

Intramolecular Reactions of Alkynes with Furans and Electron Rich Arenes Catalyzed by PtCl₂: The Role of Platinum Carbenes as Intermediates

Belén Martín-Matute, Cristina Nevado, Diego J. Cárdenas, and
Antonio M. Echavarren*

Contribution from the Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

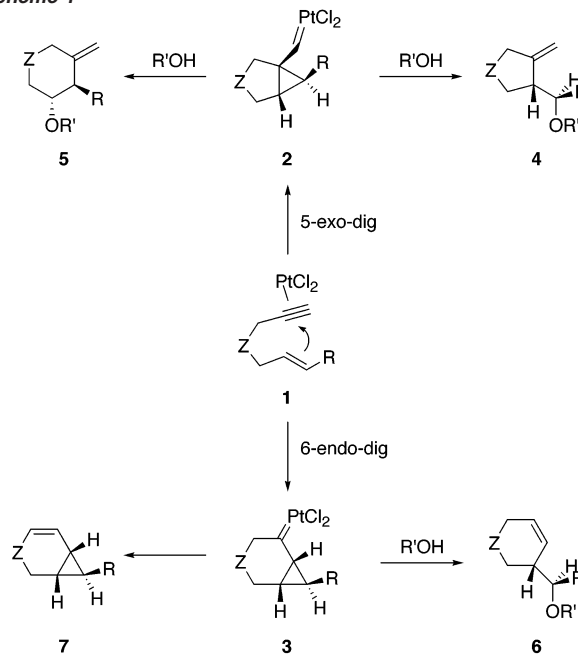
Received October 29, 2002 E-mail: anton.echavarren@uam.es

Abstract: 5-(2-Furyl)-1-alkynes react, with PtCl₂ as catalyst, to give phenols. On the basis of DFT calculations, a cyclopropyl platinacarbene complex was found as the key intermediate in the process. The cyclopropane and dihydrofuran rings of this intermediate open to form a carbonyl compound, which reacts with the platinum carbene to form an oxepin, which is in equilibrium with an arene oxide. When the reaction is carried out in the presence of water, dicarbonyl compounds are obtained, which support the proposed mechanism. Other cyclizations of alkynes with furans or electron-rich arenes give products of apparent Friedel–Crafts-type reactions, although these processes could also proceed by pathways involving the formation of cyclopropyl platinum carbenes.

Introduction

The coordination of electrophilic PtCl₂ to the alkyne of an enyne (**1**, Scheme 1) promotes the intramolecular attack of the alkene to form cyclopropyl Pt-carbene intermediates **2** and/or **3** by 5-exo-dig or 6-endo-dig pathways.¹ The attack of the nucleophile (alcohol or water) at the cyclopropane of complexes **2** and **3** gives rise to **4–6**. Some of these cyclizations are also catalyzed by AuCl₃, Ru(II),¹ and Pd(II) complexes,² although the reactions with these catalysts are more limited in scope.¹ Similar intermediates may be also involved in the transition metal-catalyzed intramolecular attack of allyl silanes and allyl stannanes to alkynes.³ The involvement of cyclopropylmetal-carbenes as intermediates was first proposed by Trost,⁴ Murai,⁵

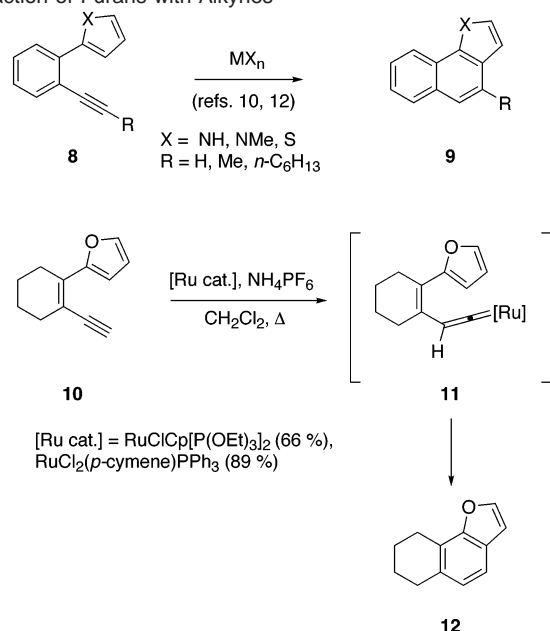
Scheme 1



and Fürstner,⁶ for the Pd(II), Rh(I), Ru(II), and Pt(II)-catalyzed skeletal rearrangement of enynes that yield conjugated dienes.^{7,8}

- (1) (a) Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11 549–11 550. (b) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10 511–10 520. (c) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, in press.
- (2) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.-N.; Genêt, J. P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706–713.
- (3) (a) Fernández-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221–1222. (b) Fernández-Rivas, C.; Méndez, M.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Org. Chem.* **2002**, *67*, 5197–5201.
- (4) (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636–1638. (b) Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647–3650. (c) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850–1852. (d) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824–832. (e) Trost, B. M.; Yanai, M.; Hoogsten, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294–5295. (f) Trost, B. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1085–1087. (g) Trost, B. M.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **1994**, *116*, 2183–2184. (h) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16. (i) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801–3810. (j) Trost, B. M.; Toste, D. F.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067–2096.
- (5) (a) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049–6050. (b) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901–903. (c) Chatani, N.; Kataoka, K.; Murai, S.; Furokawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104–9105. (d) Rearrangement of enynes catalyzed by GaCl₃; Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10 294–10 295.

- (6) (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305–8314. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786. (c) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11 863–11 869.
- (7) For a more recent formulations of the reaction mechanism: (a) Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. *Organometallics* **2001**, *20*, 3704–3709. See also: (b) Mainetti, E.; Mouries, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132–2135.
- (8) For a review: Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834.

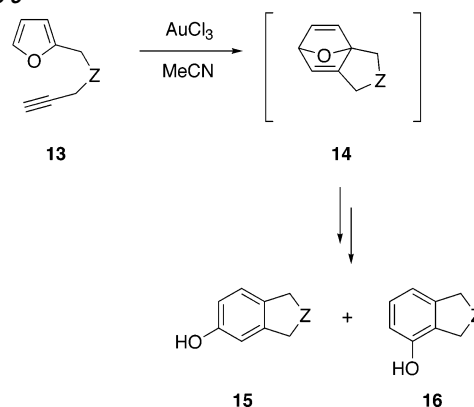
Scheme 2. Proposed Reaction Pathway for the Intramolecular Reaction of Furans with Alkynes¹⁸

Formation of cyclopropane derivatives of type **7**^{1c–d,6b–c} also supports the involvement of cyclopropyl Pt-carbene **3** as intermediates.

