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Cyclizations of Enynes Catalyzed by $PtCl_2$ or Other Transition Metal Chlorides: Divergent Reaction Pathways

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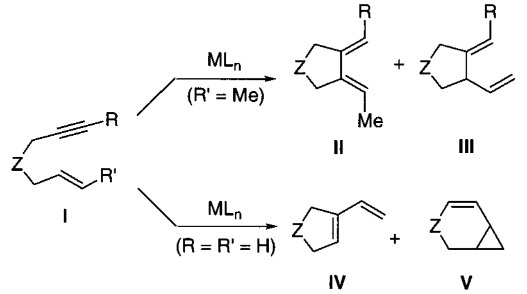
Abstract: 1-En-6-ynes react with alcohols or water in the presence of $PtCl_2$ as catalyst to give carbocycles with alkoxy or hydroxy functional groups at the side chain. The reaction proceeds by anti attack of the alkene onto the (η^2-alkyne)platinum complex. The formation of the C−C and C−O bonds takes place stereoselectively by trans addition of the electrophile derived from the alkyne and the nucleophile to the double bond of the enyne. Formation of five- or six-membered carbo- or heterocycles could be obtained from 1-en-6-ynes depending on the substituents on the alkene or at the tether. Although more limited in scope, Ru(II) and Au(III) chlorides also give rise to alkoxy- or hydroxycyclization of enynes. On the basis of density functional theory (DFT) calculations, a cyclopropyl platinacarbene complex was found as the key intermediate in the process. In the presence of polar, nonnucleophilic solvents, 1-en-6-ynes are cycloisomerized with $PtCl_2$ as catalyst. Formation of a platinacyclopentene intermediate is supported by DFT calculations. The reaction takes place by selective hydrogen abstraction of the *trans*-allylic substituent. Cycloisomerization of enynes containing disubstituted alkenes could be carried out using $RuCl_3$ or $Ru(AsPh_3)_4Cl_2$ in MeOH.

Introduction

Electrophilic transition metal complexes or halides MX_n catalyze the cyclizations of α,ω-enynes **I** to give cycles **II**−**IV** (Scheme 1).[1,2] Thus, palladium complexes $[Pd(L_2)X_2]$ favor the cycloisomerization pathway to give dienes **II** and/or **III**.[3,4] Cationic Ru(II) complexes such as $[CpRu(MeCN)_3]^+PF_6^-$ catalyze under mild conditions the cycloisomerization of enynes containing disubstituted alkenes to give selectively dienes of type **III**.[5] Enynes with disubstituted *trans*-alkenes are also cycloisomerized by the early transition metal complex $Cp_2Ti(CO)_2$.[6] A complementary reaction can be carried out with cationic Rh(I) complexes, leading to cycloisomerization of enynes containing *cis*-olefins.[7]

Scheme 1



A rearrangement that yields metathesis-type products **IV** was first found to be catalyzed by palladacyclopentadienes.[8] Subsequently, several electrophilic Ru(II) and Pt(II) complexes were also found to catalyze the formation of dienes of type **IV** from enynes **I**.[8f,9,10] In many cases, similar results were obtained using $PtCl_2$ or $[Ru(CO)_3Cl_2]_2$ as catalysts in toluene.[7b,8,11] These

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[1] Reviews of metal-catalyzed carbocyclizations: (a) Ojima, I.; Tzamarioudaki, M. L. Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662. (b) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365−393. (c) Trost, B. M. *Chem.*—*Eur. J.* **1998**, *4*, 2405−2412.

[2] (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1−16. (b) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34−42.

[3] (a) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636−644 and references therein. (b) Trost, B. M.; Phan, L. T. *Tetrahedron Lett.* **1993**, *34*, 4735−4738. (c) Trost, B. M.; Czeskis, B. A. *Tetrahedron Lett.* **1994**, *35*, 211−214. (d) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255−4267. (e) Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J.; Thomas, A. P. *J. Am. Chem. Soc.* **1999**, *121*, 6183−6192. (f) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131−6141. (g) For an alternative pathway: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 9728−9729.

[4] Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054−1059.

[5] Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714−715.

[6] Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976−1977.

[7] (a) Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490−6491. (b) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104−4106. (c) Ir(I)-catalyzed cycloisomerization or rearrangement of enynes: Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433−4436.

[8] (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636−1638. (b) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850−1852. (c) Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647−3650. (d) Trost, B. M.; Yanai, M.; Hoogsteen, K. A. *J. Am. Chem. Soc.* **1993**, *115*, 5294−5295. (e) Trost, B. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1085−1087. (f) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824−832. (g) Trost, B. M.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **1994**, *116*, 2183−2184.

[9] (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.; Sakurai, H.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104−9105.

[10] (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.

[11] (a) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801−3810. (b) Rearrangement of enynes catalyzed by cationic Pt(II) complexes in $CHCl_3$: Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. *Organometallics* **2001**, *20*, 3704−3709.

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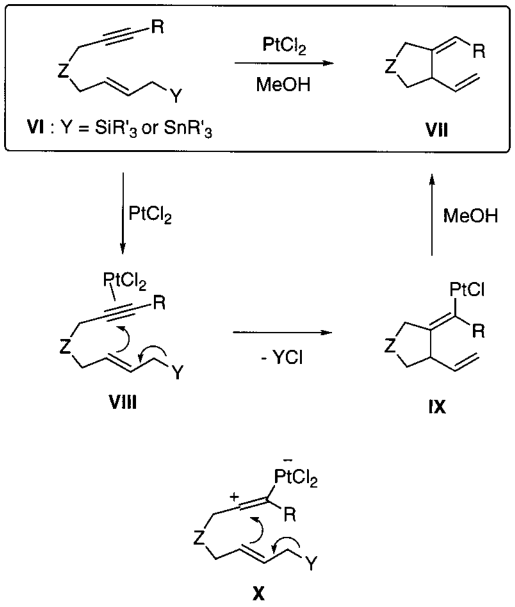
Scheme 2

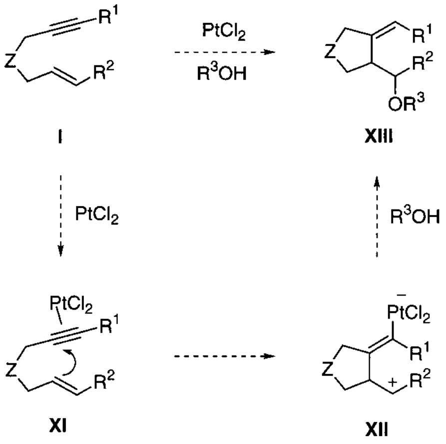


catalysts also promote the cycloisomerization of *ω*-aryl-1-alkynes.[12] On the other hand, enynes tethered by heteroatoms (Z = O or NTs) give rise to cyclopropanes **V** by using PtCl$_2$[10b] or PtCl$_4$[13] as catalyst.

