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Platinum- and Gold-Catalyzed Hydrative Carbocyclization of Oxo Diynes for One-Pot Synthesis of Benzopyrones and Bicyclic Spiro Ketones

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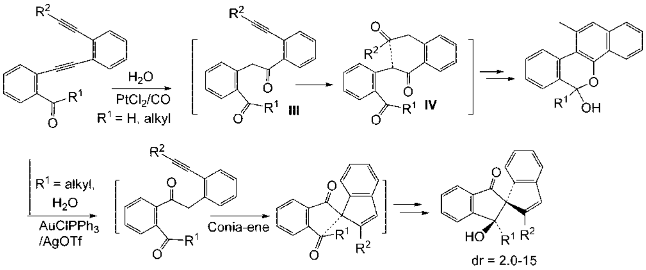
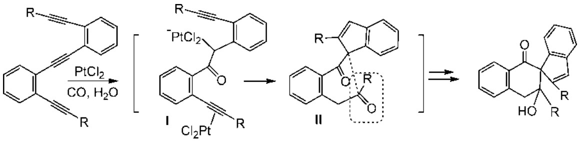
ABSTRACT



We report a one-pot synthesis of benzopyrones and tricyclic spiroketones from hydrative carbocyclization of oxodiyne substrates catalyzed by $PtCl_2$ and $PPh_3AuCl/AgOTf$, respectively. The distinct carbocyclizations with Pt and Au catalysts stem from their altered regioselectivity in the oxo-assisted hydration of the neighboring alkyne carbons.

Regiocontrolled metal-catalyzed hydrative coupling of an alkyne with another functionality is synthetically useful as this procedure provides oxygenated carbocyclic frameworks from readily available alkynes.[1−5] Known examples are reported for 1,*n*-diynes,[1] 1-yne-5-enones,[2] 1-en-5-ynes,[3] 1-allen-*n*-ynes[4] ($n = 5-7$), and triynes.[5] With $PtCl_2$ catalyst, we found that the neighboring ketone of 2-ketonyl-1-alkynylbenzenes selectively controlled the hydration regioselectivity of its tethered alkyne via formation of benzopyrilium species (eq 1).[6] We applied this ketone-assisted alkyne hydration to the one-pot synthesis of bicyclic spiro ketones using suitable triynes;[5] the reaction protocol is depicted in Scheme 1. In this hydrative carbocyclization, the ketone group of initial intermediate **I** controls a selective hydration of the neighboring propynyl C(2) carbon, whereas its

Scheme 1



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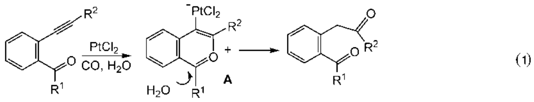
10.1021/ol801601q CCC: $40.75

platinum acyl group undergoes an addition of its enolate form to the remaining π-propyne to form intermediate **II**.



Benzopyrone frameworks are commonly found in naturally occurring compounds including amottin **I**, givocarcin **V**, and defucogilvocarcin **V**, **M**.[7] On the basis of oxo-assisted alkyne hydration depicted in eq 1,[8,9] we sought a facile synthesis of benzopyrone derivatives via platinum-catalyzed hydrative carbocyclization of readily available oxodiynes that undergo two consecutive selective alkyne hydrations to give key triketone intermediates **IV** (Scheme 2); the ketone of species **III** is presumed to be equally active and selective in the second alkyne hydration. Here, we found surprisingly that PPh$_3$AuCl/AgOTf gave bicyclic spiro ketones selectively using the same diynone substrates.

Scheme 2

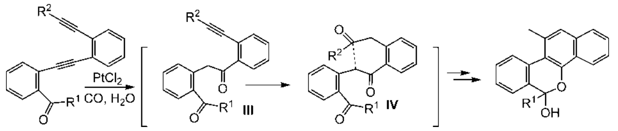
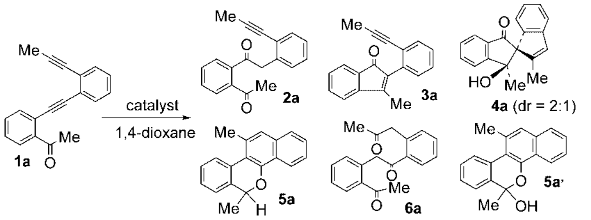


