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Gold-Catalyzed Cascade Annulations of 2-(Ynol)aryl Aldehydes: Facile Synthesis of Benzochromanes and Benzobicyclo[*n*.3.1]acetals

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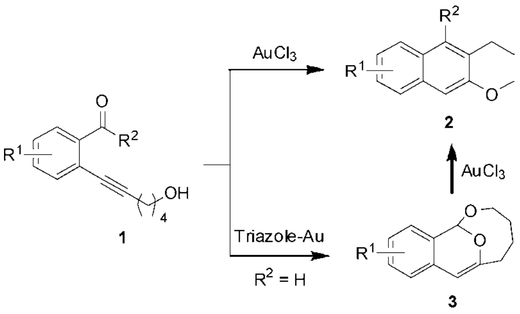
ABSTRACT

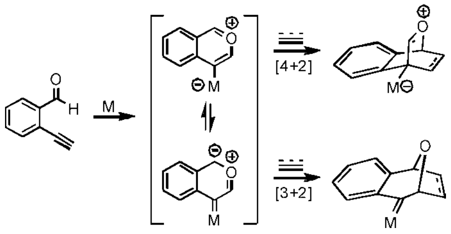


Gold-catalyzed reactions of 2-(ynol)aryl aldehydes were investigated. Benzochromanes were obtained from the reaction when $AuCl_3$ was employed as the catalyst, whereas benzobicyclo[*n*.3.1]acetals were produced when triazole−gold was employed as the catalyst. Plausible mechanisms are discussed.

The reactivity of pyrylium intermediates—formed from 2-alkynylaryl aldehydes by the mediation of transition metals or acids—has been well investigated in recent years, and a great number of synthetic interesting compounds have been obtained through this versatile methodology.[1,2] Two pathways—[4 + 2] or [3 + 2]—were generally considered for the addition of the intermediates to unsaturated carbon−carbon bonds (Scheme 1).

The high reactivity of the pyrylium intermediate toward carbon−carbon multiple bonds is attributed to its electrophilic property; thus, we wondered what novel transformations may be engendered if a nucleophile such as a hydroxyl group was introduced in the substrate. Giving gold's notable affinity toward alkynes[3] and our continuous interest on gold chemistry,[4] we investigated the gold-catalyzed trasformations of 2-alkynylaryl aldehydes bearing a nucleophile in the molecule. Herein, we wish to report the facile synthesis of

Scheme 1



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(1) For recent reviews on the reactivity of pyrylium intermediates, see: (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075. (c) Asao, N. *Synlett* **2006**, 1645. (d) Kusama, H.; Iwasawa, N. *Chem. Lett.* **2006**, *35*, 1082. (e) Kotha, S.; Misra, S.; Halder, S. *Tetrahedron* **2008**, *64*, 10775. (f) Das, A.; Sohel, S. M. A.; Liu, R.-S. *Org. Biomol. Chem.* **2010**, *8*, 960.

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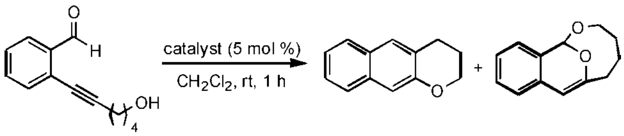
benzochromanes[5] and benzobicyclo[*n*.3.1]acetals[6] via a gold-catalyzed cascade annulation of 2-(ynol)aryl aldehydes or ketones.

2-(6-Hydroxyhex-1-ynyl)benzaldehyde **1a** was employed as the substrate for optimizing the conditions. The results are outlined in Table 1. To our satisfaction, benzochromane **2a** was isolated in good yields when gold(I or III) chloride was used as the catalyst (Table 1, entries 1 and 2). Interestingly, benzobicyclo[4.3.1]acetal[7] **3a** was obtained when cationic gold, silver, or copper catalysts were employed in the reaction, and the triazole−gold[8] seemed to be the best catalyst for this transformation (Table 1, entries 3−7).

