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Tandem reactions of *cis*-2-acyl-1-alkynyl-1-aryl cyclopropanes tuned by gold(I) and silver(I) catalysts: efficient synthesis of pyran-fused indene cores and 2,4,6-trisubstituted phenols†

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Received (in Cambridge, UK) 8th May 2009, Accepted 5th June 2009
First published as an Advance Article on the web 29th June 2009
DOI: 10.1039/b909181e

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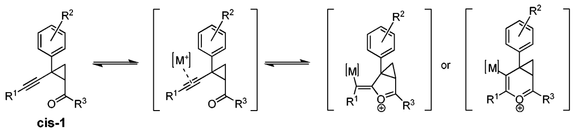
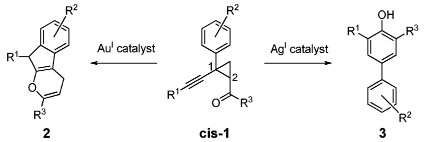
Published on 29 June 2009 on http://pubs.rsc.org | doi:10.1039/B909181E

Tandem reactions of *cis*-2-acyl-1-alkynyl-1-aryl cyclopropanes 1 tuned by gold(I) and silver(I) catalysts are described, which afford selectively the key pyran-fused indene cores 2 and the 2,4,6-trisubstituted phenols 3 in good yields, respectively.

Gold- or silver-catalyzed reactions have recently received increasing attention from chemists.[1,2] These metal catalysts have shown their exceptional ability to activate the alkynyl species,[3,4] among which, carbonyl alkyne-involved transformations have taken a particularly important part in developing synthetic methodologies for the construction of furans,[5a–c] 3(2H)-furanones,[5d,e] functionalized aromatic compounds,[5f–m] as well as 1-allenylisochromenes.[5n] In these reactions, the key oxonium intermediates are proposed, which could be terminated by various interesting domino processes. Based on these pioneering works, we envisaged that *cis*-2-acyl-1-alkynyl-1-aryl cyclopropanes **1** might also initiate a cyclic oxonium ion intermediate under the coordination of an Au or Ag cation with the triple bond; then, cleavage of the cyclopropane is expected to trigger some unknown cascade processes to construct synthetically useful building blocks (Scheme 1). Interestingly, we found that gold and silver catalysts could trigger two different processes to give two kind of products **2** and **3** (Scheme 2). In Au-catalyzed reactions, a tandem cyclization/isomerization/Friedel–Crafts reaction took place to form a key pyran-fused indene moiety of the naturally occurring indenochromone and wrightiadione compounds,[6] while in the Ag catalyzed reaction, a cyclization/isomerization process occurred to deliver substituted phenols **3**. Similar rearrangements under thermal conditions or the catalysis of group 6 metals have been reported earlier,[7] but the reactions were limited to transform ethynyl-substituted cyclopropanes to single substituted phenols. It is important that in the silver(I)-catalyzed reactions, the formed substituted phenols with three different substituents at C-2, C-4 and C-6 positions are not easily accessed by known methods, and could be potentially useful in material science.[8] Herein, we present our experimental results.



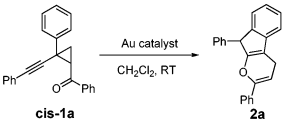
Scheme 1 The formation of two possible oxonium ions.



Scheme 2 Different tandem reactions tuned by gold(I) and silver(I) catalysts.

Our initial studies using Au catalysts commenced with the model substrate, **cis-1a**, which was readily prepared by the Simmons–Smith cyclopropanation[9] of (*Z*)-2-en-4-yn-1-ols[10] and subsequent oxidation (see the ESI†). As indicated in Table 1, in the presence of $(PPh_3)AuOTf$ in CH_2Cl_2, **cis-1a** was converted to **2a** in a good yield of 85% after 2 h. When $AuCl_3$ or AuCl were employed, the reaction systems became complex and only less than 10% yield of **2a** were obtained in two cases. Decreasing the catalyst loading to 5 mol% led to a longer reaction time and gave a lower yield of **2a**. Thus, the condition of entry 1 was selected for further expanding substrate scope.