We have recently reported a new cyclization that proceeds by the intramolecular reaction of alkynes bearing allylsilanes and allylstannanes **VI** in methanol to afford dienes **VII** (Scheme 2).[14] Although a variety of electrophilic metal halides catalyze this transformation, more general results were obtained with PtCl$_2$ in MeOH. This reaction was proposed to proceed by coordination of the metal to the alkyne (**VIII**), followed by anti attack of the allyl nucleophile to give alkenylmetal complex **IX**, which would undergo protonolysis by the solvent to give **VII**. Alternatively, zwitterionic complex **X** might be involved as an intermediate in the cyclization pathway.[15] Interaction of alkynes with $[PtRL_2]^+$ (R = Me, CF$_3$) was proposed to form cationic (η^2-alkyne)Pt(II) complexes as intermediates, which react with MeOH to form carbene or η^1-alkenyl complexes, depending on the substitution of the alkyne.[16]

We decided to essay the reaction of simple enynes **I** with neutral nucleophiles R^{3}OH in the presence of PtCl$_2$ as catalyst in the expectation that a similar intramolecular attack of the alkene onto the (η^2-alkyne)platinum complex (**XI)** would give rise to intermediate **XII**, which could be trapped by R^{3}OH to give carbo- or heterocycles **XIII** (Scheme 3). In principle, by performing the cyclization reaction in an alcohol or an aqueous solvent, the product of an alkoxy- or hydroxycyclization could be obtained. Although, on the basis of ample literature precedent,[2−12,14] the alkene-exo cyclization mode was expected to be more favorable, the alternative alkene-6-endo cyclization pathway could not be excluded.

Scheme 3



However, because of the lower reactivity of alkenes toward electrophiles, as compared with allylsilanes and stannanes,[17] the addition of R^{3}OH to the alkyne of the enyne catalyzed by PtCl$_2$ could compete with the desired pathway. Indeed, alkynes are known to react with alcohols in the presence of Pt(II) to form acetals.[18−20] Similarly, addition of water to alkynes gives ketones with Zeise's salt (K[Pt(η^2-C$_2$H$_4$)Cl$_3$]·H$_2$O) or PtCl$_2$ as catalyst.[21]

Here, we report the realization of the concept outlined in Scheme 3[22] and demonstrate that the reaction proceeds stereospecifically by using PtCl$_2$ as catalyst. Similar reactions can be promoted by using Ru(II) and Au(III) chlorides as catalysts. A general mechanistic scheme to account for the stereo- and regioselectivity of these reactions is proposed. Interestingly, by performing the reaction in a polar, nonnucleophilic solvent, enynes **I** undergo cycloisomerization by a mechanistically different pathway leading to cyclic dienes of type **III** (Scheme 1). Although more limited in scope, a similar reactivity was observed by using RuL$_4$Cl$_2$ complexes as catalysts.

Results

Cycloisomerization Catalyzed by PtCl$_2$ and Ru(II) Complexes. Reaction of enyne **1** with 5 mol % of PtCl$_2$ in 1,4-dioxane led quantitatively to cycloisomerization product **2** (Scheme 4 and Table 1, entry 1). The reaction also proceeded in acetone at room temperature (entry 2) or in HOAc at 70 °C (entry 3). Enyne **3** was similarly transformed into diene **4** in 1,4-dioxane or acetone at 65 °C (entries 4 and 5).[23] Reaction

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(12) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913−4918.

(13) (a) Blum, J.; Berr-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567−5569. (b) For the formation of a fused [4.1.0]bicycloheptene-pyranose tricycle derivative by the reaction of an enyne promoted by Co$_2$(CO)$_8$ in an atmosphere of CO (110 °C): Borodkin, V. S.; Shpiro, N. A.; Azov, V. A.; Kochetkov, N. K. *Tetrahedron Lett.* **1996**, *37*, 1489−1492.

(14) Fernández-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221−1222.

(15) A related (η^1-alkyne)ruthenium complex was proposed as an intermediate in a rearrangement reaction: Pilette, D.; Moreau, S.; Le Bozec, H.; Dixneuf, P. H.; Corrigan, J. F.; Carty, A. J. *J. Chem. Soc., Chem. Commun.* **1994**, 409−410.

(16) (a) Chisholm, M. H.; Clark, H. C. *Acc. Chem. Res.* **1973**, *6*, 202−209. (b) Michelin, R. A.; Mozzon, M.; Vialetto, B.; Bertani, R.; Bandoli, G.; Angelici, R. J. *Organometallics* **1998**, *17*, 1220−1226.

(17) (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−959. (b) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954−4961.

(18) (a) Steinborn, D.; Nünthel, R.; Krause, K. *J. Organomet. Chem.* **1991**, *414*, C54−C58. (b) Steinborn, D.; Nünthel, R.; Sieler, J.; Kempe, R. *Chem. Ber.* **1993**, *126*, 2393−2396. (c) Steinborn, D.; Gerisch, M.; Heinemann, F. W.; Scholz, J.; Schenzel, K. *Z. Anorg. Allg. Chem.* **1995**, *621*, 1421−1425. (d) Kataoka, Y.; Matsumoto, O.; Tani, K. *Organometallics* **1996**, *15*, 5246−5249.

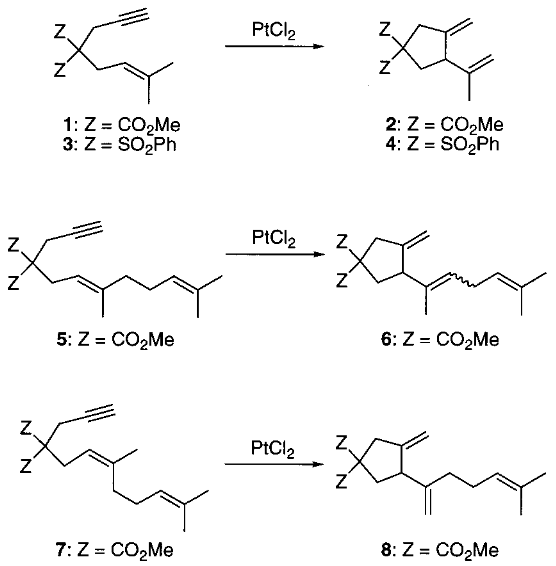
(19) Reaction of ethanol with Pt(II) and Pt(IV) chlorides, followed by addition of KCl, leads to the formation of the well-known Zeise's salt: Seyferth, D. *Organometallics* **2001**, *20*, 2−6.

(20) (a) Complex H[Pt(η^2-C$_4$H$_8$)Cl$_3$] is formed in the reaction of *n*-BuOH with hexachloroplatinic acid: Steinborn, D.; Grisch, M.; Mezweiler, K.; Schenzel, K.; Plez, K.; Bögle, H.; Magull, J. *Organometallics* **1996**, *15*, 2454−2457. See also: (b) Steinborn, D.; Grisch, M.; Hoffmann, T.; Bruhn, C.; Israel, G.; Müller, F. W. *J. Organomet. Chem.* **2000**, *598*, 286−291. (c) Nordhoff, K.; Steinborn, D. *Organometallics* **2001**, *20*, 1408−1418.