Electron-rich arenes also react with alkynes in the presence of electrophilic metal halides MX_n (or complexes ML_n) as catalysts.^{9,10,11,12} Interestingly, 4-aryl-1-ynes react preferentially by 6-endo pathways to afford six-membered cycles. The exo-mode was preferred for the cyclization of 5-aryl-1-ynes and 6-aryl-1-ynes, leading to six- and seven-membered rings, respectively.⁹ This cyclization has been proposed to take place via a Friedel–Crafts-type process.^{9,12} The cyclization of terminal alkynes can also proceed through vinylidene complexes.^{10,13,14,15}

The metal-catalyzed cyclization of some π -excessive heterocycles with alkynes is also possible. Thus, the 6-endo-cyclization of substrates **8** gave fused heterocycles **9**, presumably via a Friedel–Crafts-type reaction (Scheme 2).^{10,12} A different mechanism for the cyclization was first demonstrated by Merlic for the reaction of **10**, which was shown to proceed through ruthenium vinylidene **11** to form tetrahydronaphtho[1,2-*b*]furan **12**.^{13,16,17}

In contrast with this reaction mode, Hashmi demonstrated that the intramolecular reaction of furans with alkynes affords

Scheme 3

phenols by using $AuCl_3$ as the catalyst (Scheme 3).¹⁸ This reaction was proposed to proceed by an intramolecular [4+2] cycloaddition of **13**, promoted by the η^2 -coordination of $AuCl_3$ to the alkyne, followed by cleavage of the resulting oxabicyclic adduct **14** to form phenols **15** and **16**.¹⁹ This mechanistic proposal is reasonable, as furans undergo Diels–Alder reactions with a variety of alkynes to form the oxabicycloheptadienes.²⁰

We also found that substrates **13** give phenols **15** and **16** in the presence of $PtCl_2$ as the catalyst.²¹ For this reaction, we proposed a different mechanism based on the formation of a cyclopropyl platinum carbene similar to **2**. Herein, we report in detail the scope and limitations of the intramolecular reaction of furans with alkynes catalyzed by $PtCl_2$, as well as a mechanistic scheme based on DFT calculations and on the trapping of some intermediates. We also observed 6-exo cyclizations in the $PtCl_2$ -catalyzed reaction of other furan and benzofuran with alkynes, as well as aryl propargyl ethers and *N*-propargyl-*N*-tosylanilines.

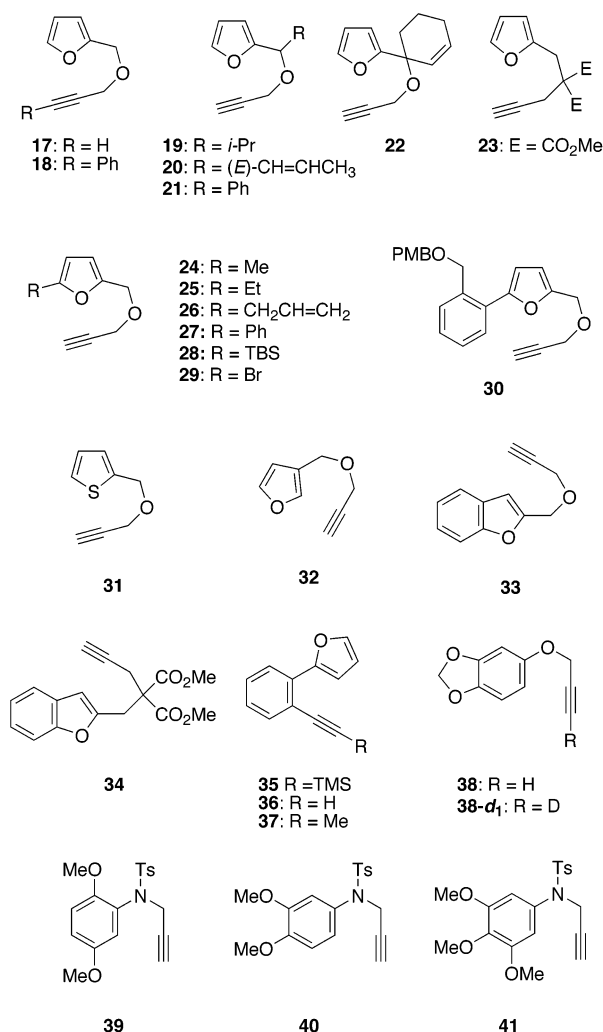
Results and Discussion

Synthesis of Furyl Alkynes and Related Substrates. Furyl alkynes **17**, **19–22**, **24–30**, and **32** were prepared by propargylation of the corresponding alcohols with propargyl bromide and NaH (Chart 1).²² Thiophene derivative **31**²³ and benzofuran **33** were also prepared by this method. The C-5 substituent of **24–26** was introduced by alkylation of the lithiated TBS protected furfuryl alcohol. The precursor of **28** was prepared by silylation of the lithiated TBS protected furfuryl alcohol. The aryl substituents of substrates **27** and **30** were attached by Suzuki or Stille coupling reactions of the corresponding arylboronic acids or phenyltributylstannane, respectively, whereas **18** was prepared by the Sonogashira reaction of iodobenzene with **17**. Substrate **23** was prepared by alkylation of the sodium enolate

- (9) (a) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913–4918. (b) Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414–1417.
 (10) Dankwardt, J. W. *Tetrahedron Lett.* **2001**, *42*, 5809–5812.
 (11) Herndon, J. W.; Zhang, Y.; Wang, K. J. *Organomet. Chem.* **2001**, *634*, 1–4.
 (12) Fürstner, A.; Mamane, V. J. *Org. Chem.* **2002**, *67*, 6264–6267.
 (13) The cyclization of alkynes with arenes can also be promoted by strong protic acids: Tovar, J. D.; Swager, T. M. *J. Organomet. Chem.* **2002**, *653*, 215–222, and references therein.
 (14) For the cyclization of similar systems with iodonium salts: Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed.* **1988**, *27*, 1546–1547.
 (15) (a) Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11 319–11 320. (b) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928–1929. (c) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1992**, *114*, 1344–1346.
 (16) Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2602–2604.
 (17) Ruthenium vinylidenes were also suggested as intermediates in the synthesis of 1*H*-naphtho[2,1-*b*]pyrans by reaction of phenols with propargyl alcohols catalyzed by $[Cp^*RuCl(\mu_2-SMe)_2RuCl^*Cl]$: Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 7900–7901.

- (18) (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11 553–11 554. (b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769–3771.
 (19) This transformation is somewhat reminiscent of the synthesis of phenols by intramolecular Diels–Alder reaction of alkynes with furans in the presence of a base, a reaction that actually takes place by previous isomerization of the alkyne to the allene: (a) Wu, H.-J.; Shao, W.-D.; Ying, F.-H. *Tetrahedron Lett.* **1994**, *35*, 729–732. (b) Wu, H.-J.; Ying, F.-H.; Shao, W.-D. *J. Org. Chem.* **1995**, *60*, 6168–6172.
 (20) (a) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14 179–14 233. (b) Moore, J. A.; Partain, E. M. *J. Org. Chem.* **1983**, *48*, 1105–1106.
 (21) Martín-Matute, B.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4754–4757.
 (22) The preparation of substrates of Chart 1 is detailed in the Supporting Information.
 (23) Boese, R.; Harvey, D. F.; Malaska, M. J.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1994**, *116*, 11 153–11 154.

Chart 1



of dimethyl propargyl malonate with (2-furylmethyl)tetramethylenesulfonium hexafluorophosphate.²⁴ All attempts to prepare 2-bromomethylfuran met with failure due to its instability. However, treatment of 2-hydroxymethylbenzofuran²⁵ with PBr₃ provided 2-bromomethylbenzofuran, which reacted with the sodium enolate of dimethyl propargyl malonate to afford **34**.

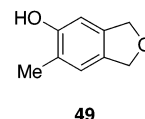
2-Arylfuran **35** was prepared by the Sonogashira coupling of trimethylsilylacetylene with 1,2-diiodobenzene, followed by a Negishi coupling of the resulting 2-iodo-1-(trimethylsilyl)ethynylbenzene²⁶ with furyl zinc chloride. Treatment of **35** with NaOH furnished **36**, which was methylated to give **37**. Substrates **38–41** were prepared by propargylation of the corresponding phenol or *N*-tosyl anilines.

