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Distinct Chemoselectivities in the Platinum-Catalyzed 1,2-Carboalkoxylations of 5-Alkoxypent-1-yn-3-ol Derivatives

Chun-Ming Ting, Chiou-Dong Wang, Rupsha Chaudhuri, and Rai-Shung Liu*

Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan, People's Republic of China

rsliu@mx.nthu.edu.tw

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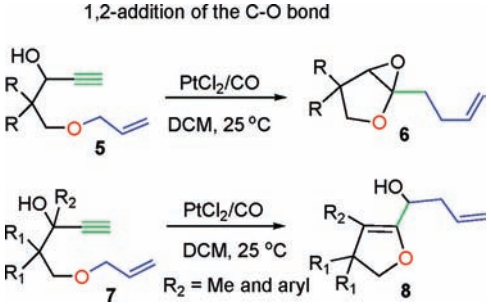
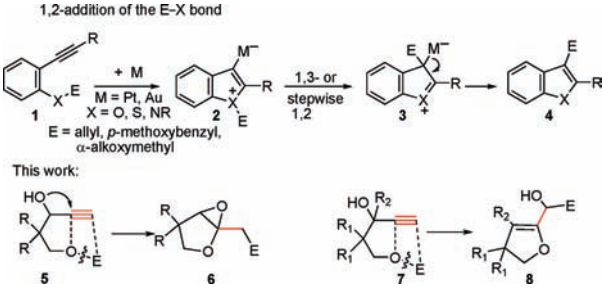
ABSTRACT



Two distinct Pt-catalyzed carboalkoxylations of alkynes are reported. The cycloisomerization of 5-alkoxypent-1-yn-3-ol derivatives 5 produces 2,6-dioxabicyclo[3.1.0]hexanes 6; the mechanism is postulated to involve a hydroxyl-triggered [3.3]-sigmatropic allyl rearrangement. As the same catalysis is extensible to their tertiary alcohol analogues 7, distinct dihydrofuranyl alcohols 8 were obtained through a [3.3]-allyl rearrangement that is not assisted by the hydroxyl group.

Metal-catalyzed electrophilic activations of alkynes are powerful tools to access heteocyclic compounds.[1] A prominent topic in Au and Pt catalysis is the cycloisomerization of *o*-alkynylanilines, *o*-alkynyl ethers, and *o*-alkynylphenyl sulfides **1** to give 2,3-disubstituted indoles, benzofurans, and benzophiophenes **4**.[2,3] Such synthetic methods have been extended to a few acyclic alkynyl ethers to produce five-membered oxacycles.[2e] This catalysis represents an appealing 1,2-carbofunctionalization of alkynes (E = carbon-based electrophiles), as depicted in

Scheme 1. Pt- and Au-Catalyzed 1,2-Carboalkoxylation of Alkynes



(1) (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (e) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.

(2) For migration of allyl group, see selected examples: (a) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (c) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (d) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001. (e) Nakamura, I.; Chan, C. W.; Araki, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 309. (f) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022.

(3) For migration of *p*-methoxybenzyl (PMB) and other groups, see selected examples: (a) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546. (b) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. (c) Nakamura, I.; Mizushima, Y.; Yamagishi, U.; Yamamoto, Y. *Tetrahedron* **2007**, *63*, 8670. (d) Fürstner, A.; Heilmann, E.; Davies, P. W. *J. Am. Chem. Soc.* **2007**, *46*, 4760.

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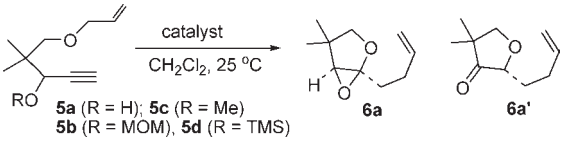
Table 1. Catalytic Activity over Various Gold and Platinum Catalysts



entry	substrate[a]	catalyst (mol %)	time	products (yields)[b]
1	**5a**	$AuCl_3$ (5)	60 min	SM (86%)[c]
2	**5a**	$ClAuPPh_3$ (5) /$AgSbF_6$ (5)	60 min	SM (72%)
3	**5a**	$ClAuPPh_3$(5) /$AgNTf_2$ (5)	60 min	SM (82%)
4	**5a**	$PtCl_2$/CO (5)	10 min	**6a** (92%)
5	**5a**	$PtCl_2$/CO (5)	5 h	**6a′** (81%)
6	**5a**	PtI_2 (5)	10 min	**6a** (83%)
7	**5b**	$PtCl_2$/CO(10)	60 min	SM (57%)
8	**5c**	$PtCl_2$/CO(10)	60 min	SM (84%)
9	**5d**	$PtCl_2$/CO(10)	20 min	

[a] [Substrate] = 0.1 M. [b] Product yields are reported after purification from a silica column. [c] Recovery yields of starting materials (SM) are given in entries 1−3, 7, and 8.