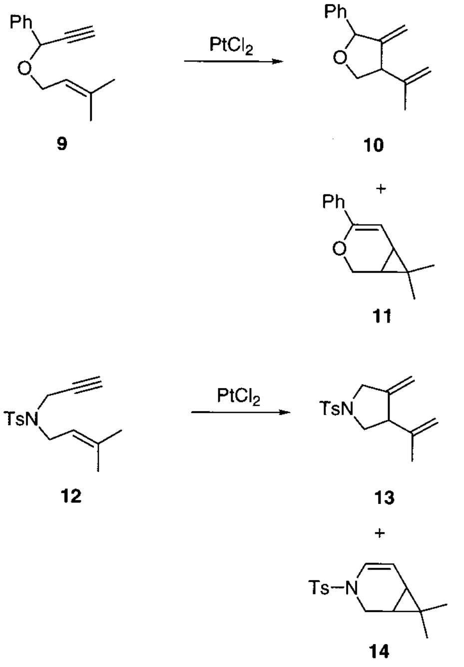
(21) (a) Hiscox, W.; Jennings, P. W. *Organometallics* **1990**, *9*, 1997−1999. (b) Hartman, J. W.; Hiscox, W. C.; Jennings, P. W. *J. Org. Chem.* **1993**, *58*, 7613−7614.

(22) Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549−11550.

Scheme 4



Scheme 5



Scheme 6

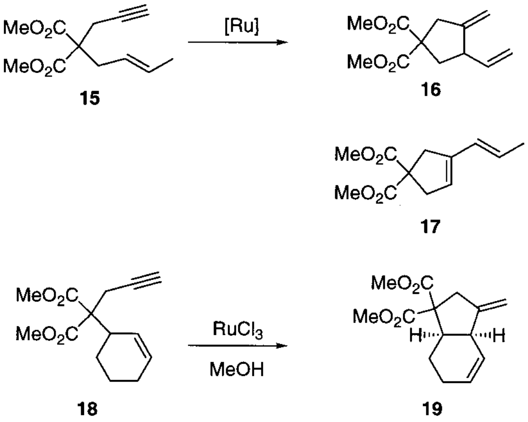


Table 1. Cycloisomerization of Enynes Catalyzed by $PtCl_2$ or RuL_nCl_2 (Schemes 4−6)[a]

entry	enyne	catalyst	solvent	product[b]	yield (%)
1	**1**	A	dioxane	**2**	100
2	**1**	A	acetone[c]	**2**	86
3	**1**	A	HOAc	**2**	69
4	**3**	A	dioxane	**4**	89
5	**3**	A	acetone	**4**	77
6	**5**[d]	A	acetone	**6**[e] + **8** (12:1)	98
7	**7**[f]	A	acetone	**8** + **6** (8:1)	93
8	**9**	A	acetone	**10**[g] + **11** (1.1:1)	66
9	**12**	A	acetone	**13** + **14** (1.2:1)	67
10	**15**	B	MeOH	**16**	42
11	**15**	C	MeOH	**16**	59[h]
12	**18**	B	MeOH	**19**	91

[a] Unless otherwise stated, all reactions were carried out with 5 mol % catalyst for 17−20 h at 70 °C. A, $PtCl_2$; B, $RuCl_3$; C, $Ru(AsPh_3)_4Cl_2$. [b] Ratio of products in parentheses. [c] Reaction at 23 °C. [d] 13:1 *E*/*Z*. [e] ~3:1 *E*/*Z*. [f] 8:1 *Z*/*E*. [g] 2.8:1 cis/trans. [h] Based on 81% conversion.

of dimethyl 2-geranyl-2-propargylmalonate (**5**) led to **6** as a 3:1 mixture of *E* and *Z* isomers, by the selective abstraction of a hydrogen from the allylic methylene (Table 1, entry 6). On the other hand, neryl derivative **7** gave **8** as a result of hydrogen abstraction from the methyl group (Table 1, entry 7).

Reaction of **9** with $PtCl_2$ in acetone gave a 1.1:1 mixture of cycloisomerization product **10** and cyclopropane **11** (Scheme 5 and Table 1, entry 8).[10b,13] Interestingly, *cis*-**10** was the major stereoisomer (2.8:1 cis/trans). This stereochemical outcome is in contrast with that obtained in the cycloisomerization of **9** catalyzed by $[CpRu(MeCN)_3]^+PF_6^-$, which led to *trans*-**10** as the major product.[5] Reaction of sulfonamide **12** with $PtCl_2$ as the catalyst in acetone also gave a mixture of cycloisomerization and cyclopropane derivatives **13** and **14** (Table 1, entry 9).

Cyclization of enyne **15** bearing a disubstituted alkene with $PtCl_2$ in 1,4-dioxane led to rearranged diene **17** in 45−50% yield (Scheme 6). Reaction of related substrates with disubstituted alkenes using $PtCl_2$ as catalyst led to mixtures of metathesis derivatives and uncharacterized products. However, treatment of **15** with $RuCl_3$ in MeOH led to cycloisomerization product **16** (Table 1, entry 10).[24] A similar result was obtained by using $Ru(AsPh_3)_4Cl_2$ (entry 11), while $Ru(PPh_3)_4Cl_2$, $Ru_2(CO)_{12}$, and $Ru(NO)Cl_3$ were not effective as catalysts. Enyne **18** was efficiently converted into bicycle **19** with $RuCl_3$ in MeOH (Table 1, entry 12). The use of $PtCl_2$ as catalyst in acetone in this case led only to unchanged starting material.

Alkoxy- and Hydroxycyclization Catalyzed by $PtCl_2$. 1-En-6-ynes led to cyclization with concomitant addition of the nucleophilic solvent in the presence of Pt(II) catalysts. In most cases, the crude reaction mixtures were notably clean. Occasionally, cycloisomerization or rearranged dienes were also formed as minor products, although these byproducts could be readily separated by chromatography because of their very different polarity. It is important to note that this cyclization is not a proton-catalyzed process, because no reaction took place in the presence of HCl, HI, or *p*-TsOH in MeOH.

Malonate **1** reacted in MeOH with $PtCl_2$ as catalyst to give methyl ether **20** and cycloisomerized diene **2** (Scheme 7 and Table 2, entry 1). Similar results were obtained by using Pt-

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(23) To avoid addition of water to the more substituted terminus of the alkene, the reactions in acetone were carried out in the presence of 4 Å molecular sieves.

(24) Under these conditions, RuL_nCl_2 species are presumably formed: Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*, 6th ed.; Wiley: New York, 1999; pp 1012−1013.