Synthesis of Phenols Catalyzed by PtCl₂. By using PtCl₂ (5 mol %) as the catalyst in acetone under reflux, **17** gave a 2.75:1 mixture of phenols **42** and **43** in 60% yield (Table 1, entry 1). The reaction in toluene or 1,4-dioxane led to poor results. Complex Pt(MeCN)₂Cl₂ could also be used as the catalyst (Table 1, entry 2), whereas the reaction failed with Pt(COD)Cl₂ in acetone (Table 1, entry 3). However, the cyclization of **17** in 1,4-dioxane under reflux with Pt(COD)Cl₂ proceeded

in good yield, giving a 5:1 ratio of **42** and **43**. The cyclization of **17** with AuCl₃ (3 mol %) as the catalyst in MeCN at room temperature also afforded a mixture of **42** and **43**, although the yields were lower (30 and 1.5%, respectively). Only traces of phenols were obtained with RuCl₃ or RhCl₃ in acetone under reflux, whereas Pd(MeCN)₂Cl₂, Cu(MeCN)₄PF₆, or NiCl₂·6H₂O led only to recovered starting material. In general, we preferred to use more readily available PtCl₂ as the catalyst, without any purification of the commercial chloride. Rigorous exclusion of water from the solvents was not necessary.

The cyclization of **18**, with a phenyl substituent at the alkyne, failed to give any phenol derivative. On the other hand, reaction of **19** took place in good yield to afford a 2.4:1 mixture of **44** and **45** (Table 1, entry 5). However, substrates **20–22** only gave depropargylated alcohols as the major products. Substrate **23** behaved normally giving a mixture of **46** and **47** (Table 1, entry 6).

Reaction of **24** afforded selectively 4-hydroxyderivative **48** (Table 1, entry 7). In this case, traces of a second phenol (ca. 1% yield) could also be isolated. On the basis of the observation of two singlets at 6.98 and 6.65 for the aryl hydrogens, structure **49** was assigned for this secondary product. The cyclization of the homologous **25** proceeded in 94% yield to give **50** (Table 1, entry 8). Allyl substituted **26**, which was obtained partially contaminated with *E*-1-propenyl isomer (ca. 20%), reacted to give an inseparable 2:1 mixture of **51** and **52** (Table 1, entry 9). Partial conjugation of the double bond with the aryl was observed under all the conditions examined. Phenyl substituted derivative **27** was cyclized in excellent yield with PtCl₂ to give **53** (Table 1, entry 10). Identical result was obtained with Pt(MeCN)₂Cl₂ as the catalyst.



The reaction of *tert*-butyldimethylsilyl derivative **28** proceeded with partial cleavage of the silyl group. When the crude reaction mixture was treated with trifluoroacetic acid, phenol **43** was isolated in good yield (Table 1, entry 11).²⁷ This procedure allowed for the selective synthesis of **43**, a phenol that was obtained as the minor product of cyclization of substrate **17**. Reaction of **30** with PtCl₂ led to **54** in moderate yield, although more satisfactory results were obtained with Pt(COD)Cl₂ in 1,4-dioxane (Table 1, entries 12–13). Analysis of the crude reactions mixtures revealed the presence of aldehydes, which suggests that the sterically demanding aryl substituent of **30** interfered with the annulation process (see below). In contrast with furan **17**, the thiophene analogue **31** was recovered unchanged under all the conditions examined.

Reactions with PtCl₂ in Aqueous Acetone. The reaction of labile bromofuran **29** with PtCl₂ as the catalyst gave complex reaction mixtures. After much experimentation, a reaction performed in aqueous acetone with PtCl₂ as the catalyst (5 mol %) gave **55** as the major compound (41%). This unexpected product arises by cleavage of the propargyl group to form 5-bromofurfuryl alcohol, formal nucleophilic displacement of

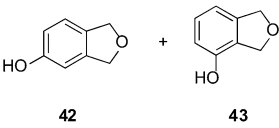
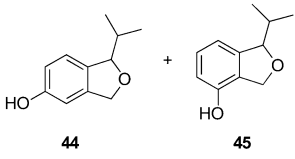
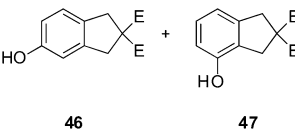
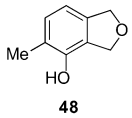
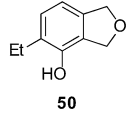
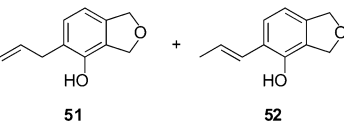
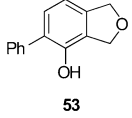
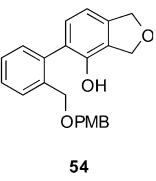
(24) Zhang, S.; Marshall, D.; Liebeskind, L. S. *J. Org. Chem.* **1999**, *64*, 2796–2804.

(25) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815–2820.

(26) Maeyama, K.; Iwasawa, N. *J. Org. Chem.* **1999**, *64*, 1344–1346.

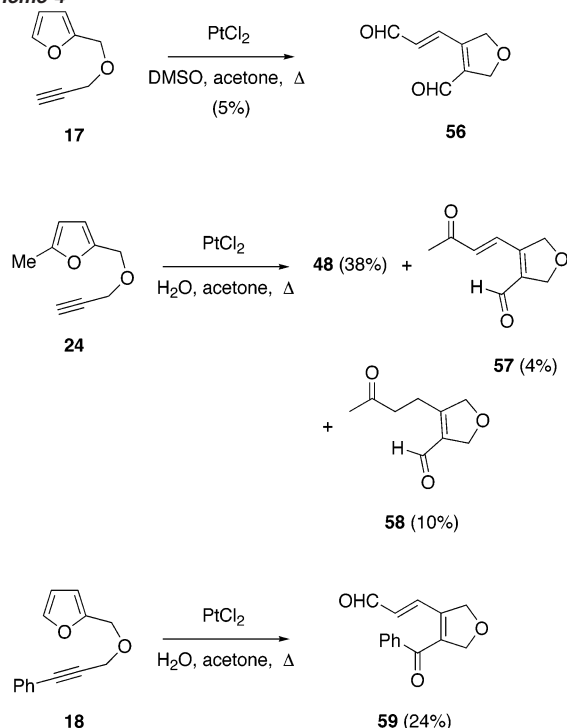
(27) For the accelerating effect of 5-silyl groups on the reactivity at C-2 of furans towards electrophiles: Herrlich, M.; Hampel, N.; Mayr, H. *Org. Lett.* **2001**, *3*, 1629–1632.

Table 1. Cyclization of Furylalkynes with PtCl₂^a

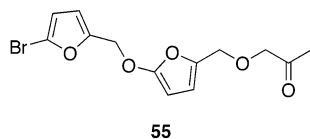
Entry	Substrate	Catalyst	Product(s)	Yield
1	17	PtCl ₂	 42 + 43	60% (2.75:1)
2	17	Pt(MeCN) ₂ Cl ₂	42 + 43	61% (1.4:1)
3	17	Pt(COD)Cl ₂	42 + 43	< 5%
4 ^b	17	Pt(COD)Cl ₂	42 + 43	78% (5:1)
5	19	PtCl ₂	 44 + 45	93% (2.4:1)
6	23	PtCl ₂	 46 + 47 (E = CO ₂ Me)	70% (3.4:1)
7	24	Pt(MeCN) ₂ Cl ₂	 48	75%
8	25	PtCl ₂	 50	94%
9	26^c	PtCl ₂	 51 + 52	89% (2:1)
10	27	PtCl ₂ or Pt(MeCN) ₂ Cl ₂	 53	98%
11	28	PtCl ₂	43^d	74%
12	30	PtCl ₂	 54	48%
13 ^b	30	Pt(COD)Cl ₂	54	57%

^a Unless otherwise stated, the reactions were carried out in acetone under refluxing conditions for 15–17 h with 5 mol % catalyst. ^b Reaction in 1,4-dioxane. ^c The starting material contained ca. 20% conjugated isomer. ^d After treatment of the crude reaction mixture with TFA.