Table 1 Effect of Au catalysts on the reaction of **cis-1a**



Entry	Catalyst	Amount	Time	Yield (%)[ab]
1	$(PPh_3)AuOTf$	10 mol%	2 h	85
2	$AuCl_3$	10 mol%	30 min	<10
3	AuCl	10 mol%	1 h	<10
4	$(PPh_3)AuOTf$	5 mol%	5 h	74

[a] Isolated yield. [b] Phenol **3a** was not observed.

During our above optimization, we interestingly found in the presence of AgOTf in CH_2Cl_2, **cis-1a** gave rise to **3a** in moderate yield, without **2a** being observed (Table 2, entry 1). This inspired us to make some investigations on this reaction. When we changed the silver catalysts or the solvents, lower yields were observed (entries 2–6). Then some additives were tested, and significantly, when 1.0 equiv $NaHCO_3$ was added, the yield of **3a** increased dramatically (entry 9). Further experiments showed that decreasing the catalyst loading or

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/b909181e

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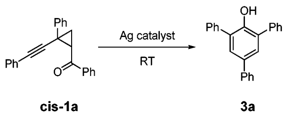
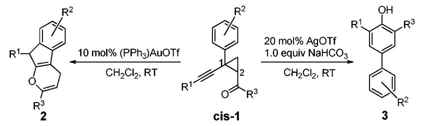
Table 2 Effect of Ag catalysts on the reaction of **cis-1a**

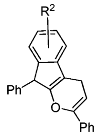
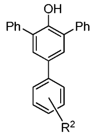
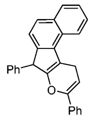
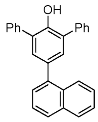
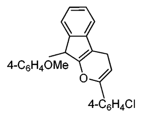
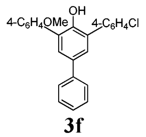
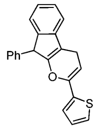
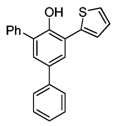
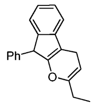
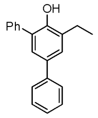


Entry	Catalyst[a]	Solvent	Additive (equiv.)	Time	Yield (%)[bc]
1	AgOTf	CH_2Cl_2	—	1.5 h	53
2	$AgSbF_4$	CH_2Cl_2	—	2 h	20
3	$AgBF_4$	CH_2Cl_2	—	2 h	13
4	AgOTf	DCE	—	40 min	50
5	AgOTf	Toluene	—	24 h	30
6	AgOTf	CH_3NO_2	—	15 min	38
7	AgOTf	CH_2Cl_2	PPh_3 (0.2)	—	0
8	AgOTf	CH_2Cl_2	Cs_2CO_3 (0.2)	—	0
9	AgOTf	CH_2Cl_2	$NaHCO_3$ (1.0)	50 min	80
10[d]	AgOTf	CH_2Cl_2	$NaHCO_3$ (1.0)	14 h	72
11	AgOTf	CH_2Cl_2	$NaHCO_3$ (2.0)	6 h	74

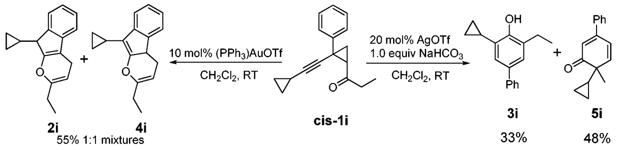
[a] Conditions: 20 mol% of silver salts were used. [b] Isolated yield. [c] Pyran-fused indene product **2a** was not observed. [d] 10 mol% of silver salts were used.

