Platinum-catalyzed cycloisomerization of 1,4-enynes *via* activation of a sp^3-hybridized C–H bond†

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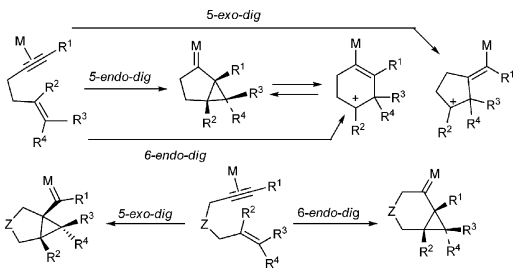
We report the cycloisomerization of 1-alkenyl-1-alkynylcyclopropanes to cyclooctatriene products catalyzed by $PtCl_2$/CO in hot xylene. In contrast to the reported enyne cycloisomerization, this 1,4-enyne cycloisomerization proceeds *via* an atypical addition of the allyl carbon to the alkyne in a 6-*endo-dig* cyclization.

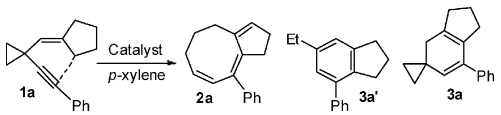
Platinum- and gold-catalyzed cycloisomerizations of enyne functionalities[1,2] have been studied exclusively for 1,5- and 1,6-enynes with very few examples for 1,4-enynes.[3] This synthetic approach provides useful and unusual carbocyclic products that are not readily prepared by common methods. The carbocyclic rings resulting from such reactions arise invariably from a bond connection between the alkenes and alkynes through various *endo*- or *exo*-cyclizations,[1,2] as depicted in Scheme 1. We sought to expand the scope of enyne cycloisomerizations so as to generate carbocyclic rings through the addition of the allylic carbon to the tethered alkyne, as depicted with 1,4-enyne substrate **1a** (Table 1). The mechanistic significance of this novel process is the activation of the allylic hydrogen with a π-alkyne functionality that has no precedents.[4,5]

Table 1 shows the optimized conditions for the cycloisomerization of 1,4-enyne **1a**. We selected this compound for the allylic C–H bond activation because its cyclopentylidene group impedes a conventional 5-*endo-dig* cyclization toward the tethered alkyne. With $PtCl_2$/CO (5 mol%)[6] as the catalyst, the cyclization efficiency is highly dependent on the solvent in which the reaction was performed in a sealed tube. We obtained desired cyclized compound **2a** with 63% yield in hot *p*-xylene (120 °C, 2 h), far superior to dichloroethane, acetonitrile and DMF that gave exclusive recovery of unreacted **1a** in 86–91% under the same conditions.[7] We observed no olefin isomerization of **1a** in the latter solvents.



Scheme 1

Table 1 Catalyst screening and optimized conditions



Entry	Catalyst[a]	Temperature (time/h)	Additive	Yield[b]
1	$PtCl_2$/CO (5)	120 °C (2)	—	**2a** (63%)
2	$PtCl_2$ (5)	120 °C (8)	—	**2a** (44%)
3	$AuCl_3$ (5)	120 °C (24)	—	**1a** (88%)
4	AuCl (5)	120 °C (24)	—	**1a** (86%)
5	PPh_3AuCl (5)/ AgOTf (5)	120 °C (5)	—	Messy
6	PtI_2(5)	120 °C (6)	—	Messy
7	HOTf (1)	120 °C (1)	—	**3a′** (63%)
8	HOTf (1)	25 °C (3)	—	**3a** (68%)
9	$PtCl_2$/CO (5)	120 °C (24)	2,6-Lutidine (5)	**2a** (43%)
10	$PtCl_2$/CO (5)	120 °C (24)	CuBr (20)	**1a** (85%)
11	—	120 °C (24)	—	**1a** (89%)

[a] The values in parentheses represent mol% for catalysts and additives. [b] Yields are reported after separation on a silica column.