Table 1. Chemoselectivity with Gold and Platinum Catalysts



entry	substrate	catalyst[a]	water n (equiv)	condition	product (yield)[c]
1	**1a**	AuCl	6	25 ^{0}C (12 h)	**2a** (65%)
2	**1a**	AuCl	6	100 ^{0}C (12 h)	**3a** (63%)
3	**1a**	$AuCl_3$	6	100 ^{0}C (14 h)	**3a** (74%)
4	**1a**	PPh$_3$AuCl/AgOTf	6	25 ^{0}C (12 h)	**4a** (78%, dr = 2:1)
5	**2a**	PPh$_3$AuCl/AgOTf	6	25 ^{0}C (12 h)	**4a** (81%, dr = 2:1)
6	**2a**	PPh$_3$AuCl/AgOTf	0	25 ^{0}C (12 h)	**4a** (85%, dr = 2:1)
7	**3a**	PPh$_3$AuCl/AgOTf	6	25 ^{0}C (12 h)	**3a** (82 %)
8	**1a**	$PtCl_2$/CO	6	100 ^{0}C (5 h)	**5a** (61%)
9	**1a**	$PtCl_2$/CO/2,6-lutidine[b]	6	100 ^{0}C (12 h)	**6a** (47%), **5a** (12%)
10	**6a**	$PtCl_2$/CO	6	100 ^{0}C (3 h)	**5a** (76%)
11	**1a**	$PtCl_2$	6	100 ^{0}C (5 h)	**5a'** (23%)
12	**5a'**	$PtCl_2$/CO	6	100 ^{0}C (5 h)	**5a** (83%)

[a] 5 mol % for gold catalyst, 8 mol % for $PtCl_2$, 1,4-dioxane, [substrate] = 0.15 M. [b] 10 mol % of 2,6-lutidine. [c] Yields are reported after separation from silica column.

Table 1 shows the results for active gold and platinum catalysts, which exhibit distinct chemoselectivities for hydrative carbocyclization of diynone **1a**. The use of AuCl (5 mol %) in wet 1,4-dioxane at 25 °C (12 h) led to a 65% yield of diketone product **2a** (entry 1), of which the neighboring alkynyl C(1) carbon was selectively hydrated. At 100 °C (12 h), we obtained satisfactory yields (63−74%) of 1*H*-inden-1-one **3a** from AuCl and $AuCl_3$. Notably, the use of PPh$_3$AuCl/AgOTf afforded spiro ketone **4a** with a yield up to 78% (dr = 2:1). Species **2a** was confirmed to be an intermediate for spiro ketone **4a** because it was convertible to **4a** efficiently with PPh$_3$AuCl/AgOTf (5 mol %) in both wet and dry dioxane (entries 5 and 6). In contrast, 1*H*-inden-1-one **3a** was unrelated to ketone **4a** because it remained unreacted in the presence of gold catalyst. $PtCl_2$/CO catalyst[10] (8 mol %) showed a distinct chemoselectivity to give benzoisochromene **5a** in a 61% yield. The addition of 2,6-lutidine (10 mol %) to $PtCl_2$/CO allowed the isolation of key triketone intermediate **6a** (47%), which was convertible to compound **5a** by $PtCl_2$/CO catalyst (entries 9 and 10). In the absence of CO, we obtained a messy mixture of products, from which ketal **5a′** was isolated in a 23% yield. Conversion of ketal **5a′** to its hydrogenated form **5a** was achieved in 83% yield by this $PtCl_2$/CO/water system. The role of CO is 2-fold: (1) to increase the electrophilicity of platinum(II) via formation of $PtCl_2(CO)_n$[10] and (2) to hydrogenate unstable ketal product **5a′** to give stable benzoisochromene using H_2O/CO reactant; the latter process was verified by a D_2O-labeling experiment (vide infra).

Table 2 shows the applicability of this hydrative carbocyclization to diynones **1b**−**h**. We obtained benzoisochromene species **5b**−**h** rather than original ketals because H_2O/CO caused their secondary hydrogenation. Entries 1−3 show the variation of R^4 and R^5 substituents of substrates **1b**−**d**, which produced desired isochromenes **5b**−**d** in moderate yields (48−59%). For diynones **1e**−**h** bearing fluoro and methoxy at substituents R^1, R^2, and R^3 of the two benzenes, the corresponding carbocyclization products **5e**−**h** were obtained in 52−61% yields.