Scheme 7

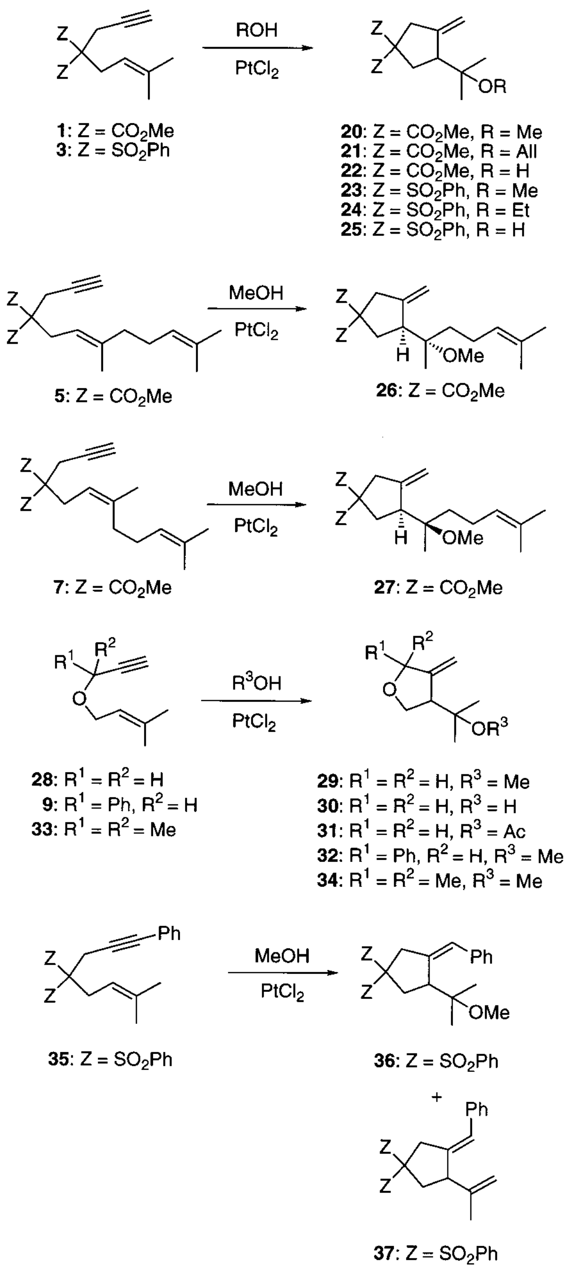

Table 2. Effect of the Pt Catalysts on the Selectivity of the Methoxycyclization versus Cycloisomerization of Enyne **1**[a]

entry	catalyst	**20** (%)	**2** (%)
1	$PtCl_2$	63	34
2	$Pt(MeCN)_2Cl_2$	67	12
3	K_2PtCl_4	62	23
4	K_2PtCl_6	62	10
5	$PtCl_2/NaPF_6$[b]	66	5
6	$Pt(MeCN)_2Cl_2/AgSbF_6$[b]	69	5
7	$Pt(MeCN)_2Cl_2/AgOTf$[b]	80	7
8	$Pt(MeCN)_2Cl_2/AgBF_4$[b]	99	<1
9	$Pt(MeCN)_2Cl_2/P(OR)_3$[b,c]	96	<1
10	$K_2PtCl_4/P(OR)_3$[b,c]	100	

[a] Unless otherwise stated, all reactions were carried out in MeOH under reflux with 5 mol % catalyst for 14−17 h. [b] 10 mol % of additive. [c] $P(OR)_3 = P(OCH_2)_3CEt$.

Table 3. Pt(II)-Catalyzed Cyclization of Enynes[a]

entry	enyne	catalyst	nucleophile	product(s)	yield (%)
1	**1**	$PtCl_2$	AllOH	**21**	57
2	**1**	$PtCl_2$[b]	H_2O	**22** + **2** (3.3:1)	74
3	**3**	$PtCl_2$	MeOH	**23**	88
4	**3**	$Pt(MeCN)_4(BF_4)_2$	MeOH	**23**	98
5	**3**	$PtCl_2$	EtOH	**24**	86
6	**3**	$PtCl_2$	H_2O	**25**	70
7	**5**[c]	$PtCl_2$	MeOH	**26**	61
8	**5**[c]	$Pt(MeCN)_2Cl_2$	MeOH	**26**	63
9	**7**[d]	$PtCl_2$	MeOH	**27** + **8** (3.3:1)	72
10	**28**	$PtCl_2$	MeOH	**29**	59 (76)[e]
11	**28**	$PtCl_2$	H_2O	**30**	73 (94)[e]
12	**28**	$PtCl_2$	AcOH[f]	**31**	55
13	**9**	$PtCl_2$	MeOH	**32**	64
14	**33**	$PtCl_2$	MeOH	**34**	68
15	**35**	$PtCl_2$[g]	MeOH	**36** + **37** (2:1)	79
16	**35**	$Pt(MeCN)_2Cl_2$[h]	MeOH	**36** + **37** (3.9:1)	77
17	**38**[i]	$PtCl_2$	MeOH	**39** + **40** (4:1)	83
18	**41**	$PtCl_2$	MeOH	**42**	77
19	**41**	$PtCl_2$	H_2O	**43** + **44** (6.7:1)	85
20	**45**	$PtCl_2$	MeOH	**46**	60
21	**45**	$Pt(MeCN)_2Cl_2$	MeOH	**46**	98
22	**45**	$PtCl_2$	H_2O	**47**	86
23	**45**	$Pt(MeCN)_2Cl_2$	H_2O	**47**	95
24	**48**	$PtCl_2$	MeOH	**49**	72
25	**18**	$PtCl_2$	MeOH	**50**	67
26	**15**[i]	$PtCl_2$	MeOH	**51** + **52** (1:1.5)	67
27	**15**[i]	$Pt(MeCN)_2Cl_2/AgSbF_6$	MeOH	**51** + **52** (1.3:1)	44
28	**53**	$PtCl_2$	MeOH	**54**	63
29	**55**	$PtCl_2$	MeOH	**56** + **57** (5.7:1)	94

[a] Unless otherwise stated, all reactions were carried out under reflux with 5 mol % catalyst. Reactions with water were carried out in 50% aqueous acetone at 40 °C. [b] 10 mol % $PtCl_2$. [c] 13:1 *E/Z*. [d] 8:1 *Z/E*. [e] Based on converted starting material. [f] Reaction at 70 °C. [g] 50 mol % $PtCl_2$. [h] 10 mol % $Pt(MeCN)_2Cl_2$; reaction time = 48 h. [i] 5:1 *E/Z*.

$(MeCN)_2Cl_2$, K_2PtCl_4, or K_2PtCl_6 (Table 2, entries 2−4). The addition of $NaPF_6$ or $AgSbF_6$ had little effect on the selectivity (Table 2, entries 5 and 6). Better results were obtained by using AgOTf or $AgBF_4$ (Table 2, entries 7 and 8). The increased selectivity on going from SbF_6^- to OTf^- to BF_4^- is different from that found in other transition metal-catalyzed reactions.[25] Reaction of **1** with a platinum complex with bicyclic phosphite $P(OCH_2)_3CEt$[26] as the ligand led also to an improvement in the selectivity of the cyclization favoring methoxycyclization product **20** (Table 2, entries 9 and 10). Importantly, diene **2** was recovered unchanged after being heated in MeOH with $PtCl_2$.