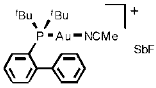
Table 1. Optimization of Reaction Conditions[a]



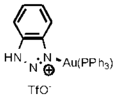
1a **2a** **3a**

entry	catalyst	yield[b]/[%] 2a	3a
1	AuCl	79	0
2	***AuCl$_3$***	***86***	***0***
3	AgOTf	40	28
4[c]	Cu(OTf)$_2$	0	53
5	Ph$_3$PAuCl/AgOTf	36	23
6[c]	**Au-1**	0	58
7	***Triazole-Au***	***0***	***82***

Au-1:



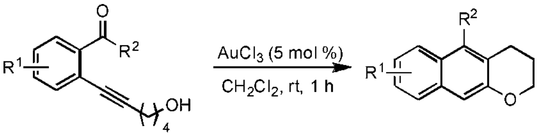
Triazole-Au:



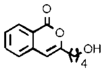
[a] General conditions: **1a**, 0.2 mmol; catalyst, 5 mol %; CH$_2$Cl$_2$, 1.0 mL. [b] Isolated yields. [c] Prolonged to 12 h.

Next, various 2-(ynol)aryl aldehydes were subjected to our gold-catalyzed cascade annulations. By using AuCl$_3$ as the catalyst, several benzochromanes—possessing either electron-donating or electron-withdrawing groups on the aromatic rings—were obtained in moderate to good yields under the same conditions (Table 2, entries 1−5). 2-(Ynol)aryl ketones were also investigated in the reaction, and the corresponding products were obtained; however, prolonged reaction time or higher temperature was needed (Table 2, entries 6 and 7). A 2-(ynol)aryl ester was also subjected to this cascade annulation reaction, but instead of the corresponding benzochromane, the product **4** was accompanied by starting material (Table 2, entry 8). These substrates were also employed in the triazole−Au-catalyzed transformation to the corresponding benzobicyclo[4.3.1]acetal (Table 3). Compounds **3b**, **3c**, and **3f** could be isolated in good yields from the reactions (Table 3, entries 1, 2, and 5). However, none of the desired product could be obtained when substrates **1d**, **1e**, and **1g**−**1i** were utilized, which may be due to either the low reactivity of the substrates or the low stability of the products (Table 3, entries 3, 4, and 6−8).

Table 2. AuCl$_3$-Catalyzed Cascade Annulations of (2-Ynol)aryl Aldehydes to Benzochromanes[a]



1 **2**

entry	R^1/R^2	yield[b]/[%]
1	4-Me/H (**1b**)	**2b**, 72
2	5-MeO/H (**1c**)	**2c**, 68
3	4,5-(MeO)$_2$/H (**1d**)	**2d**, 52
4	4,5-OCH$_2$O/H (**1e**)	**2e**, 54
5	5-F/H (**1f**)	**2f**, 82
6[c]	H/Me (**1g**)	**2g**, 43
7[d]	H/Ph (**1h**)	**2h**, 36
8[c]	H/OMe (**1i**)	 **4**, 39

[a] General conditions: **1**, 0.2 mmol; AuCl$_3$, 5 mol %; CH$_2$Cl$_2$, 1.0 mL. [b] Isolated yields. [c] Prolonged to 12 h. [d] At 50 °C for 12 h.

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(2) Selected notable examples, see: (a) Asao, N.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (c) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (d) Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226. (e) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814. (f) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028. (g) Oh, C. H.; Lee, J. H.; Lee, S. J.; Kim, J. I.; Hong, C. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7505. (h) Oh, C. H.; Lee, J. H.; Lee, S. J.; Yi, H. J.; Hong, C. S. *Chem.—Eur. J.* **2009**, *15*, 71. (i) Bhunia, S.; Wang, K.-C.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5063. (j) Hsu, Y.-C.; Ting, C.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2009**, *131*, 2090. (k) Yue, D.; Cá, N. D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581. (l) Yue, D.; Cá, N. D.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3381. (m) Hu, Z.-L.; Qian, W.-J.; Wang, S.; Wang, S.-Z.; Yao, Z.-J. *Org. Lett.* **2009**, *11*, 4676. (n) Hu, Z.-L.; Qian, W.-J.; Wang, S.; Wang, S.-Z.; Yao, Z.-J. *J. Org. Chem.* **2009**, *74*, 8787. (o) Dyker, G.; Hildebrandt, D.; Liu, J.; Merz, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4399. (p) Hildebrandt, D.; Hüggenberg, W.; Kanthak, M.; Dyker, G. *Chem. Commun.* **2006**, 2260.