We extended this hydrative carbocyclization to various diynals **7a**−**g** using the same $PtCl_2$/CO catalyst. Unlike their ketone analogues **1a**−**h**, we obtained the primary lactol products **8a**−**g** in good yields (72−88%) without a secondary hydrogenation. Entries 1−3 show the applicability of this hydrative carbocyclization to substrates **7a**−**c** bearing R^3 = methyl, butyl, and 4-methoxyphenyl, which gave cyclized

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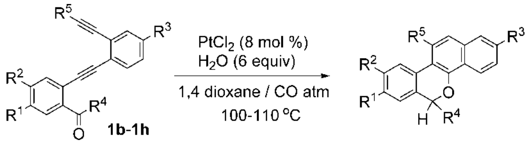
[8] (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (b) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814.

[9] Oxo-assisted alkyne hydration was recently reported by Pd(II) catalyst, see: Momiyama, N.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2007**, *129*, 2230.

[10] (a) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (c) Zhang, G; Catalano, V. J; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 11358. (d) Taduri, B. P.; Ran, Y.-F.; Huang, C.-W.; Liu, R.-S. *Org. Lett.* **2006**, *8*, 883. (e) Lo, C.-Y.; Lin, C.-C.; Cheng, H.-M.; Liu, R.-S. *Org. Lett.* **2006**, *8*, 3153.

Table 2. Platinum-Catalyzed Synthesis of Benzoisochromenes

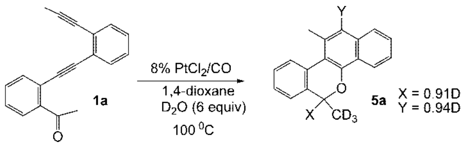


entry	diynone[a]	R^1	R^2	R^3	R^4	R^5	time (h)	product (yield, %)[b]
1	**1b**	H	H	H	CH_2CH_3	CH_3	6	**5b** (59)
2	**1c**	H	H	H	CH_2Ph	CH_3	5	**5c** (56)
3	**1d**	H	H	H	CH_3	C_3H_7	9	**5d** (48)
4	**1e**	H	H	OCH_3	CH_3	C_3H_7	6	**5e** (52)
5	**1f**	H	OCH_3	H	CH_3	C_3H_7	5.5	**5f** (53)
6	**1g**	H	F	H	CH_3	C_3H_7	4.5	**5g** (61)
7	**1h**	F	H	H	CH_3	C_3H_7	4.5	**5h** (60)

[a] [Substrate] = 0.15 M. [b] Yields are reported after separation from a silica column.

products **8a**−**c** in good yields (75−82%). The same reaction is also extendible to diynones **7d**−**g** bearing methoxy and fluoro at substituents R^1 and R^2 of the two benzenes; the resulting acetals **8d**−**g** were obtained with yields exceeding 63%.

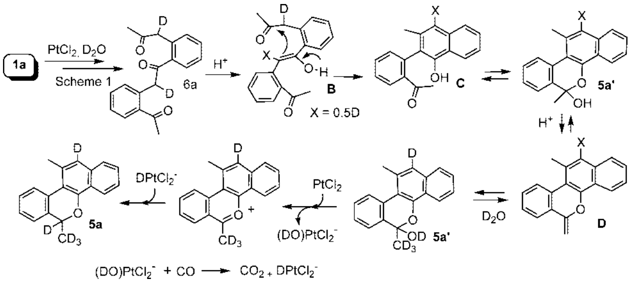
We performed deuterium-labeling experiments to understand the mechanism of formation of benzoisochromene **5a**. With D_2O, we obtained species **5a** with deuterium labeling exclusive at its methyl, OC***H***−, and −MeC=C***H***− positions (eq 2). This deuterium-labeling experiment confirms the source of hydrogen given from the water−gas shift reaction.



(2)

Scheme 3 shows a plausible mechanism including the secondary hydrogenation of primary ketal product **5a′**. With isolation of triketone **6a** by 2,6-lutidine (Table 1, entry 9), we propose that diynone **1a** likely undergoes repeated formation of benzopyriliums **A** to give observed triketone **6a**. We envisage that a Brønsted acid[11] or $PtCl_2$ catalyzes aldol condensation of triketone **6a** via enol intermediate **B** to produce 1-naphtanol **C**, which ultimately provides tetracyclic ketal **5a′**. The deuterium-labeling result confirms that D_2O serves as the hydrogen source for the reduction of ketal **5a′**, which likely forms oxonium intermediate **E** to undergo hydride addition by $DPtCl_2^-$. Formation of $DPtCl_2^-$ from CO and $HOPtCl_2^-$ has been reported in the literature.[12,13] This model also rationalizes that ketal products **5a**−**h** are more prone to secondary hydrogenation than their acetal analogues **8a**−**g**. The proton enhances reversible addition of H_2O to species **D** to produce lactol **5a′**; this effect also contributes to complete deuteration of the methyl group of benzoisochromenes. Formation of enol ether **D** is responsible for the low yield (23%) of tetracyclic ketal **5a′** because of its facile cycloaddition with benzopyriliums.[14]

