 4 h) to give ketone **4j** having the stereochemistry matching the core of gibberic acid; the structure of **4j** was determined by ^{1}H NOE spectra.

In summary, we report gold-catalyzed cycloisomerizations of epoxide−alkyne functionalities in both aromatic and nonaromatic systems, leading to 3-1*H*-indenyl ketones and polycyclic 2*H*-pyrans, respectively. Gold-catalyzed cycloisomerization is proposed to involve generation of gold-carbenoid intermediates, which are identified by a series of trapping experiments.[10] Although AgSbF$_6$ is very efficient for cycloisomerization of aromatic trisubstituted epoxides, the cyclization pathway is distinct from those of gold catalyst. For epoxides of special types such as species **8g**, Au(I) gave distinct 3-1*H*-indenyl ketones, reflecting the effects of epoxide substituents. The diversity of such cycloisomerizations enables one-pot construction of various carbocyclic and heterocyclic frameworks, including the cores of pallidol[6a] and gibberic acid.[6b]

Acknowledgment. We thank the National Science Council, Taiwan, for supporting this work.

Supporting Information Available: NMR spectra and spectral data of new compounds **1a−j**, **2a−j**, **3a−d**, **4a−j**, **5a**,**b**, **6a−f**, **7a**,**b**, **8a−h**, **9a−f**, **10a**,**b**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Krische and co-workers reported[13a] AgSbF$_6$-catalyzed aldehyde/alkyne metathesis at elevated temperatures (50−80 °C) rather than ambient conditions (23 °C).

(15) During preparation of this manuscript, Hashmi reported gold-catalyzed cycloisomerization of aromatic 1,2-disubsituted epoxides using different gold catalysts, which overlaps with the initial portion of this work. We note that the gold−carbenoid intermediate was not identified therein. See: Hashmi, A. S. K.; Buhrle, M.; Salathe, R.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 2059 (published online August 19, 2008)