The use of $PtCl_2$ alone gave a diminished yield of **2a** (44%). AuCl and $AuCl_3$ each at 5 mol% loading led to exclusive recovery of **1a** whereas PPh_3AuCl/AgOTf gave a messy mixture of products in hot xylene. This observation again reflects the unsuitability[4a] of gold catalysts to activate the C–H bond induced with a π-alkyne. Under the same conditions, PtI_2 (5 mol%) also provided a messy mixture of products (entry 6), whereas HOTf (1 mol%) in hot xylene (120 °C, 1 h) gave distinct product **3a′** in 63% yield (entry 7), but 5-cyclopropyl-1,3-hexadiene **3a** in 68% yield near 25 °C. Added 2,6-lutidine (5 mol%) gave a decreased yield (43%) of desired **2a**, whereas CuBr[8] (20 mol%) completely inhibited the reaction (entries 9 and 10). Thermal activation alone failed to give a traceable amount of **2a** (entry 11).

We prepared various 1-alkenyl-1-arylalkynylcyclopropanes[9] **1b–1i** and **1j–1l** to assess the generality of such a bicyclo-[6.3.0]undecatriene synthesis (Table 2). Notably, resulting products **2b–2i** and **2j–2l** have varied olefin positions, according to ^{1}H NMR analysis. The electronic effect of 4-phenyl substituent X has a pronounced effect on product yield. For X = Me, F and Cl derivatives (**1b–1d**), we obtained desired products **2b–2d** in 51–61% yields. This platinum-catalyzed cycloisomerization is inapplicable to 1,4-enyne **1e** bearing a *para*-methoxy group, which we recovered exclusively even after a long period (24 h). The cycloisomerization works well

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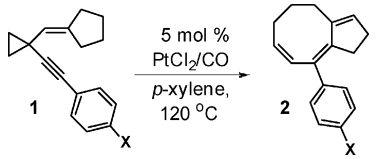
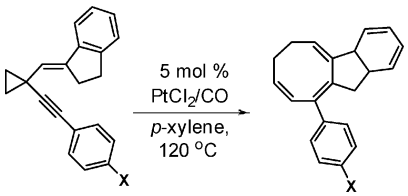
† Electronic supplementary information (ESI) available: Experimental details and characterization data and ^{1}H and ^{13}C NMR spectra of compounds **1a**–**8**. CCDC 755454. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc00071j

Table 2 Catalytic synthesis of bicyclo[6.3.0]undecatrienes

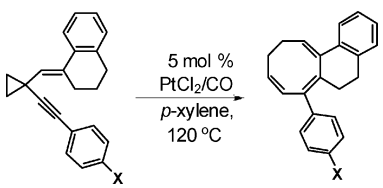
Entry	Enyne[a]	Time/h	Compound (yield)[b]
			
1	X = Me (**1b**)	1.5	**2b** (61%)
2	X = F (**1c**)	1	**2c** (51%)
3	X = Cl (**1d**)	1	**2d** (55%)
4	X = OMe (**1e**)	24	**1e** (75%)
5	X = C(=O)Me (**1f**)	2.5	**2f** (80%)
6	X = NO_2 (**1g**)	4.5	**2g** (79%)
7	X = CO_2Et (**1h**)	5	**2h** (84%)
8	X = CN (**1i**)	5	**2i** (72%)
			
9	X = H (**1j**)	2.5	**2j** (67%)
10	X = Me (**1k**)	2	**2k** (61%)
11	X = Cl (**1l**)	2	**2l** (71%)

[a] [Enyne] = 0.5 M. [b] Products are reported after separation on a silica column.

with enynes **1f–1i** bearing an electron-withdrawing group such as acyl, nitro, ester and cyano, giving corresponding products **2f–2i** in satisfactory yields. On comparison of their respective yields, we found the cycloisomerization of 1,4-enynes **1j–1l** bearing a 1-indanylidene moiety to be more efficient than of their cyclopentylidene analogues **1a**, **1b** and **1d**.