Scheme 3



In contrast with $PtCl_2$, $PPh_3AuCl/AgOTf$ produced bicyclic spiro ketone **4a** using the same diynone **1a** (Table 1, entry 4). Table 4 shows the generality of this spiro ketone synthesis. Diynones **1b**−**d** and **1i** are suitable for this carbocyclization to give desired spiro ketones **4b**−**d** and **4i** in satisfactory yields (63−82%,). Relative to spiro ketone **4a**, the diasteromeric ratios of products **4b**,**c** and **4i** were significantly enhanced (dr = 4.5−15:1) with an increasing size of ketone substituent R^4 (R^4 = *n*-C_3H_7, CH_2Ph, *n*-C_6H_{13}).

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[11] In the $PtCl_2/CO/H_2O$ system, aldol reactions between two ketones can be catalyzed by either Brønsted acid or $PtCl_2$; see control experiments described in ref 5.

[12] Treatment of styrene or 1-phenylpropyne with $PtCl_2/CO$ in wet 1,4-dioxane (100 °C, 10 h) led to their exclusively recovery (>95%) without any hydrogenation product, and we did not detect hydrogen with GC analysis. This information indicates that a $PtCl_2$-catalyzed water−gas shift reaction did not occur in this system.

[13] For platinum-catalyzed water−gas shift reaction, see: Yoshida, T.; Ueda, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3941.

[14] We reported a facile synthesis of chrysenes from $PtCl_2$-catalyzed dimerization of diketone via [4 + 2]-cycloaddition of its benzopyrilium with enol intermediate; see ref 6.

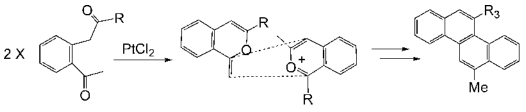
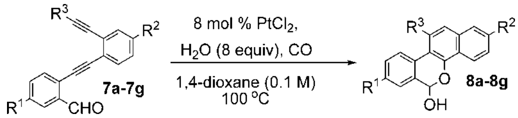


Table 3. Platinum-Catalyzed Carbocyclization of Diynals



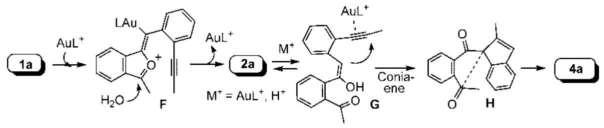
entry	diynal	R^1	R^2	R^3	time (h)	product (yield, %)
1	**7a**	H	H	Me	2	**8a** (75)
2	**7b**	H	H	*n*-Bu	2	**8b** (78)
3	**7c**	H	H	4-MeOC$_6$H$_4$	4	**8c** (82)
4	**7d**	H	OMe	Me	4	**8d** (88)
5	**7e**	OMe	H	Me	1.5	**8e** (63)
6	**7f**	F	H	Me	2	**8f** (86)
7	**7g**	F	OMe	Me	4	**8g** (72)

[a] [Substrate] = 0.15 M. [b] Yields are reported after separation froma silica column.

For diynones **1g** and **1h** bearing fluoro at the phenyl R^1 and R^2 positions, the desired ketones **4g** and **4h** were obtained in 73−78% yields (dr = 2.1−2.2:1). This spiro ketone synthesis is applicable to substrate **1k** bearing a naphthalene group, which gave ketone **4k** in a 78% yield (dr = 2.4:1). Its analogue **1l** gave ketone **4l** in great dr ratio (>15:1), reflecting the influence of a long R^4 substituent (R^4 = *n*-C_6H_{13}). This spiro ketone synthesis, however, failed to work with diynal **7a** and other aldehyde analogues (entry 10). The structures of spiro ketones **4c**, **4d**(**A**), **4d**(**B**), and **4h**(**A**) were determined by ^{1}H NOE, and the molecular structure of **4h**(**A**) was confirmed by an X-ray diffraction study.[15]