Although the results summarized in Table 2 indicate that the best results are obtained by using either $Pt(MeCN)_2Cl_2/AgBF_4$ or $Pt(II)/P(OCH_2)_3CEt$, in most cases $PtCl_2$ gave satisfactory results. Thus, reaction of **1** in allyl alcohol gave ether **21** (Table 3, entry 1), while the reaction in aqueous acetone afforded alcohol **22** (Table 3, entry 2). Cyclization of **3** with $PtCl_2$ as

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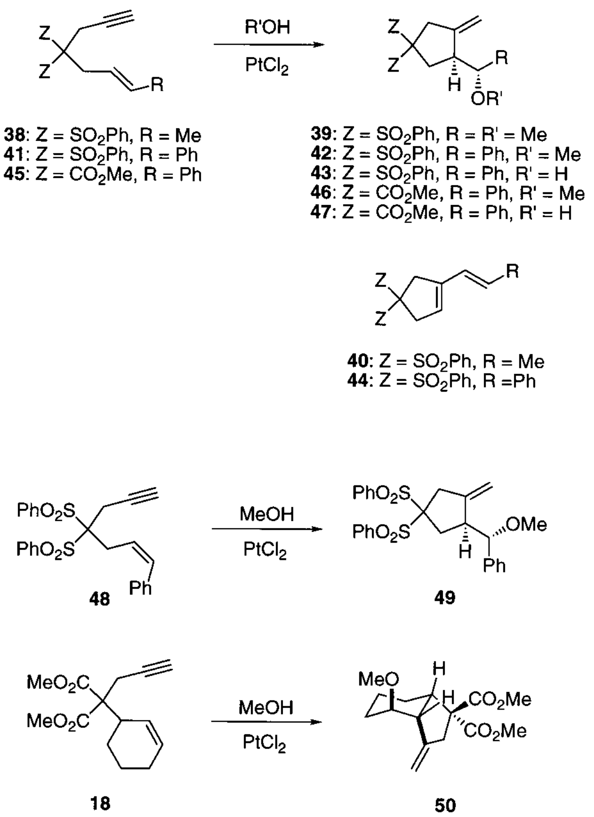
(25) (a) Evans, D. A.; Murray, J. A.; Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798−800. (b) Gosh, A. K.; Matsuda, M. *Org. Lett.* **1999**, *1*, 2157−2159. (c) Künding, E. P.; Saudan, C. M.; Bernardinelly, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1220−1223. (d) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233−1236. (e) Fürstner, A.; Voigtländer, D.; Schradewr, W.; Giebel, D.; Reetz, M. T. *Org. Lett.* **2001**, *3*, 417−420.

(26) (a) Serron, S. A.; Luo, L.; Stevens, E. D.; Nolan, S. P.; Jones, N. L.; Fagan, P. J. *Organometallics* **1996**, *15*, 5209−5215. (b) Stahl, L.; Trakarnpruk, W.; Freeman, J. W.; Arif, A. M.; Ernst, R. D. *Inorg. Chem.* **1995**, *34*, 1810−1814. (c) Ernst, R. D.; Freeman, J. W.; Stahl, L.; Wilson, D. R.; Arif, A. M.; Nuber, B.; Ziegler, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 5075−5081.

Scheme 8



38: Z = SO_2Ph, R = Me
41: Z = SO_2Ph, R = Ph
45: Z = CO_2Me, R = Ph

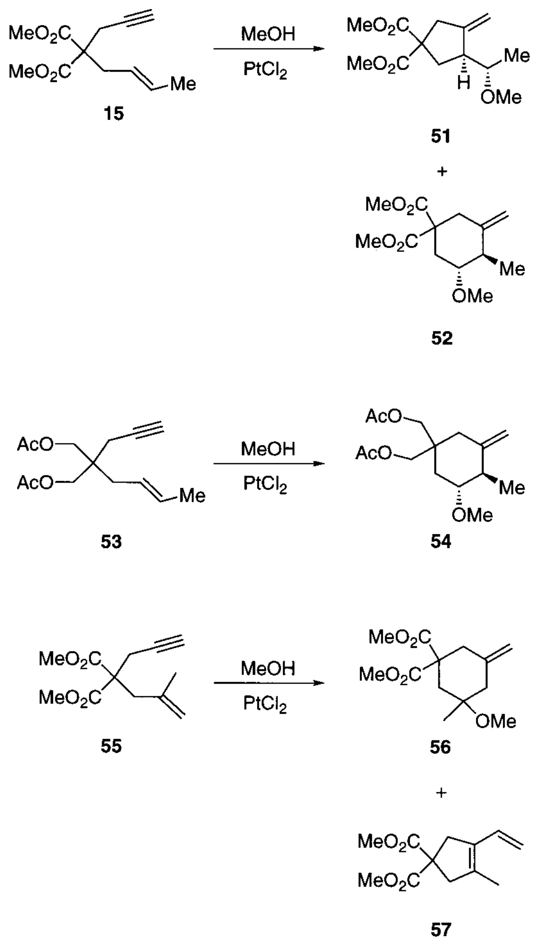
39: Z = SO_2Ph, R = R' = Me
42: Z = SO_2Ph, R = Ph, R' = Me
43: Z = SO_2Ph, R = Ph, R' = H
46: Z = CO_2Me, R = Ph, R' = Me
47: Z = CO_2Me, R = Ph, R' = H

40: Z = SO_2Ph, R = Me
44: Z = SO_2Ph, R =Ph

48 **49**

18 **50**

Scheme 9



15 **51** + **52**

53 **54**

55 **56** + **57**

catalyst in MeOH as the solvent gave **23** in high yield (Table 3, entry 3). In this case, an almost quantitative transformation was realized with Pt(MeCN)$_4$(BF$_4$)$_2$ (Table 3, entry 4). Reaction of **3** in EtOH led to **24**, while reaction in aqueous acetone afforded alcohol **25** (Table 3, entries 5 and 6).

Geranyl (**5**) and neryl (**7**) malonates reacted with MeOH to afford **26** and **27**, respectively (Scheme 7, Table 3, entries 7−9). Cyclization in MeOH or water also proceeds with propargyl prenyl ether (**28**) to give **29** and **30**, respectively (Table 3, entries 10 and 11). Use of acetic acid as solvent gave acetate **31** (Table 3, entry 12). Reaction of **9** and **33** in MeOH shows that the reaction tolerates steric hindrance at the propargylic position (Table 3, entries 13 and 14). Substitution at the alkyne led to a decrease on the cyclization rate. Thus, enyne **35** reacted sluggishly to afford a 2:1 mixture of methoxycyclization (**36**) and cycloisomerization (**37**) products (Table 3, entry 15). Use of more soluble Pt(MeCN)$_2$Cl$_2$ led to improved results (Table 3, entry 16).

Disubstituted alkenes also undergo the cyclization reaction (Scheme 8). Thus, **38** (5:1 trans/cis) reacted with MeOH to give **39** as a 5:1 mixture of stereoisomers, along with rearranged diene **40** as a minor product (Table 3, entry 17). Cinnamyl derivative **41** reacted with MeOH to give exclusively **42** (Table 3, entry 18). When the reaction was performed in aqueous acetone, in addition to alcohol **43**, rearranged diene **44** was also obtained (Table 3, entry 19). Malonate **45** afforded **46** and **47** as single isomers (Table 3, entries 20−23). Use of Pt(MeCN)$_2$Cl$_2$ as catalyst led to higher yields and faster reactions (Table 3, entries 21 and 23). Interestingly, cis derivative **48** reacted with MeOH to give **49**, the stereoisomer of **42** (Table 3, entry 24). Cyclization of enyne **18** in MeOH afforded **50** as a single isomer (Table 3, entry 25), whose configuration was determined by NOE experiments.