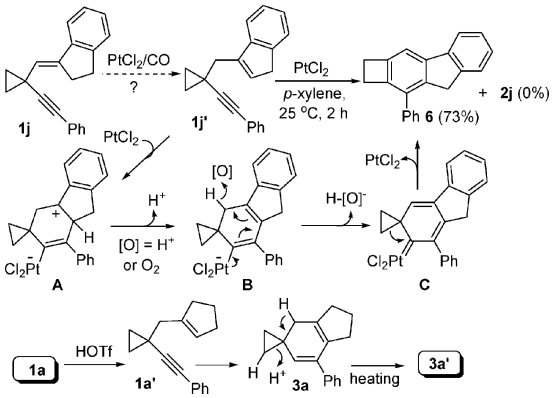
This platinum catalysis is extensible to the synthesis of bicyclo[6.4.0]dodecatrienes **5a–5e** through the cycloisomerization of 1,4-enynes **4a–4e** bearing a cyclohexylidene group (Table 3). For unsubstituted substrate **4a**, its corresponding product **5a** was obtained in 56% yield, less than that (67%) of bicyclo-[6.3.0]undecatriene **2j**. This information indicates that the

Table 3 Catalytic synthesis of bicyclo[6.4.0]dodecatriene



Entry	Enyne[a]	Time/h	Compound (yield)[b]
1	X = H (**4a**)	4	**5a** (56%)
2	X = CO_2Me (**4b**)	5.3	**5b** (84%)
3	X = COMe (**4c**)	5.3	**5c** (83%)
4	X = CN (**4d**)	5.0	**5d** (81%)
5	X = NO_2 (**4e**)	5.3	**5e** (83%)

[a] [Enyne] = 0.5 M. [b] Products are reported after separation on a silica column.



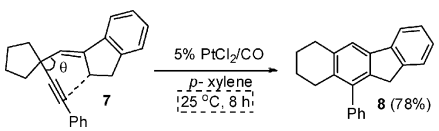
Scheme 2

allylic C–H activation proceeds more efficiently with a cyclopentylidene than a cyclohexylidene ring. Again, we observed enhanced yields (81–84%) of products **5b–5e** bearing an electron-withdrawing ester, acyl, cyano and nitro moieties at the 4-phenyl position.

The preceding cyclization might occur with an initial platinum-catalyzed olefin isomerization of 1,4-enyne **1j** to 1,5-enyne **1j′** (Scheme 2) that ultimately gave desired bicyclo-[6.3.0]undecatriene **2j** through a 6-*endo-dig* cyclization. To test this hypothesis, we prepared 1,5-enyne **1j′** from a separate route; its treatment with $PtCl_2$/CO in xylene at room temperature leads to a distinct cycloisomerization/oxidation cascade, giving 1,2-dihydrocyclobutabenzene **6** in 73% yield.

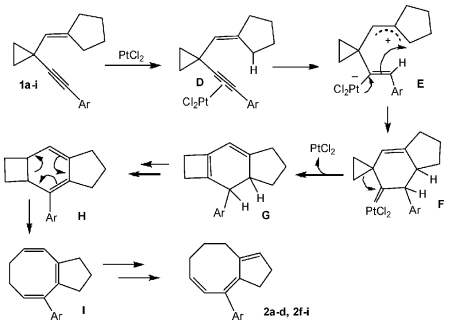
The structure of compound **6** was determined by ^{1}H-NOE and confirmed by X-ray crystallographic study.[9] The absence of desired **2j** excludes the participation of 1,5-enyne **1j′** as an intermediate for initial 1,4-enyne **1j**. We envisage that the formation of bicyclic benzene **6** likely proceeds from intermediate **B**, of which the cyclopropyl and platinum-dienyl groups activate oxidation of the methylene protons with protons or residual oxygen. This proposed mechanism provides a convincing rationale for the HOTf-catalyzed carbocyclization that gave distinct products **3a** and **3a′** (Table 1, entries 7–8).