Scheme 4



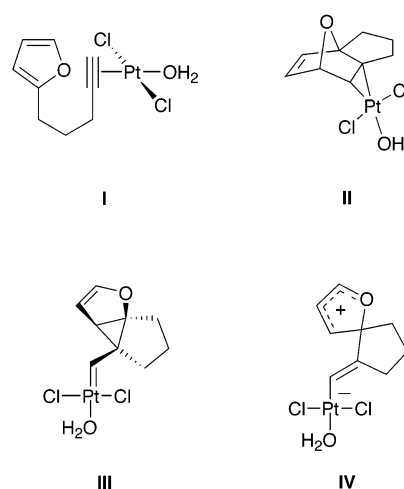
the bromide of a second molecule of **29**, and Markovnikov hydration of the alkyne.²⁸



Reaction of **17** or **24** with PtCl_2 in aqueous solvents led to very complex reaction mixtures, whose ^1NMR indicated the presence of aldehydes. Thus, reaction of **17** in aqueous acetone gave very labile **56** (Scheme 4), which could be isolated only in low yield, along with phenols **42** and **43** and oligomeric material. Reaction of **17** in a mixture of acetone and DMSO provided **56**. Although the yield was low (5%), it is significant that in the presence of DMSO no phenols **42** and **43** were formed. Reaction of **24** in aqueous acetone allowed for the isolation of phenol **48** (38%), and keto aldehydes **57** (4%) and **58** (10%). Although furyl alkyne **18** failed to provide any phenol under the standard conditions, its reaction with PtCl_2 in aqueous acetone gave keto aldehyde **59** as the major product, which was isolated in 24% yield.

Mechanism for the Formation of Phenols in the PtCl_2 -Catalyzed Cyclization of 5-(2-furyl)-1-Alkynes. Formation of 2,5-dihydrofurans **56**–**59** suggests that the formation of the C–C bonds of the final phenols is a stepwise process that starts by formation of a C–C bond between the α carbon of the furan and C-2 of the alkyne. Similarly, formation of **59** in an aqueous solvent indicates that the failure of **18** to give a phenol under the standard conditions can be attributed to the lack of reactivity

Chart 2



of an advanced intermediate, once the first C–C bond has already been formed.

To determine the reaction profile for the intramolecular reaction of alkynes and furans, we performed density functional calculations (DFT) on 5-(2-furyl)-1-pentyne as a model compound. Several pathways could be envisaged in principle starting by coordination of the alkyne to the metal center (**I**, Chart 2), which was assumed to be also coordinated to a water molecule. This is not an unrealistic assumption because the cyclizations were carried out with solvents that contained some water. Moreover, we have shown that water is an excellent ligand for Pt(II) , which can displace an alkene from the coordination sphere of square planar Pt(II) .^{1b} From complex **I**, a Diels–Alder reaction between the furan and the coordinated alkyne could give intermediate **II**.¹⁸ Alternatively, in analogy with the reaction of enynes (Scheme 1), formation of a cyclopropyl Pt -carbene **III** by reaction of the alkyne with the C2–C3 double bond of furan could also be conceived.^{1,29} A third plausible mechanism involves a Friedel–Crafts type reaction of the electron-deficient alkyne at C2 of the furan to form zwitterionic intermediate **IV**.

The Diels–Alder cycloaddition of complex **I** leads to endo adduct **II** in an endothermic transformation (+8.5 kcal mol^{−1}) (Chart 2 and Figure 1).³⁰ The transition state **TS**₁ lies 30.2 kcal mol^{−1} above **I** and shows relatively short C–C distances for the bonds that are being formed, especially for the one involving the alkyne terminal carbon (2.025 Å). The Cl–Pt–Cl angle diminishes from **I** to **II** (171.6° to 161.9°) due to the steric hindrance imposed by the side chain. Alternatively, the internal carbon of the alkyne can react with the nucleophilic C2–C3 bond of the furan to give the cyclopropylcarbene **III**. This complex shows a very short C(sp²)–Pt distance (1.890 Å), similar to that found for model **2** ($\text{MCl}_n = \text{Pt}(\text{H}_2\text{O})\text{Cl}_2$, $\text{Z} = \text{CH}_2$; $\text{R} = \text{Me}$) (1.881 Å).^{1b} The formation of **III** is exothermic (−3.4 Kcal mol^{−1}) and the activation energy to reach transition state **TS**₂ is much lower (9.4 Kcal mol^{−1}) than the corresponding to the Diels–Alder reaction. The reaction of **I** to give **III** would be the preferred pathway from both thermodynamic and kinetic

(28) (a) Hiscox, W.; Jennings, P. W. *Organometallics* **1990**, *9*, 1997–1999. (b) Hartman, J. W.; Hiscox, W.; Jennings, P. W. *J. Org. Chem.* **1993**, *58*, 7613–7614. (c) Kataoka, Y.; Osamu, M.; Tani, K. *Organometallics* **1996**, *15*, 5246–5249. (d) Baidossi, W.; Lahav, M.; Blum, J. J. *Org. Chem.* **1997**, *62*, 669–672. (e) Weber, L.; Barlmeyer, M.; Quasdorff, J.-M.; Sievers, H. L.; Stämmler, H.-G.; Neumann, B. *Organometallics* **1999**, *18*, 2497–2504.

(29) Structure of Pt(II) carbenes: (a) Cucciolito, M. A.; Panunzi, A.; Rufo, F.; Albano, V. G.; Monari, M. *Organometallics* **1999**, *18*, 3482–3489. (b) Cave, G. W. V.; Hallett, A. J.; Errington, W.; Rourke, J. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3270–3272. (c) Anderson, G. K.; Cross, R. J.; Manojlovic-Muir, L.; Muir, K. W.; Wales, R. A. *J. Chem. Soc., Dalton Trans.* **1979**, *4*, 684–689.

(30) Atomic coordinates for the structures of Figures 1 and 2 are given in the Supporting Information.

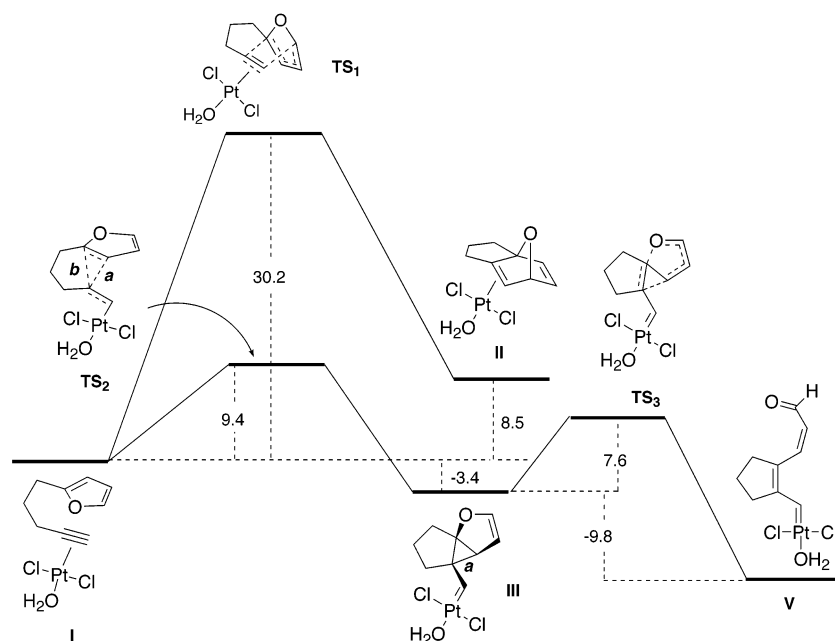
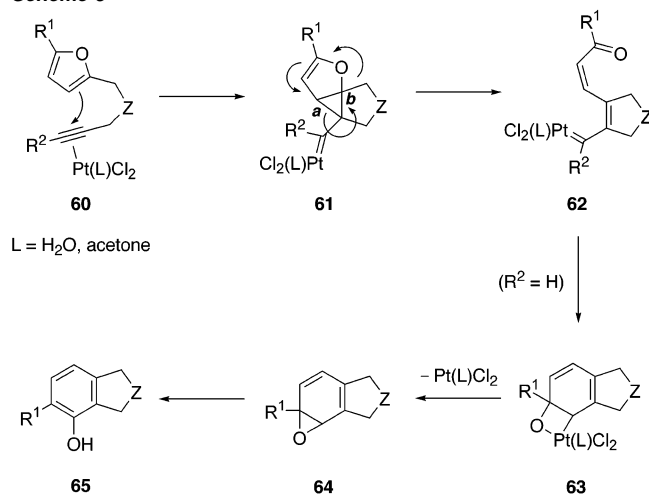


Figure 1. Reaction coordinate for the first (two alternative pathways) and the second steps of intramolecular reaction of furans with alkynes with PtCl_2 . ZPE corrected energies are given in kcal mol^{-1} .