(3) Selected recent reviews on gold catalysis, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (f) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

(4) For gold chemistry from our group, see: (a) Liu, L.-P.; Xu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642. (b) Liu, L.-P.; Hammond, G. B. *Chem. Asian J.* **2009**, *4*, 1230. (c) Liu, L.-P.; Hammond, G. B. *Org. Lett.* **2009**, *11*, 5090. (d) Wang, W.; Xu, B.; Hammond, G. B. *J. Org. Chem.* **2009**, *74*, 1640.

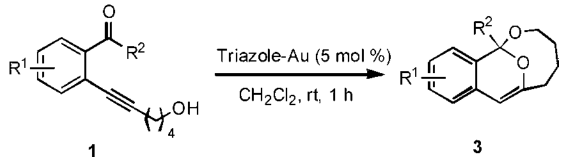
(5) (a) Ferreira, S. B.; da Silva, F. de C.; Pinto, A. C.; Gonzaga, D. T. G.; Ferreira, V. F. *J. Heterocycl. Chem.* **2009**, *46*, 1080. (b) Shi, Y.-L.; Shi, M. *Org. Biomol. Chem.* **2007**, *5*, 1499.

(6) (a) Kotsuki, H. *Synlett* **1992**, 97. (b) Jun, J.-G. *Synlett* **2003**, 1759.

(7) Yu, X.; Ding, Q.; Wang, W.; Wu, J. *Tetrahedron Lett.* **2008**, *49*, 4390.

(8) (a) Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2009**, *131*, 12100. (b) Chen, Y.; Yan, W.; Akhmedov, N. G.; Shi, X. *Org. Lett.* **2010**, *12*, 344. (c) Wang, D.; Ye, X.; Shi, X. *Org. Lett.* **2010**, *12*, 2088.

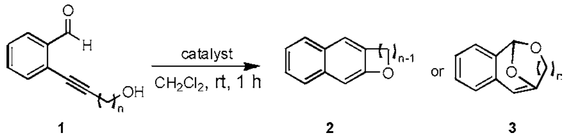
Table 3. Triazole−Au-Catalyzed Cascade Annulations of (2-Ynol)aryl Aldehydes to Benzobicycloacetals[a]



entry	R^1/R^2	yield[b]/[%]
1	4-Me/H (**1b**)	**3b**, 76
2	5-MeO/H (**1c**)	**3c**, 69
3	4,5-(MeO)$_2$/H (**1d**)	complex
4	4,5-OCH$_2$O/H (**1e**)	complex
5	5-F (**1f**)	**3f**, 88
6	H/Me (**1g**)	no reaction
7	H/Ph (**1h**)	no reaction
8	H/OMe (**1i**)	no reaction

[a] General conditions: **1**, 0.2 mmol; triazole−Au, 5 mol %; CH$_2$Cl$_2$, 1.0 mL. [b] Isolated yields.

Table 4. Length Effect of Side Chain in the Reaction[a]



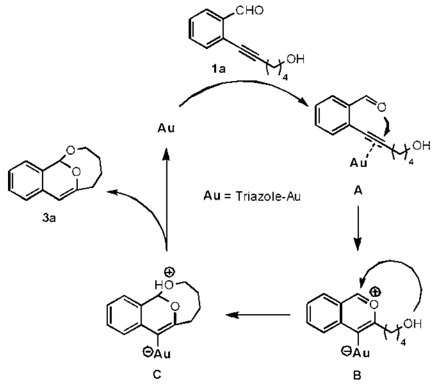
entry	*n*	catalyst	yield[b]/[%]
1	1 (**1j**)	AuCl$_3$	complex
2	2 (**1k**)	AuCl$_3$	complex
3	3 (**1l**)	AuCl$_3$	**2l**, 38
4	1 (**1j**)	triazole−Au	**3j**, —[c]
5	2 (**1k**)	triazole−Au	**3k**, 78
6	3 (**1l**)	triazole−Au	**3l**, —[c]

[a] General conditions: **1**, 0.2 mmol; catalyst, 5 mol %; CH$_2$Cl$_2$, 1.0 mL. [b] Isolated yields. [c] Product was found by TLC.

We proceeded to study the effect of length on the side chain of the substrate. Substrates **1j**−**1k** were synthesized and subjected to our gold-catalyzed annulation (Table 4). When AuCl$_3$ was used as the catalyst, only product **2l** (*n* = 3) could be isolated from the corresponding reaction. No product was obtained from either substrates **1j** or **1k** possibly due to the short length of their side chain. On the other hand, only **3k**[7] (*n* = 2) was isolated from the reaction mixture when triazole−Au was employed as the catalyst. Products **3j** and **3l** were detected by TLC, but because of their poor stability, they were not isolable even when an alumina chromatography column was used for their purification.