Eqn (1) depicts a crucial control experiment to assist in the understanding of the reaction mechanism. For 1,4-enyne **7**, its $PtCl_2$-catalyzed cycloisomerization proceeds even under ambient conditions (25 °C, 8 h), giving ring-expansion product **8** in 78% yield. Such a low temperature excludes the involvement of a Brønsted acid such as $PtCl_2(H_2O)$ to effect an olefin isomerization.[7] The ease of this cycloisomerization is attributed to a small angle $\theta = 111.7°$ between the interacting alkene and alkyne substituents.[10] In contrast, the corresponding angle for 1-alkenyl-1-alkynylcyclopropane **1j** is as large as 116.0°, rendering the cyclization difficult. More importantly, the formation of compound **8** involves a 1,2-migration of its cyclopentyl group toward the alkynyl rather than alkenyl group.[11]



(1)

Scheme 3 shows a plausible mechanism involving a π-alkyne-activated 1,6-hydrogen shift of 1,4-enynes. This mechanism is



Scheme 3

proposed based on an activity/structure relationship and a control experiment. We propose that the initial step involved a π-alkyne-activated hydride shift,[12] giving alkenylplatinum species **E**. This process is accelerated by an electron-withdrawing group at the aryl group because of a stabilization of the negative charge developing on the platinum center.[13] Intramolecular cyclization of species **E** *via* an attack of alkenylplatinum at the allyl cation forms cyclohexenyl carbenoid species **F**, further inducing an expansion of the cyclopropyl ring.

The support of this cyclopropyl shift is provided by the isomerization of 1,4-enyne **7** to compound **8**. Species **G** contains a strained cyclobutene fragment, and is prone to a rapid olefin isomerization to give thermodynamically stable species **H**, catalyzed by platinum or *via* a thermal 1,5-hydrogen shift. A ring opening of species **H** through a retro 6-π-electrocyclization forms bicyclo[6.3.0]undecatriene **I** that ultimately produces the observed products **2a–2d** and **2f–2i**.

In summary, we report the cycloisomerization of 1-alkenyl-1-alkynylcyclopropanes to cyclooctatriene products catalyzed by $PtCl_2$/CO in hot xylene. In contrast to reported enyne cycloisomerization, this 1,4-enyne cycloisomerization proceeds *via* an atypical addition of the allyl carbon to the alkyne *via* a 6-*endo*-*dig* cyclization. Control experiments exclude the involvement of Brønsted acid and a prior alkene isomerization. On the basis of experimental data, we propose a carbocyclization involving a π-alkyne activated 1,6-hydride shift as the key step. In a control experiment, we discovered that such a carbocyclization can proceed at room temperature if the allyl C–H bond is near its tethered functionality. We believe that this original observation will assist the design of novel catalytic reactions.

The authors wish to thank the National Science Council, Taiwan for supporting this work.

Notes and references

1 Leading references for gold catalyzed 1,*n*-enyne cycloisomerizations: (*a*) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326; (*b*) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Commun.*, 2007, 333; (*c*) L. Zhang, J. Sun and S. A. Kozmin, *Adv. Synth. Catal.*, 2006, **348**, 2271.

2 (*a*) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410; (*b*) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395; (*c*) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2005, **44**, 6990.

3 All reported 1,4-enynes comprised a tethered acetate that is prone to a 1,3-shift to give allenyl acetates; such gold-catalyzed carbocyclizations actually proceed through an allene-ene cyclization. See: (*a*) X. Shi, D. J. Gorin and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 5802; (*b*) A. Buzas and F. Gagosz, *J. Am. Chem. Soc.*, 2006, **128**, 12614; (*c*) N. Marion, S. Diez-Gonzalez, P. De Fremont, A. R. Noble and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2006, **45**, 3647.