Scheme 1. The accepted mechanisms involve the 1,3- or stepwise 1,2-electrophilic migration of key intermediate **2** to form species **3**, as Yamamoto and Fürstner proposed (see Scheme 1).[1] In the literature, there appears no instance of a violation of this mechanism in the Au- and Pt-catalyzed 1,2-carbofunctionalizations of alkynes. Herein, we report two distinct 1,2-carboalkoxylations of alkynes as manifested by the cycloisomerizations of 5-alkoxypent-1-yn-3-ol derivatives **5** and **7** to form 2,6-dioxabicyclo-[3.1.0]hexanes **6** or dihydro-2*H*-pyran-4(3*H*)-ones **8**, respectively.[4]

Table 1 shows our tests of activity of substrates **5a**−**d** over commonly used platinum and gold catalysts. For alkynol **5a** (R = H), the use of $AuCl_3$, $ClAuPPh_3/AgSbF_6$, and $ClAuPPh_3/AgNTf_2$, each at 5 mol %, led only to its exclusive recovery (72−86%, entries 1−3). To our delight, $PtCl_2$/CO (5 mol %)[2a,5] in CH_2Cl_2 gave 2,6-dioxabicyclo-[3.1.0]hexane **6a** in 92% yield within 10 min (entry 4); a protracted period (5 h) gave ketone **6a′** through a secondary reaction of epoxide **6a**. Similarly, PtI_2 gave desired **6a** in 83% yield (entry 6). We examined the same reactions of species **5b**−**d** bearing a methoxymethyl (MOM), methoxy, and siloxy group, respectively, but we either recovered unreacted **5b** and **5c** (entries 8 and 9) or observed a complete decomposition of starting **5d** (entry 10). The workability of species **5a** reflects the important role of its hydroxy group in this platinum catalysis.

We prepared substrates **5e**−**q** to examine the generality of this new catalysis (Table 2). $AuCl_3$ (5 mol %) was used to implement the cycloisomerization of diol substrates **5p** and **5q** (E = H),[6] whereas $PtCl_2$/CO (10 mol %) was employed for the remaining substrates bearing carbon-based electrophiles. Most substrates contain an alkyl substituent (R = alkyl) to ensure the kinetic stability of epoxide products **6**. Furthermore, a large R substituent induces a small θ angle to accelerate the cyclization via the Thorpe−Ingold effect.[7] Herein, the tricyclic ketals **6j″** and **6o″** were produced from the dimerization of epoxide products **6a**; these ketals showed proton NMR spectral patterns distinct from those of epoxides **6**. The structure of **6o″** was solved by X-ray diffraction.[8] Entries 1−5 show the applicability of this catalysis to substrates **5e**−**i** bearing various CR_2 (R = methyl, ethyl, cyclopentyl, and cyclohexyl) and allyl groups (R = allyl, 2-methyl, 2-phenylallyl), giving epoxide species **6e**−**i** in 58−85% yields. We examined this reaction with unsubstituted substrate **5j** (R = H, E = allyl, entry 6), which gave tricyclic ketal **6j″** in 46% yield. This catalysis is applicable also to substrate **5k** and **5*l*** bearing a *p*-methoxybenzyl (PMB) ether that gave epoxides **6k** and **6*l*** in 82% and 83% yields, respectively (entries 7 and 8). For substrate **5m**, a brief reaction (5 min) gave no initial epoxide in pure form, but a longer period (3 h) delivered ketone **6m′** in 56% yield (entry 9). The migration of a *p*-methoxybenzyl group is feasible also for cyclohexyl substrate **5n** that gave epoxide **6n** in 83% yield (entry 10). Similar to **5j**, unsubstituted substrate **5o** (R = H, entry 11) gave dimerization product **6o″** of which the structure was confirmed by X-ray diffraction.[8]

(4) $PtCl_2$-catalyzed cycloisomerization of 2-propargyl anilines gave indole products through a typical 1,2-addition pathway, with no epoxide product **6** in this case. See: Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881.