Scheme 5



reasons. The attack of the furan takes place on the opposite side to the metal through an early asymmetric transition state with very different C–C distances (2.528 and 2.293 Å for *a* and *b* in TS_2 , Figure 1). The formation of a Friedel–Crafts complex **IV** was also considered but the only minimum energy structure that could be located was again **III**. Apparently, the delocalization of the positive charge in **IV** is not enough to compensate the stability of the Pt–cyclopropylcarbene **III**. Cleavage of the cyclopropane bond *a* of **III** takes place with the concerted opening of the dihydrofuran to form complex **V** in an exothermic transformation ($-9.8 \text{ kcal mol}^{-1}$) that implies only bond dissociations and proceeds with an activation energy of $7.6 \text{ kcal mol}^{-1}$ (Figure 1).

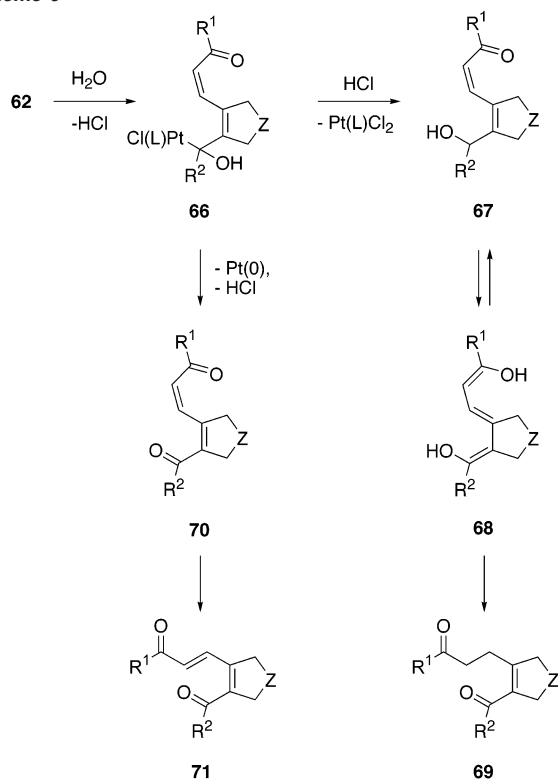
These findings led to the mechanistic proposal summarized in Scheme 5. The initially formed complex **60** would give intermediate **61** exothermically. An intramolecular [2+2] cycloaddition of the platinum carbene of **62** with the carbonyl could then give **63**, which would suffer reductive elimination to form arene oxide **64**. This last intermediate, which explains

the formation of the isolated phenols (i.e. **65**), has also been proposed by Hashmi in the AuCl_3 -catalyzed synthesis of phenols.¹⁸ In the last step, it was demonstrated that the OH of the phenol is derived from the oxiranyl oxygen.^{18b,31} The isolation of phenol **49** from **24** indicates that arene oxide **64** could rearrange to form an isomeric arene oxide by the “oxygen walk” mechanism,³² although this is only a minor side process.^{18b,33}

Formation of dicarbonyl derivatives **56–59** when the reaction was carried out in the presence of aqueous acetone can be explained by the addition of water to the platinum carbene to give **66** (Scheme 6), which could be cleaved by traces of acid to form **67**. Isomerization of **67** via **68**, would give more stable dicarbonyl compounds **69**. Alternatively, decomposition of **66** could give **70**, which would suffer cis to trans isomerization to yield **71**.³⁴ The transformation of **66** to **70** involves a formal β -hydrogen elimination to form a platinum hydride that decomposes to give Pt(0) and HCl. We have previously observed the formation of an aldehyde from a proposed platinum carbene intermediate that could take place by a similar process.^{1b,35} DMSO as a cosolvent might also oxidize carbene **62** to give dicarbonyl compounds of type **71**.³⁶

- (31) For reviews on arene oxides and their isomeric oxepins: (a) Vogel, E.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385–401. (b) Boyd, D. R.; Sharma, N. D. *Chem. Soc. Rev.* **1996**, *25*, 289–296. (c) For a recent lead reference on the structure of arene oxides, see: Jia, Z. S.; Brandt, P.; Thibblin, A. *J. Am. Chem. Soc.* **2001**, *123*, 10 147–10 152.
- (32) (a) Bruice, P. Y.; Kasperek, G. J.; Bruice, T. C.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1973**, *95*, 1673–1674. (b) Kasperek, G. J.; Bruice, P. Y.; Bruice, T. C.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1973**, *95*, 6041–6046.
- (33) The preferred formation of 5-hydroxy derivatives in the cyclizations of **17**, **19**, and **23** presumably reflects the higher stability of the corresponding carbocationic intermediates. Modeling the opening of 1,3-dihydroisobenzofuran-4,5-oxide (**64**, $\text{R}^1 = \text{H}$) by H^+ , we estimated a difference of $2.7 \text{ kcal mol}^{-1}$ in the ΔH_f (PM3 calculations) favoring the intermediate that leads to major isomer **42**.
- (34) The isomerization of **67** into α,β -unsaturated-1,6-dicarbonyl derivative **69** is a thermodynamically driven process [$\Delta H_{\text{calc}} = -12.8 \text{ kcal mol}^{-1}$ ($\text{R}^1 = \text{R}^2 = \text{H}$) or $-10.8 \text{ kcal mol}^{-1}$ starting from the E isomer of **72**; PM3 calculations].
- (35) For the related oxidation of a nickel carbene intermediate, see: Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6775–6776.

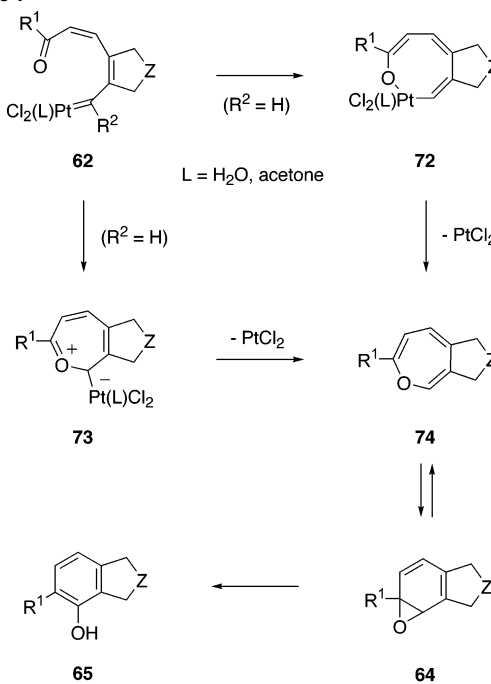
Scheme 6



Although the reactions in the presence of water give support for the involvement of intermediate **62** in the reaction pathway, the proposed [2+2] cycloaddition and subsequent reductive elimination³⁷ was somewhat speculative. Related rhodium carbenes have been shown by Murai to react intramolecularly with alkenes to form cyclopropanes.^{5c} However, the transformation of **62** to **63** appears to have no precedent. In support for this transformation, we performed DFT calculations for the [2+2] cycloaddition between $\text{Cl}_2(\text{H}_2\text{O})\text{Pt}=\text{CH}_2$ and formaldehyde as a simplified model system.³⁸ Although the calculations were in rough agreement with the mechanistic proposal advanced in Scheme 5, the activation energy for the [2+2] cycloaddition was found to be rather high ($31.4 \text{ kcal mol}^{-1}$). We therefore searched for alternative evolutions of intermediate **62** in route to the final phenols.