In contrast with disulfone **38**, malonate **15** reacted in MeOH to afford a 1:1.5 mixture of five- and six-membered ring carbocycles **51** and **52** (Scheme 9 and Table 3, entries 26 and 27).[27] Remarkably, enyne **53** led selectively to six-membered ring carbocycle **54** (Table 3, entry 28). The configuration of **54** was determined on the basis of $^1H-^1H$ couplings and NOE experiments. Similarly, substrate **55** reacted with MeOH in a 6-endo-trig process to give **56** along with rearranged diene **57** (Table 3, entry 29). Carbocycle **56** results from the attack of the nucleophile at the more substituted carbon of the double bond. None of the alternative 5-exo-trig product methoxycyclization derivatives were formed in the reactions of **53** and **55**. Enynes with monosubstituted alkenes are poor substrates for this reaction and led only to poor conversions after long reaction times.

The cyclization of 3-arylallyl propargyl ethers such as **58** had been shown to afford hydroxycyclization derivatives in aqueous 1,4-dioxane such as **59** with a Pd catalyst with *m*-sulfonated triphenylphosphine (TPPTS) ligand.[28] Interestingly, reaction of **58** in aqueous acetone with PtCl$_2$ as the catalyst also afforded **59**[29] (12%) along with the cyclopropyl aldehyde **60** (12%), whose configuration was confirmed by NOE experiments (Scheme 10).

Attempted methoxycyclization of enynes **1**, **15**, or **58** with PdCl$_2$, Pd(OAc)$_2$, or Pd(PPh$_3$)$_2$Cl$_2$ in MeOH met with failure,

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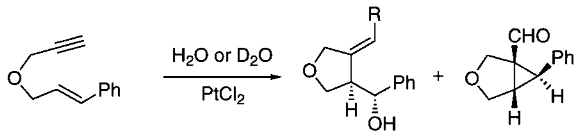
(27) We originally assumed that the reaction mixture contained **51** and its five-membered ring diastereomer.[22] However, the clean formation of **54** from **53** allowed us to assign unambiguously the structure of the second product as **52**.

(28) (a) Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **1997**, *38*, 8695−8698. (b) Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron* **2001**, *57*, 5137−5148.

(29) Compound **59** is identical to that obtained by a Pd-catalyzed process, whose configuration has been demonstrated by X-ray crystallography.[28b]

Scheme 10



58 **59**: R = H **60**
59-d_1: R = D

while that with Pd(MeCN)$_2$Cl$_2$ led to poor yields. Similarly negative were the results with enyne **1** and Cu(MeCN)$_4$(PF$_6$) as the catalyst in MeOH.

Alkoxycyclization Catalyzed by Ru(II) and Au(III). Enynes with trisubstituted alkenes also undergo methoxycyclization with RuCl$_3$ in MeOH. Thus, enyne **1** gave **20** in 62% yield (reflux, 17 h). However, dienynes **5** and **7** reacted with RuCl$_3$ (5 mol %) in MeOH under reflux to give more complex reaction mixtures from which **26** and **27** were isolated in 26 and 28% yields, respectively. Cu(MeCN)$_4$PF$_6$, Ru$_3$(CO)$_{12}$, CpRu(PPh$_3$)$_2$Cl/NaPF$_6$, RhCl$_3$, and Co$_2$(CO)$_8$ in MeOH are not suitable catalysts.

Recently, AuCl$_3$ has been shown to catalyze the intramolecular reaction of ω-furanyl-1-alkynes to give substituted phenols.[30] Therefore, we decided to essay highly electrophilic AuCl$_3$ as a catalyst for the methoxycyclization reactions. Heating of enyne **1** in MeOH under reflux with AuCl$_3$ (5 mol %) for 16 h gave **20** in 98% yield. Similarly, **7** gave **27** in 82% yield under these conditions, although a higher amount of catalyst was required (20 mol %). However, in contrast with the broad scope and excellent reproducibility of the Pt(II)-catalyzed cyclizations, AuCl$_3$ gave rise to erratic results or to complete failure in the cyclization of other enynes, probably because of the hygroscopic nature of this metal chloride.

Deuteration Studies. Deuteration experiments were also performed to shed light on the mechanisms of these processes. The configurations of the deuterated products were determined by comparison with the parent compounds, whose alkenyl methylene hydrogens were assigned by NOE experiments.

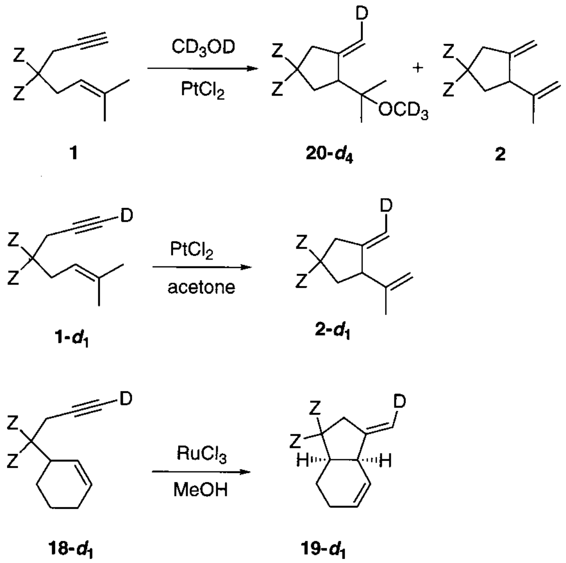
The reaction of **58** with PdCl$_2$ and TPPTS in D$_2$O led selectively to **59**-d_1 (Scheme 10). Analogously, cyclization of **1** in methanol-d_4 led to **20**-d_4 as a result of a stereoselective anti addition of the alkene and deuterium to the alkyne function (Scheme 11).

In contrast with these results, the cyclization of **1** in DOAc yielded **2** without any deuterium incorporation, while reaction of **1**-d_1 in acetone with PtCl$_2$ gave **2**-d_1. The same result was obtained in the cycloisomerization of **1**-d_1 in DOAc. Similar results were obtained in the cycloisomerization catalyzed by RuCl$_3$. Thus, reaction of **18** in methanol-d_4 afforded **19** and the corresponding treatment of enyne **18**-d_1 with RuCl$_3$ in MeOH gave **19**-d_1. These results demonstrate that the cycloisomerization proceeds intramolecularly.

Mechanistic Hypotheses

Cycloisomerization. The lack of reactivity of diene **2** with MeOH and PtCl$_2$ demonstrates that dienes are not intermediates in the formation of products **XIII** (Scheme 3). Furthermore, the deuteration results demonstrate that the cycloisomerization and the alkoxy- or hydroxycyclization reactions are mechanistically distinct. This conclusion is also supported by the formation of derivatives **36** and **37** with different configurations at the exocyclic alkenes in the Pt(II)-catalyzed cyclization of enyne **35** (Scheme 7).