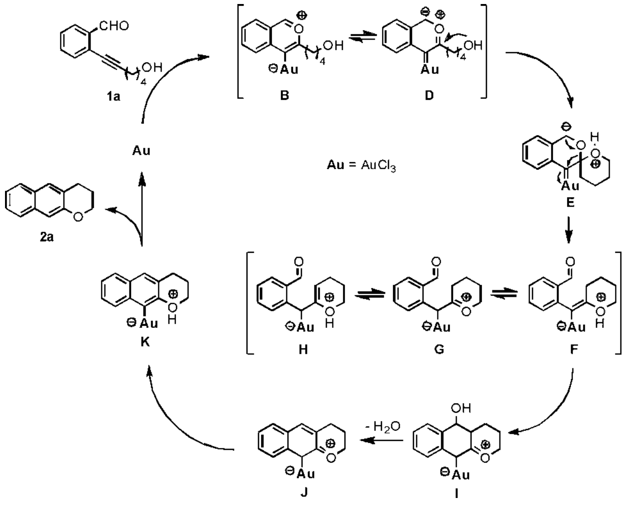
For the formation of these interesting compounds, we proposed that the pyrylium intermediate **B**[1,2] formed first and then cyclized to form **C**. A subsequent proton deauration would give product **3** (Scheme 2).

Scheme 2. Proposed Mechanism for the Formation of Benzobicycloacetals



Intermediate **B** could also transform to **D**[9] from which **E** is formed by an intramolecular attack. Intermediate **E** could then rearrange to **F**, which may exist in equilibrium with intermediates **G** and **H**.[10] Intermediate **I** is formed through an intramolecular aldol reaction, transforming itself into **J** by dehydration. Intermediate **J** would then rearrange into **K** before furnishing the product **2** (Scheme 3).

Scheme 3. Proposed Mechanism for the Formation of Benzochromanes



Although the mechanism proposed in Scheme 3 is plausible, a hydration pathway[11] cannot be ruled out (Scheme 4). Thus, intermediate **L** could be generated from the hydration of **B**. Subsequent aldol reaction, hemiketalization, and dehydration would generate the product **2**. This pathway

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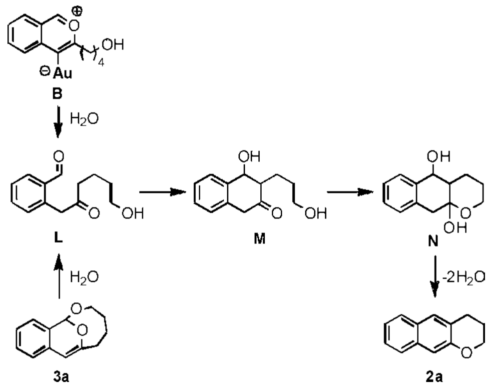
(9) (a) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289. (b) Oh, C. H.; Lee, S. M.; Hong, C. S. *Org. Lett.* **2010**, *12*, 1308.

(10) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442.

(11) Zhu, J.; Grigoriadis, N. P.; Lee, J. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 9342.

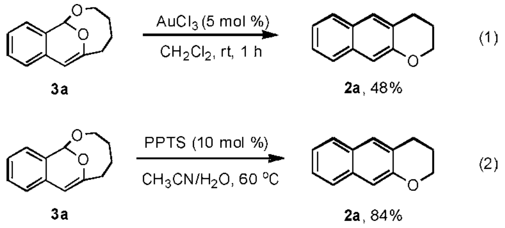
Scheme 4. Proposed Alternative Mechanism for the Formation of Benzochromanes



is available for compound **3**, as confirmed by two controlled reactions (Scheme 5).

In summary, we have developed a facile synthesis of benzochromanes and benzobicycloacetals from the gold-catalyzed cascade annulations of 2-(ynol)aryl aldehydes and have advanced mechanisms for the formation of these compounds.

Scheme 5. Controlled Reactions



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Supporting Information Available: The ^{1}H and ^{13}C NMR spectroscopic data, HRMS and IR of the new compounds shown in Tables 1−4 and Scheme 5, and a detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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