Herndon has proposed that the intramolecular reaction of aldehydes with Fischer chromium carbenes gives tetrahedral intermediates by attack of the carbonyl oxygen to the carbene carbon.³⁹ Similarly, rhodium carbenes react with carbonyl compounds to form carbonyl ylides.^{40,41} Particularly relevant is the proposal by Padwa of an 8π -electrocyclization of

Scheme 7



unsaturated rhodium(I) carbenes to afford oxepins, which finally evolve to afford substituted phenols.⁴²

On the basis of these mechanistic proposals, two alternative cyclization pathways for complex **62** were considered (Scheme 7). Thus, an 8π -electrocyclization of **62**, similar to that proposed by Padwa,⁴² would give **72**. On the other hand, a direct attack of the carbonyl oxygen to the electrophilic carbene carbon would generate intermediate **73**. Oxepin **74** could be formed by reductive elimination of PtCl_2 from **72**, or by a cleavage of the C-Pt bond of **73**.⁴³ Equilibration of oxepin **74** with arene oxide **64**,^{31,32,44} and epoxide opening (as in Scheme 5) would finally afford phenols **65**. Alternatively, **73** could directly cyclize to give arene oxide **64**. Valence tautomers **74** and **64** probably coexist in solution, favoring the more stable oxepins,⁴⁵ because the activation energy for the isomerization has been shown to be low.⁴⁴

Two different mechanisms for the evolution of intermediate **V** were considered. First, an intramolecular attack of the aldehyde oxygen on the carbene carbon would afford an oxepin derived complex such as **VI** (Figure 2). This slightly endothermic transformation is geometrically feasible due to the *s-cis* conformation of the carbene of **V'**, a slightly less stable

- (36) Oxidation of carbenes with DMSO: (a) Casey, C. P.; Anderson, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 1230–1231. (b) Dötz, K. H. *J. Organomet. Chem.* **1979**, *182*, 4869. (c) Ezquerro, J.; Pedregal, C.; Merino, I.; Flórez, J.; Barluenga, J.; García-Granda, S.; Llorca, M. A. *J. Org. Chem.* **1999**, *64*, 6554–6565. (d) See also: Perdichchia, D.; Licandro, E.; Maiorana, S.; Vandoni, B.; Baldoli, C. *Org. Lett.* **2002**, *4*, 827–830.
- (37) Formation of epoxides from four-membered ring oxametallacycles: (a) Mavrikakis, M.; Doren, D. J.; Barteau, M. A. *J. Phys. Chem. B* **1998**, *101*, 394–399. (b) Linic, S.; Barteau, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 310–317.
- (38) Calculations on the formation of epoxides by [2+2] cycloaddition/reductive elimination are given as part of the Supporting Information.
- (39) (a) Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, *63*, 4564–4565. (b) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267–1269. (c) Zhang, Y.; Herndon, J. W. *J. Org. Chem.* **2002**, *67*, 4177–4185. (d) Ghorai, B. K.; Herndon, J. W.; Lam, Y.-F. *Org. Lett.* **2001**, *3*, 3535–3538.
- (40) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223–270.

- (41) (a) Doyle, M. P.; Hu, W.; Timmons, D. *J. Org. Lett.* **2001**, *3*, 933–935. (b) Chiu, P.; Chen, B.; Cheng, K. F. *Org. Lett.* **2001**, *3*, 1721–1724. (c) Hamaguchi, M.; Matsubara, H.; Nagai, T. *Tetrahedron Lett.* **2000**, *41*, 1457–1460. (d) Jiang, B.; Zhang, X.; Luo, Z. *Org. Lett.* **2002**, *4*, 2453–2455.
- (42) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1997**, *62*, 1642–1652.
- (43) Oxepins have also been proposed as intermediates in the synthesis of phenols from (2-acylcyclopropyl)vinylidene-metal (Cr, Mo, W) complexes: Ohe, K.; Yokoi, T.; Miki, K.; Nishino, F.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 526–527.
- (44) For theoretical work on the oxepin/arene oxide equilibrium: (a) Hayes, D. M.; Nelson, S. D.; Garland, W. A.; Kollman, P. A. *J. Am. Chem. Soc.* **1980**, *102*, 1255–1262. (b) Schulman, J. M.; Disch, R. L.; Sabio, M. L. *J. Am. Chem. Soc.* **1984**, *106*, 7696–7700. (c) Bock, C. W.; George, P.; Stezowski, J. J.; Glusker, J. P. *Struct. Chem.* **1990**, *1*, 33–39. (d) Bock, C. W.; George, P.; Glusker, J. P. *THEOCHEM* **1991**, *80*, 227–246. (e) Contreras, J. G.; Madariaga, S. T. *Bol. Soc. Chil. Quím.* **2001**, *46*, 471–480.
- (45) According to PM3 calculations, the oxepins **74** ($\text{Z} = \text{O}, \text{CH}_2$; $\text{R}^1 = \text{H}, \text{Ph}$) are $10.3\text{--}12.7 \text{ kcal mol}^{-1}$ more stable than the corresponding arene oxides.

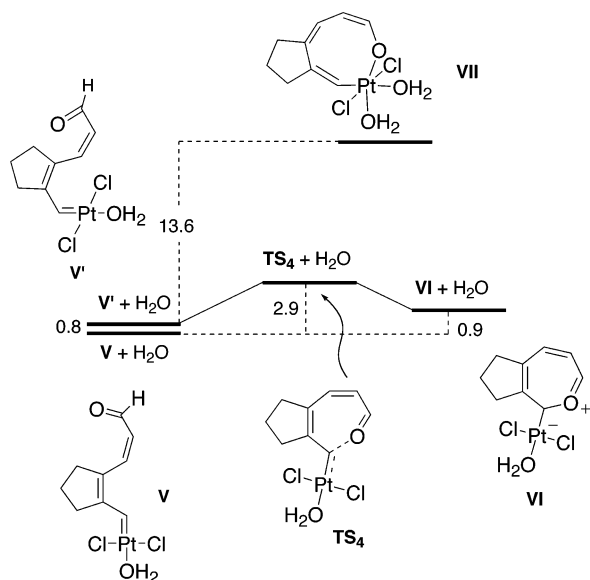


Figure 2. Reaction coordinate for the evolution of intermediate **V**. ZPE corrected energies are given in kcal mol^{−1}.

conformer of **V** lying on the way to **VI**. The reaction takes place through **TS₄** with an activation energy of 2.9 kcal mol^{−1}. The alternative electrocyclicization pathway (**62** → **72**, Scheme 7) would give complex **VII** with much higher energy than **TS₄**. The alternative five-coordinated complex, without the second molecule of water, is even less stable than **VII**. Therefore, attack of the aldehyde oxygen to the carbene carbon would be the preferred reaction. The calculations of the evolution of intermediate **V** agree with the proposal by Herndon for the intramolecular reaction of carbonyl groups with Fischer carbene complexes.³⁹ A similar pathway might be also followed by the Rh(I) carbenes involved in the reaction of cyclopropanes with alkynes catalyzed by [RhCl(CO)₂]₂.⁴²

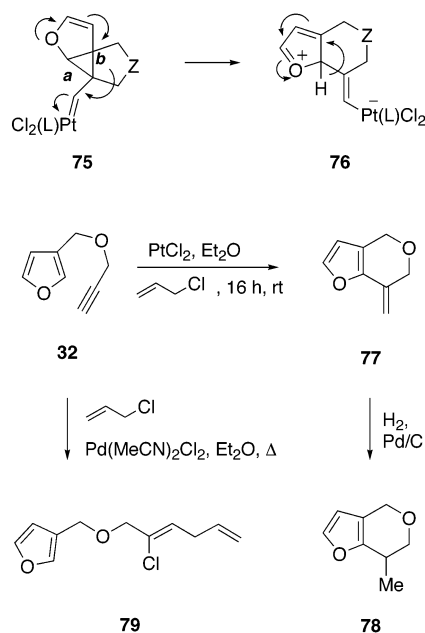
The result of Figure 2 sheds light on the nature of the Pt–C bonds in complexes **III**, **V**, and **V'**, which display relatively short Pt–C distances (1.890, 1.885, and 1.878 Å, respectively).²⁹ The electrophilic behavior of the coordinated carbon suggests a Fischer type carbene character for these complexes.