Scheme 11

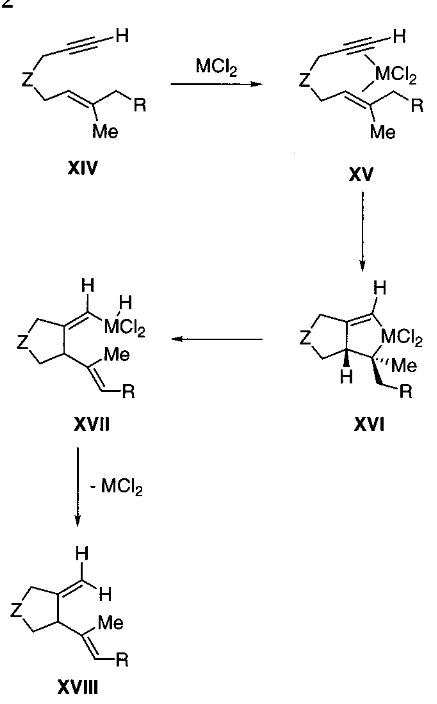


1 **20-d_4** **2**

1-d_1 **2-d_1**

18-d_1 **19-d_1**

Scheme 12



XIV **XV**

XVII **XVI**

XVIII

The cycloisomerization of enynes **XIV** with MCl$_2$ as catalysts (M = Pt, Ru) probably takes place by coordination of the transition metal to both unsaturated ligands (**XV**) (Scheme 12). Complex **XV** might suffer an oxidative cyclometalation to form key metalacycle **XVI**. Alternatively, a slipped (η^1-alkyne)metal species[15] could react with the alkene to give **XVI**. Metalacycle **XVI** might evolve by β-hydrogen elimination from an alkyl substituent to form **XVII**. As demonstrated in the specific formations of **6** and **8** from **5** and **7**, respectively (Scheme 4), the β-hydrogen elimination in the Pt(II)-catalyzed process takes place from the *trans*-allylic chain, which presumably adopts an equatorial disposition in the intermediate platinacycle.[5,6] Finally, a reductive elimination leads to cycloisomerized products **XVIII** and regenerates catalytically active MCl$_2$. The cycloisomerization of enynes **15** and **18** with Ru complexes (Scheme 6) proves that the ruthenacycles can suffer elimination from either *trans*- or *cis*-allylic positions.

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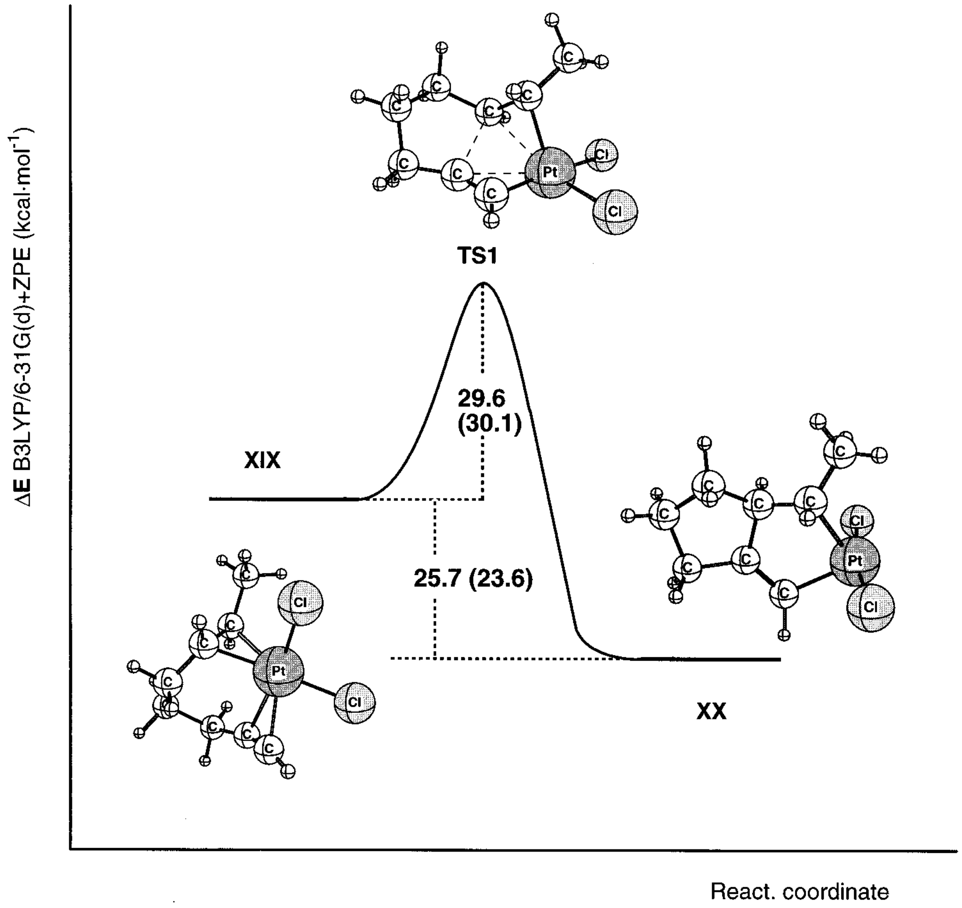
(30) (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553−11554. (b) See also: Dyker, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237−4239.

Scheme 13. Reaction Coordinate for the First Step of the Hydroxycyclization of Enynes; ΔG (kcal·mol^{-1}) Energies Are Given in Parentheses



To get deeper knowledge of the mechanism of this reaction, density functional theory (DFT) calculations were performed on complexes modeling the intermediates involved in the cycloisomerization reaction. Thus, (*E*)-2-octen-1-yne complexed to $PtCl_2$ (**XIX**) was selected as a model for complexes of type **XV**. The minimized geometry (Scheme 13) shows the expected square-planar coordination around the metal. The alkene is arranged perpendicularly to the coordination plane [(C=C)−Pt−*cis*-Cl dihedral = 86.90°][31] whereas the alkyne ligand is less tilted [(C≡C)−Pt−*cis*-Cl dihedral = 37.4°]. A slipped (η^1-alkyne)Pt(II) species was not located as an intermediate. Oxidative cyclometalation would give rise to platinacycle **XX** (Scheme 13). The optimized structure of this Pt(IV) complex shows an octahedral arrangement of the ligands around the d^6 metal center, with two vacant coordination sites. The trans chloride ligands are arranged cis to the alkyl and σ-alkenyl ligands. It is important to note that this arrangement of ligands around Pt was the energy minimum that could be located, which is in accord with the high trans influence of alkyl and alkenyl ligands. Although the coordination sites trans to the organic ligands remain vacant, in the presence of coordinating solvents, such as acetone or 1,4-dioxane, the coordination sphere might be completed by two additional ligands. Reaction from **XIX** to **XX** is significantly exothermic (24.2 kcal·mol^{-1}; energies include zero-point energy (ZPE) correction) even in the absence of other ligands. We have been able to locate complex **TS1** as the transition state in the oxidative cyclometalation of **XIX** to give **XX**, which was confirmed by internal reaction coordinate (IRC) studies. This transformation proceeds with a significant activation energy (29.6 kcal·mol^{-1}). In the transition state, **TS1**, the alkene and alkyne functional groups are significantly elongated (from 1.401 to 1.467 Å for the alkene bond and from 1.233 to 1.289 Å for the alkyne), and a new C−C bond is being formed (C−C distance = 2.163 Å). A chloride ligand is trans to the new σ-alkenyl−Pt bond, which leads to an increase in the Pt−Cl distance from 2.355 to 2.437 Å. Interestingly, the Cl−Pt−Cl angle remains around 90° in **TS1** (it changes from 86.3 to 95.4°), although it opens to 167.9° in the reaction product **XX**. This means that the cyclometalation takes place by an initial shift of the alkene from its location at the coordination plane in **XIX** to an axial position with concomitant formation of the C−C bond and new σ-alkenyl−Pt and alkyl−Pt bonds. The opening of the Cl−Pt−Cl angle to the final trans arrangement is probably pushed by the trans influence of the σ-alkenyl ligand. Although the activation energy for the cycloisomerization process is quite high, it might be lowered by interaction of **TS1** with coordinating solvents.