4 Metal-catalyzed alkyne-induced hydrogen shifts can be initiated by π-alkyne[4] or metal vinylidene intermediates,[5] see: (*a*) I. D. Jurberg, Y. Odabachian and F. Gagosz, *J. Am. Chem. Soc.*, 2010, **132**, 3543; (*b*) P. A. Vadola and D. Sames, *J. Am. Chem. Soc.*, 2009, **131**, 16525; (*c*) D. Shikanai, H. Murase, T. Hada and H. Urabe, *J. Am. Chem. Soc.*, 2009, **131**, 3166; (*d*) S. Yang, Z. Li, X. Jian and C. He, *Angew. Chem., Int. Ed.*, 2009, **48**, 3999; (*e*) J.-J. Lian, C.-C. Lin, H.-K. Chang, P.-C. Chen and R.-S. Liu, *J. Am. Chem. Soc.*, 2006, **128**, 9661.

5 (*a*) M. Tobisu, H. Nakai and N. Chatani, *J. Org. Chem.*, 2009, **74**, 5471; (*b*) A. Odedra, S. Datta and R.-S. Liu, *J. Org. Chem.*, 2007, **72**, 3289; (*c*) G. B. Bajracharya, N. K. Pahadi, I. D. Gridnev and Y. Yamamoto, *J. Org. Chem.*, 2006, **71**, 6204; (*d*) S. Datta, A. Odedra and R.-S. Liu, *J. Am. Chem. Soc.*, 2005, **127**, 11606.

6 For the original use of $PtCl_2$/CO, see: (*a*) A. Fürstner, P. W. Davies and T. Gress, *J. Am. Chem. Soc.*, 2005, **127**, 8244; (*b*) A. Fürstner and P. W. Davies, *J. Am. Chem. Soc.*, 2005, **127**, 15024.

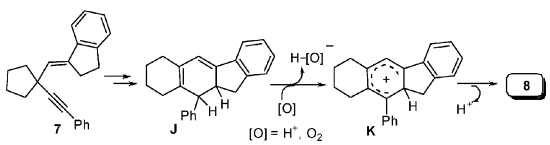
7 We obtained recovery yields of starting **1a** for the following solvents in a sealed tube (120 °C, 24 h), DMF (91%), CH_3CN (86%) and 1,2-dichloroethane (90%). This information suggests that olefin isomerization, as exemplified by **1j** → **1j′** is not a facile process using $PtCl_2$/CO alone.

8 The enhancement of CuBr on benzyl C–H bond activation was reported by He and co-workers, see ref. 4*d*.

9 Preparation details for 1-alkenyl-1-alkynylcyclopropanes are provided in the ESI†; CCDC 755454.

10 Optimizations of the molecular structures of compounds **1j** and **7** were performed using B3LYP/6-31G* opt.

11 The mechanism of formation of compound **8** is also rationalized according to the pathway below. According to the mechanism (Scheme 3) starting species **7** will form compound **J** that is prone to oxidation in solution, as activated by the two phenyl groups, to give the observed product **8** ultimately.



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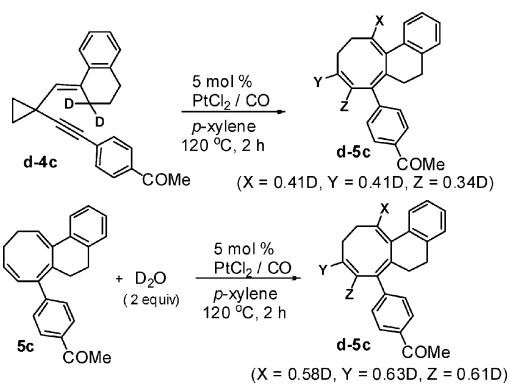
12 We have performed a deuterium-labeling experiment to elucidate the reaction mechanism. We prepared **d-4c** that gave desired **d-5c** with deuterium at the three olefin protons following the same catalytic sequence. However, this observation is probably meaningless because the olefin protons of compound **5c** undergo deuterium exchange with external D_2O.



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13 We observed no activity for substrate **1e** (Table 2, entry 4) because its 4-methoxyphenyl substituent will destabilize the alkenylplatinum functionality of hypothetical intermediate **E**.