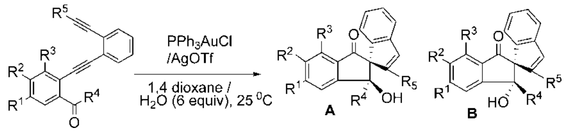
On the basis of control experiments,[16] we proposed that the ketone group of diynone **1a** facilitates the hydration of the proximate C(1)-carbon of the neighboring alkyne via intermediate **F** (Scheme 4). As we observed that diketone **2a** was convertible to spiro ketone **4a** with PPh$_3$AuOTf in dry dioxane (Table 1, entry 6), we envisage that species **2a** likely undergoes Conia−ene reaction[3b,16] via attack of the enol group of its enol form **G** at the π-alkyne group to form indenyl ketone **H**. A subsequent gold- or proton-catalyzed aldol reaction of species **H** produces the desired spiro ketone **4a**.

Scheme 4



In summary, we report a one-pot synthesis of benzopyrone derivatives from PtCl$_2$-catalyzed[18] hydrative carbocyclization of oxodiynes. This hydrative carbocyclization proceeds through a sequential oxo-assisted hydration of two tethered alkynes to give oxo dione intermediates, followed by intramolecular aldol reactions. With the same diynones, we obtained tricyclic spiro ketones using PPh$_3$AuOTf catalyst in wet dioxane. This gold species alters regioselectivity in the hydration of the neighboring alkyne to give ynedione intermediate, followed by Conia−ene and aldol condensation to complete a distinct hydrative carbocyclization.

Table 4. Au(I)-Catalyzed Synthesis of Spiro Ketones



entry	diynone	R^1	R^2	R^3	R^4	R^5	time (h)	product (yield)	dr (A:B)
1	**1b**	H	H	H	CH_2CH_3	CH_3	8	**4b** (63%)	4.5:1
2	**1i**	H	H	H	n-C_3H_7	CH_3	9	**4i** (78%)	7.1:1
3	**1c**	H	H	H	CH_2Ph	CH_3	8	**4c** (82%)	> 15:1
4	**1j**	H	H	H	n-C_6H_{13}	CH_3	9	**4c** (76%)	9.1:1
5	**1d**	H	H	H	CH_3	n-C_3H_7	18	**4d** (81%)	2.3:1
6	**1g**	H	F	H	CH_3	n-C_3H_7	18	**4g** (78%)	2.1:1
7	**1h**	F	H	H	CH_3	n-C_3H_7	18	**4h** (73%)	2.2:1
8	**1k**	H	R^2, R^3 = 		CH_3	n-C_3H_7	26	**4k** (76%)	2.4:1
9	**1l**	H	R^2, R^3 = 		n-C_6H_{13}	CH_3	20	**4l** (72%)	> 15:1
10	**7a**	H	H	H	H	CH_3	12	messy	—

[a] 5 mol % of PPh$_3$AuCl and AgOTf, [substrate] = 0.15 M. [b] Yields were reported after separation from silica column.

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

Supporting Information Available: Experimental procedures including detailed synthesis, X-ray data of compound **4h**(**A**), spectral data and NMR spectra of new compounds is available free of charge via the Internet at http://pubs.acs.org.

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(15) The ^{1}H-NOE spectra of key compounds and X-ray structure of ketone **4h**(**A**) are provided in the Supporting Information.

(16) Upon treatment of the triyne substrate (Scheme 1, R = Me) with PPh$_3$AuCl/AgOTf (5 mol %) in wet dioxane (80 °C, 8 h), we recovered the triyne substrate with a 95% recovery yield. This observation was described in the Supporting Information of ref 5. With this control experiment, the ketone of substrate facilitates the hydration of the neighboring alkynyl C(1) carbon catalyzed by this gold catalyst.

(17) (a) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350. (b) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168.

(18) (a) For divergent reactivities between platinum and gold catalysts, see: Zhang, G.; Catalano, V.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 11358. (b) Hashimi, A. S. K.; Kurpejovic, E.; Frey, W.; Bats, J. W. *Tetrahedron* **2007**, *63*, 5879. (c) Godet, T.; Vaxelaire, C.; Michel, C.; Milet, A.; Belmont, P. *Chem.—Eur. J.* **2007**, *13*, 5632.