Table 3 Tandem reactions of various *cis*-2-acyl-1-alkynyl-1-aryl cyclopropanes tuned by Au(I) and Ag(I) catalysts



Entry	Product **2**	Yield (%)[a]	Product **3**	Yield (%)[a]
				
1	R^2 = H **2a**	85	R^2 = H **3a**	80
2	R^2 = 4-OMe **2b**	80	R^2 = 4-OMe **3b**	81
3	R^2 = 2-OMe **2c**	86	R^2 = 2-OMe **3c**	58
4	R^2 = 4-F **2d**	94	R^2 = 4-F **3d**	68
5	 **2e**	83	 **3e**	70
6	 **2f**	90	 **3f**	57
7	 **2g**	85	 **3g**	53
8	 **2h**	83	 **3h**	67

[a] Isolated yield.



Scheme 3 Tandem reactions of **cis-1i**.

increasing the amounts of $NaHCO_3$ led to a longer reaction time and gave a lower yield of **3a** (entries 10 and 11). Thus, the condition of entry 9 was selected as the general reaction condition.

Following the above two optimized conditions, we investigated a range of *cis*-2-acyl-1-alkynyl-1-aryl cyclopropanes. As depicted in Table 3, we first performed the Au(I)-catalyzed reactions, and found that substrates containing both the electron-rich and electron-deficient groups on the C-1 phenyl ring were effective in this reaction, and all gave the expected products **2a–d** in good to high yields (entries 1–4). Changing the C-1 phenyl group to l-naphthyl still gave a good result (entry 5). Replacing the substituents R^1 and R^3 with other aromatic or aliphatic groups did not affect the reaction significantly, and the corresponding products **2f–h** were obtained in good yields (entries 6–8). As for the Ag(I)-catalyzed reactions, different substrates were also tolerated just like the Au(I)-catalyzed reaction, but the yields were lower than the corresponding Au-catalyzed examples. Notably, in all Au-catalyzed reactions, phenol products were not detected and isolated, except for some unknown side products. For the case of Ag-catalyzed reactions, the pyran-fused indene products **2** were not observed.

To further expand the substrate scope, employment of the substrate **cis-1i** bearing two aliphatic groups R^1 and R^3 under Au(I) catalysis led to the formation of two inseparable isomers **2i** and **4i** in 55% total yield (Scheme 3),[11] in which formation of **4i** resulted from a formal 1,3-H shift in **2i**. As for the Ag(I)-catalyzed reaction of **1i**, the desired product **3i** was only isolated in 33% yield, wherein an unexpected by-product **5i** was formed.[12] Moreover, the substrate with C-1 alkyl substituent instead of aryl group was examined, neither the pyran-fused indene product nor the phenol product was isolated in either reaction.

Based on the results above together with some literature reports,[4c,5,7,13] two plausible mechanisms were envisioned (Scheme 4). For Au(I)-catalyzed reaction as presented in cycle A, a cationic Au(I) species would first coordinate with the triple bond. The subsequent nucleophilic attack of the carbonyl group took place *via* a 5-*exo-dig* cyclization to give intermediate **7**, which generated **8** after cleavage of the cyclopropane. Then, gold carbene **8** underwent an intramolecular Friedel–Crafts reaction and protodemetallation to yield products **2**, with the Au(I) species being regenerated. For Ag(I)-catalyzed process (cycle B), the coordination of AgOTf with both the triple bond and the ketone oxygen led to the cleavage of the cyclopropane to give **10**; subsequently, **10** underwent a cyclization to deliver oxepin **11**, which transformed into arene oxide **12**.[7,13] Then, under the catalysis of AgOTf, now as a Lewis acid, ring opening of **12** and migration of R^3 finally led to the formation of **3**.