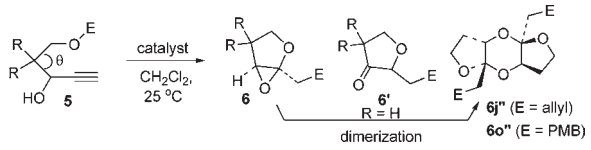
(5) (a) Fürstner, A.; Aissa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306. (b) Chang, H.-K.; Datta, S.; Das, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4744.

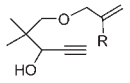
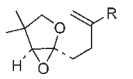
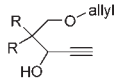
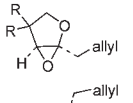
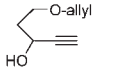
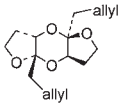
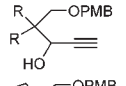
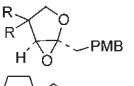
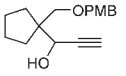
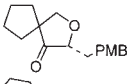
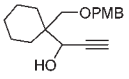
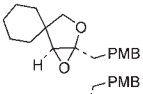
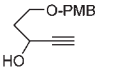
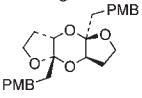
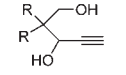
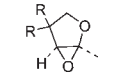
(6) We obtained products **6p** and **6q** in complicated mixtures of products when diol substrates **5p** and **5q** were treated with $PtCl_2$/CO (5 min) in CH_2Cl_2 (25 °C, 10 min).

(7) For the *gem*-dialkyl effect of this cyclization, see selected examples: (a) Kostal, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2010**, *32*, 8766. (b) Jager, J.; Graafland, T.; Schenk, H.; Kirby, A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1984**, *106*, 139. (c) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080.

(8) X-ray crystallographic data of compound **6o″** is provided in the Supporting Information.

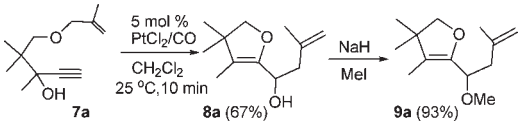
Table 2. 1,2-Additions of the C−O Bond to an Alkyne



entry	substrates[a]		catalyst[b] (mol %, min)	products[c]	
1		**5e** (R = Me)	Pt (10, 50)		**6e** (85%)
2		**5f** (R = Ph)	Pt (5, 10)		**6f** (58%)
3		**5g** (R = Et)	Pt (5, 5)		**6g** (91%)
4		**5h** (R = -$(CH_2)_4$-)	Pt (5, 5)		**6h** (93%)
5		**5i** (R = -$(CH_2)_5$ -)	Pt (5, 5)		**6i** (92%)
6		**5j**	Pt (10, 10)		**6j"** (46%)
7		**5k** (R = Me)	Pt (5, 5)		**6k** (82%)
8		**5l** (R = Et)	Pt (5, 5)		**6l** (83%)
9		**5m**	Pt (10, 180)		**6m'** (56%)
10		**5n**	Pt (5, 5)		**6n** (83%)
11		**5o**	Pt (5, 5)		**6o"** (71%)
12		**5p** (R = Me)	Au (5, 5)		**6p** (62%)
13		**5q** (R = -$(CH_2)_4$-)	Au (5, 10)		**6q** (68%)

[a] [Substrate] = 0.1 M. [b] Pt = $PtCl_2$/CO, Au = $AuCl_3$. [c] Product yields are reported after purification from a silica column.

Scheme 2. Variation of Chemoselectiviry for Species **7a**

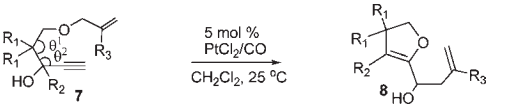


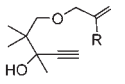
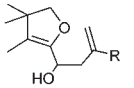
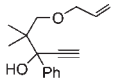
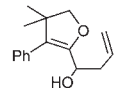
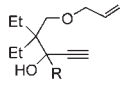
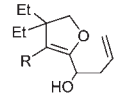
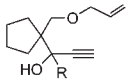
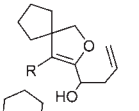
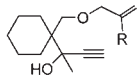
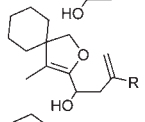
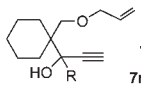
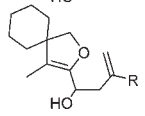
This epoxide synthesis worked well with diols **5p** and **5q** to give desired products **6p** and **6q** (entries 12 and 13) in yields 62% and 68%, respectively.