Cyclizations that Proceed through (apparent) Friedel–Crafts-Type Reactions. According to the mechanistic proposal of Scheme 5, attaching the alkyne-containing chain at C-3 of the furan was expected to give intermediate **75**, which might evolve in this case by cleavage of the bond labeled **b** of the cyclopropyl ring to form **76**, which could afford a furan by deprotonation (Scheme 8).

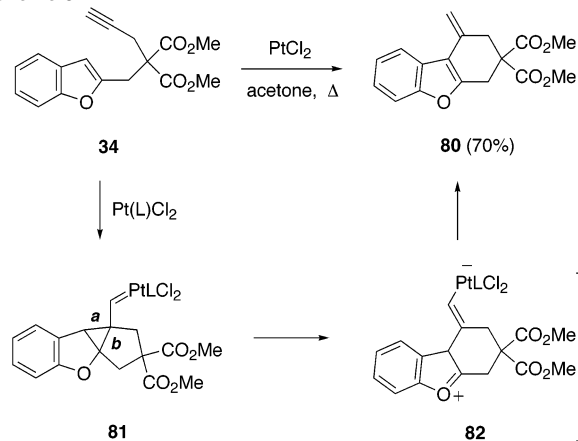
In the event, treatment of 3-furylmethyl propargyl ether (**32**) with PtCl₂ (5 mol %) led to **77** as the only new product, although the isolated yield was low due to its ready polymerization. For this reason, the crude product was immediately hydrogenated to give **78** (Scheme 8). Curiously, the best result (34% overall yield) was realized in the presence of allyl chloride, although the role of this additive is not clear. In contrast, the use of Pd-(MeCN)₂Cl₂ (5 mol %) as the catalyst (Et₂O, reflux) gave rise to chloroallylation of the terminal alkyne⁴⁶ furnishing **79**.

Benzofuran **33** suffered depropargylation under the standard cyclization conditions. However, malonate derivative **34** reacted

Scheme 8



Scheme 9



with PtCl₂ by an exo-mode attack of C-3 of the benzofuran to the alkyne to give **80** (70%) (Scheme 9). Formation of **80** can be rationalized by the formation of intermediate **81**, which would suffer preferential opening via cleavage of bond **b** to form **82**, and then **80**. Although cleavage of bond **a** appears to be possible (as in **61**, Scheme 6), benzannulation probably prevents subsequent formation of an intermediate similar to **62**.

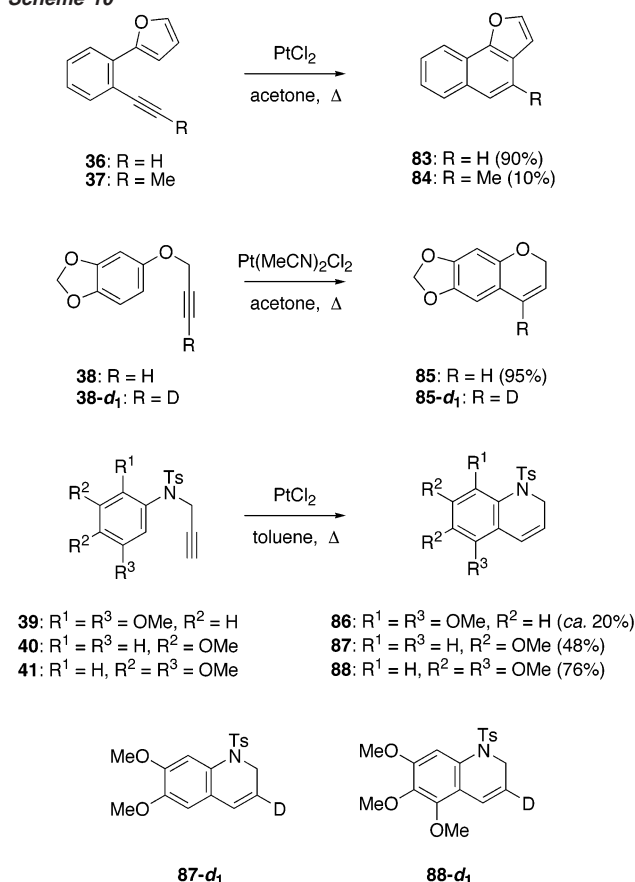
According to the proposal of Scheme 5, a tether of one or two atoms between the furan and the alkyne should not favor formation of an intermediate like **61**, because a three or four-membered ring would have to be formed. Thus, **36** reacted with PtCl₂ by a different pathway to that followed by 5-(2-furyl)-1-alkynes, leading to naphthol[1,2-*b*]furan (**83**)⁴⁷ in excellent yield (Scheme 10). This result is in keeping with shown in Scheme 2 for heterocycles **8**.^{10,12} Trimethylsilyl substituted substrate **35** failed to react under these conditions, while the reaction of **37** was very sluggish, leading to **84** in only 10% yield after 80 h.

Arylalkynes **38–41** also reacted with PtCl₂ (Scheme 9). Aryl propargyl ether **38** was cyclized with Pt(MeCN)₂Cl₂ in refluxing acetone to give **85**. Although this transformation proceeds in excellent yield (95%), decomposition of **85** by traces of acids

(46) (a) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55–63. (b) Bäckvall, J.-E.; Nilsson, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242–4246, and references therein.

(47) Narasimhan, N. S.; Mali, R. S. *Tetrahedron* **1975**, *31*, 1005–1009.

Scheme 10

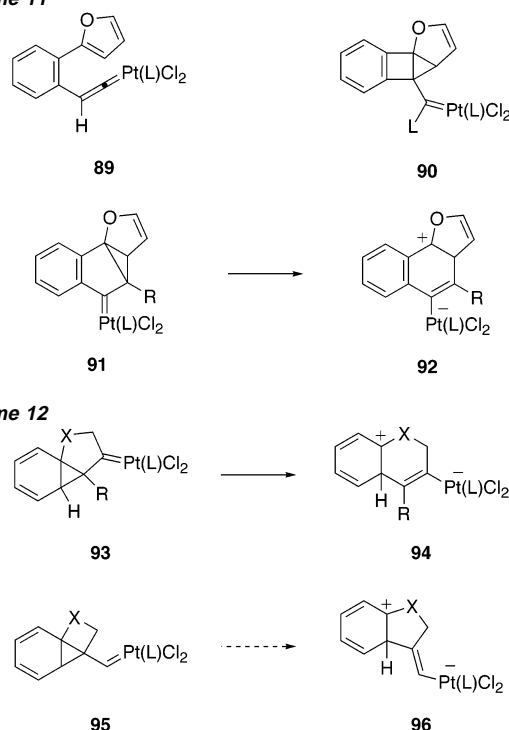


or by radical pathways led in occasions to much lower yields. When the reaction mixture was immediately hydrogenated (1 atm H₂, Pd/C), dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromene could be obtained in 83% overall yield. The reaction of **38** in toluene under refluxing conditions afforded a mixture of **85**, the regioisomer resulting from attack at C-2 of the aryl, and depropargylated phenol. However, at 80 °C in toluene, only **85** was obtained. Deuterated derivative **38-*d*₁** furnished **85-*d*₁** exclusively.