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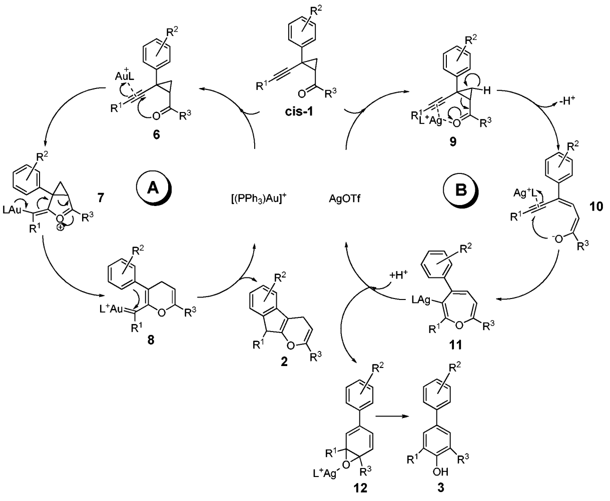
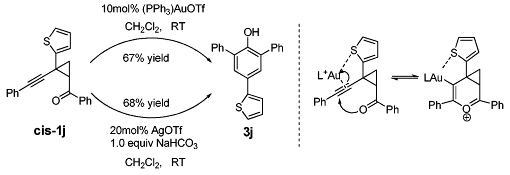


Scheme 4 Proposed reaction mechanisms.



Scheme 5 Tandem reactions of **cis-1j**.

Further investigation showed that when there was a ligand atom near the triple bond, the Au-catalyzed reaction could also undergo a 6-*endo-dig* cyclization to give the same product as the Ag-catalyzed reaction. The substrate **cis-1j** with a C-1 thienyl group transformed into the phenol product **3j** under Au(I) catalysis, probably because in this case the Au atom would coordinate with both the sulfur atom and the triple bond to trigger a 6-*endo-dig* cyclization process (Scheme 5).

In summary, we have developed two transition-metal catalyzed tandem reactions of *cis*-2-acyl-1-alkynyl-1-aryl cyclopropanes. These reactions can be tuned by using gold(I) or silver(I) as the catalyst. From common substrates, structurally divergent compounds can be readily synthesized by our tandem protocols.

Notes and references

1 For recent reviews on gold-catalyzed reactions, see: (*a*) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180; (*b*) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395; (*c*) A. M. Echavarren and E. Jiménez-Núñez, *Chem. Commun.*, 2007, 333; (*d*) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239; (*e*) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326; (*f*) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351.

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3 For selected very recent examples of gold-catalyzed alkyne activation, see: (*a*) G.-Y. Lin, C.-W. Li, S.-H. Hung and R.-S. Liu, *Org. Lett.*, 2008, **10**, 5059; (*b*) C. Zhang, D.-M. Cui, L.-Y. Yao, B.-S. Wang, Y.-Z. Hu and T. Hayashi, *J. Org. Chem.*, 2008, **73**, 7811; (*c*) Y. Zou, D. Garayalde, Q. Wang, C. Nevado and A. Goeke, *Angew. Chem., Int. Ed.*, 2008, **47**, 10264; (*d*) J.-M. Tang, T.-A. Liu and R.-S. Liu, *J. Org. Chem.*, 2008, **73**, 8479; (*e*) X.-Y. Liu and C.-M. Che, *Angew. Chem., Int. Ed.*, 2008, **47**, 3805; (*f*) T. Jin and Y. Yamamoto, *Org. Lett.*, 2008, **10**, 3137; (*g*) M.-C. Cordonnier, A. Blanc and P. Pale, *Org. Lett.*, 2008, **10**, 1569; (*h*) G. Li, X. Huang and L. Zhang, *J. Am. Chem. Soc.*, 2008, **130**, 6944; (*i*) S. G. Sethofer, S. T. Staben, O. Y. Hung and F. D. Toste, *Org. Lett.*, 2008, **10**, 4315; (*j*) D. J. Gorin, I. D. G. Watson and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 3736; (*k*) P. H.-Y. Cheong, P. Morganelli, M. R. Luzung, K. N. Houk and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 4517; (*l*) I. D. G. Watson, S. Ritter and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 2056.

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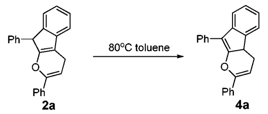
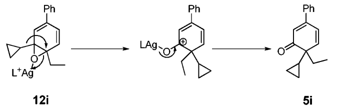
11 **2i** and **4i** were obtained as inseparable mixtures and identified by comparing their spectra with **2a** and **4a**. **2a** could be converted completely to **4a** by heating.



12 This major by-product might be formed from the intermediate **12i**



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