We prepared compound **7a** bearing a tertiary alcohol, but its platinum-catalyzed reaction in CH_2Cl_2 (25 °C, 10 min) gave a 67% yield of five-membered oxacycle **8a** (Scheme 2). We obtained also its methoxy derivative **9a** that resembled **8a** in both ^{1}H and ^{13}C NMR spectra. The structure of **8a** was identified with the ^{1}H NOE effect, HMBC and HMQC spectra, further suppoting the assigned structure.

The preceding **7a** → **8a** transformation represents a distinct 1,2-carboalkoxylation of alkynes. We assessed its generality with various tertiary alcohols **7b**−**m** bearing variable R^1, R^2, and R^3 substituents (Table 3). The catalytic cycloisomerizations of these substrates gave desired products **8b**−**m** efficiently using $PtCl_2$ (5 mol %) in CH_2Cl_2 (25 °C). This 1,1-carboalkoxylation worked well with substrates **7b**−**f** (entries 1−5) to give desired products **8b**−**f** in 48−90% yields. Here, large R^1 = Et or R^2 = Ph groups resulted in small θ^1 and θ^2 angles and facilitated a 5-*exo*-*dig* cyclization. Substrates **7g** and **7h** bearing a cyclopentyl group were less efficient in this catalysis than their cyclohexyl analogues **7i**−**k**, as shown by their respective yields (entries 6−10). Both electron-deficient and electron-rich phenyl groups as in alcohols **7*l*** and **7m** were suitable for this catalysis, giving products **8*l*** and **8m** in 93% and 85% yields, respectively (entries 11 and 12).

Table 3. $PtCl_2$-Catalyzed 1,1-Addition of the C−O Bond to an Alkyne

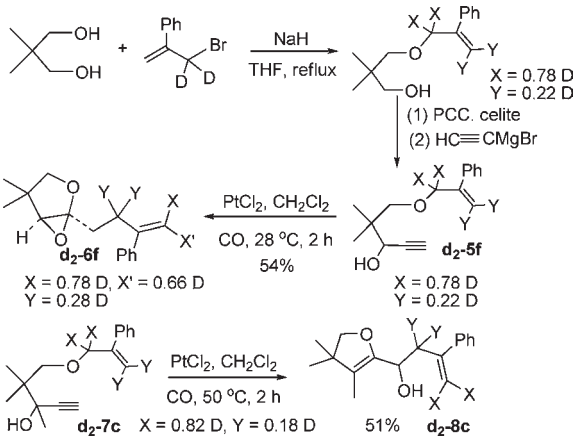


entry	substrate[a]		time (min)	products[b]	
1		**7b** (R = H)	10		**8b** (48%)
2		**7c** (R = Ph)	30		**8c** (72%)
3		**7d**	10		**8d** (83%)
4		**7e** (R = Me)	10		**8e** (54%)
5		**7f** (R = Ph)	60		**8f** (90%)
6		**7g** (R = Me)	360		—
7		**7h** (R = Ph)	360		**8h** (56%)
8		**7i** (R = H)	180		**8i** (72%)
9		**7j** (R = Me)	60		**8j** (53%)
10		**7k** (R = Ph)	60		**8k** (87%)
11		**7l** (R = 4-$CF_3C_6H_4$)	20		**8l** (93%)
12		**7m** (R = 4-$MeOC_6H_4$)	20		**8m** (85%)

[a] [Substrate] = 0.1 M. [b] Product yields are reported after purification from a silica column.

To clarify the reaction mechanism, we prepared d_2-**5f** bearing 78% and 22% deuterium content, respectively, at the O—CH_2 and =CH_2 positions with the synthesis shown in Scheme 3. The catalytic cycloisomerization of d_2-**5f** delivered expected d_2-**6f** that contained Y = 0.28 D at the allylic positions, and X = 0.78 D and X' = 0.66 D at the two vinyl hydrogens. We prepared also tertiary alcohol

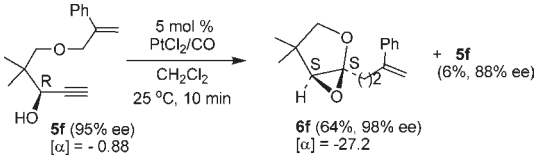
Scheme 3. Preparation of Deuterated Samples



d_2-**7c** bearing 82% and 18% deuterium content at the allylic and vinyl positions; its corresponding product d_2-**8c** comprises 18% and 82% deuterium contents at allylic and vinyl positions respectively. These observations indicate that both reactions involve an S_E2' route for the migration of allyl to the alkynyl C(1)-carbon.[9]