Aniline derivatives **39–41** reacted with PtCl₂ under reflux in acetone or toluene, although the best results were obtained in toluene. The reaction of **39** was quite slow and gave **86** in poor yield along with substantial amounts of depropargylated material.⁴⁸ Substrate **40** gave **87** (48%) and *N*-tosyl-3,4-dimethoxyaniline (50%). More electron-rich **41** gave **88** and *N*-tosyl-3,4,5-trimethoxyaniline in 76% and 20% yield, respectively. When the reactions of **40** and **41** were carried out in the presence of methanol-*d*₄, deuterated **87-*d*₁** and **88-*d*₁** were obtained.

The cycloisomerization of **36** into **83** could take place through vinylidene **89** (Scheme 11),^{10,13} although such a process would be impossible for substituted derivative **37**. It could be argued, however, that the slow reaction and low yield of this reaction indicates that the system is forced to follow an alternative, higher energy pathway. Deuteration experiments do not exclude the participation of intermediate **89** in the cyclization of **36**. Thus, when the reaction of **36** was performed in the presence of

Scheme 11



methanol-*d*₄, almost complete deuteration was observed at both C-4 and C-5 of **83**. This unexpected result could be explained by the ready deuteration of the relatively acidic arylalkyne facilitated by η^2 -coordination to PtCl₂. It is important to note that substrate analogous to **37**, with a pyrrole instead of a furan, was cyclized in excellent yield by Danwardt,¹⁰ which excluded the vinylidene pathway.

The results of Scheme 10 could be explained by invoking an electrophilic aromatic substitution pathway (Friedel–Crafts-type reaction).^{9,12} Although this proposal is quite plausible, alternative explanations based on the formation of cyclopropyl platinum carbenes also account for the experimental results. Thus, the exo-cyclization of **36** and **37** would have formed high energy intermediates such as **90** (Scheme 11), less likely than cyclopropyl platinum carbenes **91**, which would open to form zwitterionic intermediates **92**, precursors of **83** and **84**.

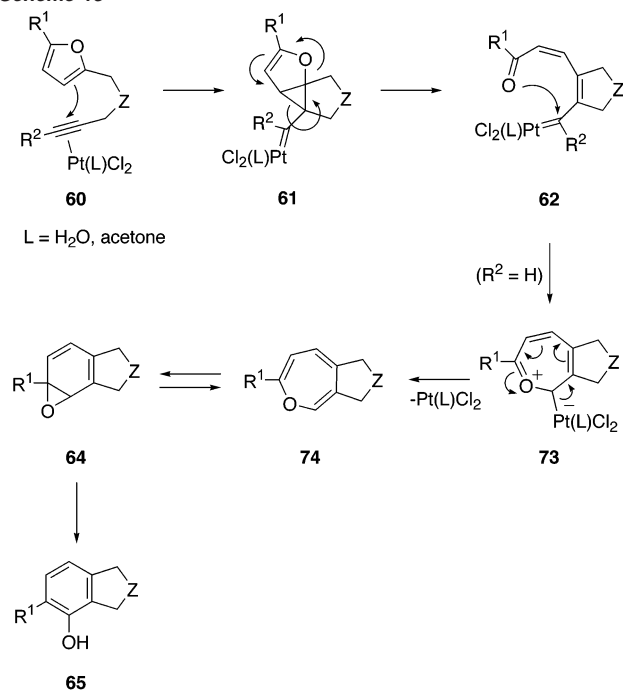
Deuteration studies exclude the participation of vinylidenes in the reactions of **38–41**, which would have led to deuteration at C-4 by methanol-*d*₄. In these cases, a mechanism involving formation of cyclopropyl platinum carbenes **93**, which would open to form **94**, nicely justifies the formation of 2*H*-chromenes and 1,2-dihydroquinolines by endo cyclizations (Scheme 12). The alternative exo pathways, via **95** and **96**, would be clearly disfavored processes.

Conclusions

In summary, the intramolecular reaction of furans with alkynes catalyzed by PtCl₂ is mechanistically related to that of enynes in polar solvents and is initiated by the nucleophilic attack of the furan on a (η^2 -alkyne)platinum(II) complex **60** (Scheme 13) to form a cyclopropyl platinum carbene **61**. This step is followed by cleavage of a C–C and a C–O bond of the tricyclic intermediate to form a carbonyl compound **62**, which cyclizes to form **73**. The active Pt(L)Cl₂ catalyst is then probably eliminated to form oxepin **74** in equilibrium with arene oxide

(48) *N*-tosyl-1,2-dihydroquinolines have been prepared by Pd(II)-catalyzed cyclization of *o*-allylic tosylanilides: Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585.

Scheme 13



64, which is then transformed to substituted phenol **65**.^{18,31,32} In this remarkable transformation, the first C–C bond is formed in the first step, whereas the second C–C bond formation takes place in the oxepin tautomerization, the penultimate step of the process. An alternative pathway involving a [2+2] cycloaddition of the carbonyl with the carbene seems less likely because of the high activation energy involved.

This work also sheds light on the reactivity of intermediate platinum carbenes formed in the PtCl₂-catalyzed reactions of alkynes with alkenes or furans, which behave as reactive Fischer-type carbenes toward nucleophiles. Other cyclizations of alkynes with furans or electron-rich arenes give products of apparent Friedel–Crafts-type reactions, although these transformations could also be explained by mechanisms involving the formation of cyclopropyl platinum carbenes.^{9,12,49}

(49) Carbenoids (L_nM–CRR′X) could be favored over carbenes (L_nXM=CRR′) with some metals: (a) Bernardi, F.; Bottoni, A.; Miscione, G. P. *Organometallics* **2000**, *19*, 5529–5532. (b) For platinum carbenoids: Hanks, T. W.; Ekland, R. A.; Emerson, K.; Larsen, R. D.; Jennings, P. W. *Organometallics* **1987**, *6*, 28–32.

Computational Methods

The calculations were performed with the GAUSSIAN 98 series of programs.⁵⁰ The geometries of all complexes were optimized applying the density at the functional theory (DFT) at the generalized gradient approximation using the B3LYP⁵¹ hybrid functional. The standard 6-31G(d) basis set was used for C, H, and Cl. For Pt we used the standard LANL2DZ basis set, which includes a relativistic ECP and the explicit description of 18 valence electrons by a double- ζ basis set. Harmonic frequencies were calculated at B3LYP level to characterize the stationary points and to determine the zero-point energies (ZPE). The starting approximate geometries for the transition states (TS) were located graphically. Intrinsic reaction coordinate calculations (IRC) showed that the TS found actually connect the reagents and the products.

Acknowledgment. This work is dedicated to Prof. T. Ross Kelly on the occasion of his 60th birthday. We are grateful to the MCyT (Project BQU2001-0193-C02-01) for support of this research. We also acknowledge the *Ministerio de Ciencia y Tecnología* and the *Comunidad Autónoma de Madrid* for predoctoral fellowships to B. M.-M. and C. N., respectively. We acknowledge the Centro de Computación Científica (UAM) for computation time and Johnson Matthey PLC for a generous loan of PtCl₂.

Supporting Information Available: Experimental details, characterization data for new compounds, results for the calculation on the [2+2] cycloaddition/reductive elimination pathway, and atomic coordinates for computed structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA029125P

- (50) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.
- (51) (a) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627. (b) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12 974–12 980.