Scheme 4 illustrates the enantiospecificity in the transformation of enantiomerically enriched alcohol **5f** into epoxide **6f**. We prepared (*R*)-alcohol substrate **5f** with 95% ee ([α] −0.88);[10] its treatment with $PtCl_2$/CO in CH_2Cl_2 (25 °C, 10 min) gave desired epoxide **6f** with ee 98% ([α] −27.2) together with unreacted (*R*)-**5f** in small proportions (6%, ee 88%).

Scheme 4. Catalytic Transformation Using a Chiral Alcohol

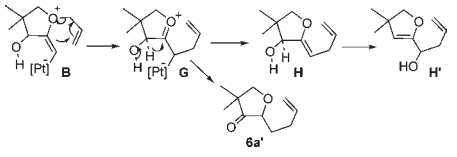


The distinct chemoselectivities for alcohol **5a** and its tertiary alcohol analogue **7b** are mechanistically interesting.

(9) A [3.3]-allyl shift was mentioned in the cycloisomerization of 2-propargyl anilines, but in a distinct mechanism. See ref 4.

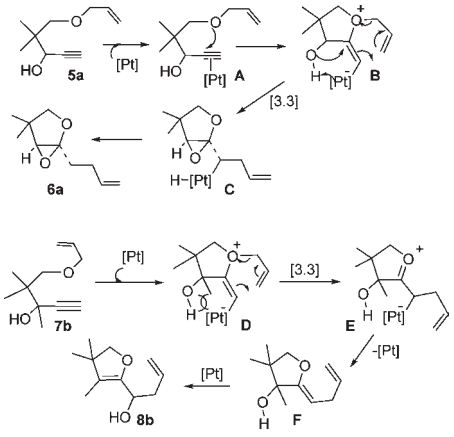
(10) The detailed procedure for the preparation of enantiomerically enriched alcohol (*R*)-**5f** is provided in the Supporting Information.

(11) For the cycloisomerization of compound **5**, we exclude a prior 1,3-electrophilic migration as shown by the **B** → **G** transformation because we obtained no tractable amount of compound **H** or **H′**. Although species **G** might produce ketone **6a′** alternatively through a 1,2-hydride shift (Pinacol rearrangement), not ketone **6a′** but epoxide **6a** is verified to be the primary product in this catalysis.



Scheme 5 shows a plausible mechanism to rationalize the formation of epoxide **6a** from substrate **5a**. An initial 5-*exo*-*dig* cyclization of platinum-π-alkyne **C** forms intermediate **A**. We envisage that the platinum of this intermediate abstracts a proton from the neighboring hydroxyl group to facilitate a [3.3]-sigmatropic rearrangement as depicted by species **B**. This reaction model explains well the catalytic inactivity of other oxy functionalities **5b**−**d** bearing a methoxymethyl (MOM), methoxy, or siloxy group.[11] In contrast, formation of dihydrofuran products **8b** from alcohol **7b** seems to follow a traditional route, in which a [3,3]-allyl rearrangement replaces a [1,3]-shift in key intermediate **D**. We envisage that the neighboring methyl substituent of intermediate **D** impedes the ability of platinum to abstract the hydroxyl proton, thus ultimately giving a distinct product **F**. We expect that species **F** readily undergoes Pt-catalyzed isomerization of the allylic alcohol to give the observed compound **8b**.

Scheme 5. Proposed Reaction Mechanism



In summary, we report two atypical Pt-catalyzed carboalkoxylations of alkynes. In the cycloisomerization of 5-alkoxypent-1-yn-3-ols **5**, the mechanism does not follow a traditional route involving a 1,3-shift of the electrophiles. We envisage that the hydroxyl group of intermediate **B** activates a [3.3]-sigmatropic rearrangement to give observed 2,6-dioxabicyclo[3.1.0] hexanes **6**. For tertiary alcohol substrates **7**, we obtained distinct dihydrofuranyl alcohols **8** through a [3.3]-allyl rearrangement with no assistance of the hydroxyl group.

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Supporting Information Available. Procedures for synthesis of starting substrates and catalytic operations, NMR spectra, and spectral data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.