Selective abstraction of an allylic hydrogen trans to the side chain has also been demonstrated in the cycloisomerization catalyzed by $[CpRu(MeCN)_3]^+PF_6^-$.[5] The opposite regiochemistry had been achieved by using $Pd_2(dba)_3$/P(*o*-Tol)$_3$ in benzene−HOAc as solvent.[3b] Interestingly, although enynes with trans alkenes are isomerized with $Pd(OAc)_2$,[3a] the cycloisomerization of **5** with this catalyst leads to **8** (compare Scheme 4),[32] presumably as a result of the coordination of the remote double bond to Pd.[3a]

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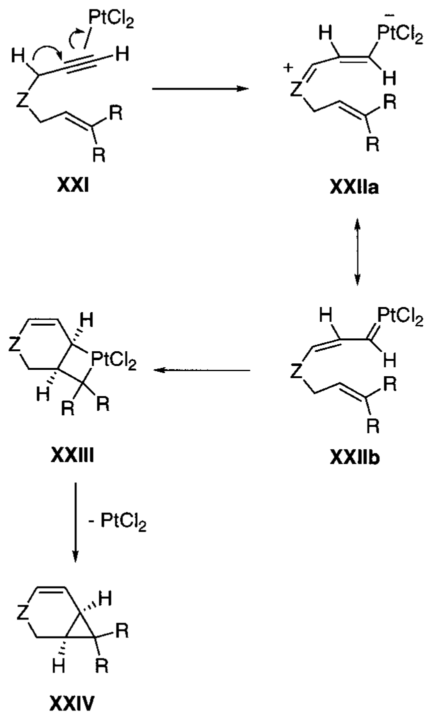
(31) It has been recognized that for alkene−Pt complexes, perpendicular and coplanar arrangements of the ligand with respect to the coordination plane have similar energies, and therefore, the actual configuration may be governed by steric hindrance: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 41−42.

Scheme 14



Formation of Cyclopropanes. We and others[10b,13] have observed that formation of cyclopropanes takes place only with heteroatom-tethered enynes such as **9** and **12**. A mechanistic rationale for the formation of these cyclopropanes is summarized in Scheme 14. Accordingly, the (η^2-alkyne)platinum complex **XXI** (Z = O, TsN) could suffer a 1,2-hydrogen migration to form an alkenyl platinum carbene **XXII** stabilized by the donor heteroatom.[33] The platinum carbene might then undergo an intramolecular [2 + 2] cycloaddition with the alkene to form a platina(IV)cyclobutane **XXIII**,[34] which could evolve by reductive elimination of $PtCl_2$ to form cyclopropanes **XXIV**.

Alkoxy- and Hydroxycyclization. The deuteration experiments on the hydroxy- and methoxycyclizations of **58** and **1**, respectively, and the selective formation of **36** from phenyl substituted enyne **35** point to a mechanism for these reactions similar to that proposed in the cyclization of allylsilanes and allylstannanes with alkynes,[14] in which the metal coordinates the alkyne as shown in Scheme 2. The selective transformations of the stereoisomeric pairs **5**/**7** and **41**/**48** into **26**/**27** and **42**/**49**, respectively (Schemes 7 and 8), demonstrate that this new reaction is stereospecific. On the other hand, formation of **50** (Scheme 8), **52**, and **54** (Scheme 9) demonstrates that the overall process corresponds to an anti addition of the alkyne and nucleophile across the double bond.

DFT calculations were performed on (*E*)-2-octen-1-yne with the alkyne η^2-coordinated to $PtCl_2(H_2O)$ (**XXV**) (Scheme 15) as a model for complexes of type **XI** (Scheme 3). H_2O was employed as an additional ligand, because the coordination of an alkyne to $PtCl_2$ gives rise to a tricoordinate 14-electron complex, which would incorporate a solvent molecule. This complex has the alkyne perpendicular to the coordination plane[31] and shows different distances for both Pt−C bonds. The terminal alkyne carbon (C1) lies closer to the metal than the internal one (C2) (2.086 and 2.195 Å, respectively). After coordination, the C−C bond is polarized with an electrophilic center at C2 (natural charges −0.25 and +0.05 for C1 and C2, respectively). Calculated natural charges (B3LYP/6-31G(d)) for these carbons in free propyne are −0.25 and −0.02. Nevertheless, the short C2−Pt distance suggests that the structure is better described as a η^2-coordinated alkyne rather than a η^1-coordinated vinyl cation. Starting from this metal complex, we explored the possibility that an energy minimum structure could be localized by approaching the nucleophilic alkene to the coordinated alkyne. In this way, we were able to locate bicyclic complex **XXVI** (Scheme 15). This complex can be described as methylcyclopropane cation stabilized by Pt. The Pt−C distance is relatively short (1.881 Å),[35] which indicates that this bond has carbene character despite the absence of coplanarity between the plane of the carbene substituents and the metal coordination plane (dihedral angles Cl−Pt−C−H = 53−57°).[36] The steric hindrance imposed by the chlorides probably prevents coplanarity. No other minimum could be localized by exploring conformers around the Pt−C bond. Reaction from **XXV** to **XXVI** is significantly exothermic (19.5 kcal·mol^{-1}) and takes place through transition state **TS2** (Scheme 15). This result indicates that bicyclic intermediate **XXVI** can be formed spontaneously in a single step by reaction of the alkene with the activated alkyne with a moderate activation energy (10.3 kcal·mol^{-1}). **TS2** shows relatively long C−C distances for the bonds that are being formed (C2−C6 = 2.422 Å and C2−C7 = 2.527 Å). Additionally, the C2−Pt bond significantly elongates from 2.195 Å in **XXV** to 2.681 Å in **TS2**. The alkyne bond shows an increased polarization in **TS2** (natural charges −0.36 and +0.15 for C1 and C2, respectively). Thus, the transition state resembles a vinyl cation[37] stabilized by bonding to the alkene. Coordination of the alkyne to Pt enhances the electrophilicity of the former and makes possible the reaction with the C−C double bond. Importantly, a complex similar to **XXVI** had been proposed in a remarkable cyclization reaction of dienynes catalyzed by Ru(II),[9c] and it was suggested that these type of intermediates might be involved in the metathesis-type cyclizations catalyzed by electrophilic transition metals.[38]

Involvement of **XXVI** as an intermediate in the alkoxy- and hydroxycyclization is further supported by the isolation of cyclopropyl aldehyde **60** (Scheme 10), which could arise by the air oxidation of the corresponding platinacarbene.[39]

The experimental and theoretical results are in accord with the general mechanistic interpretation summarized in Scheme 16. Thus, coordination of MCl_2 (M = Pt, Pd, Ru) or ML_nCl_2 (L = MeCN, MeOH, H_2O, or other ligand) to the alkyne would form (η^2-alkyne)metal complexes **XXVII** or a slipped (η^1-

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[32] Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, *26*, 4887−4890.

[33] For a lead reference on Pt carbenes, see: Cave, G. W. V.; Hallett, A. J.; Errington, W.; Rourke, J. P. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 3270−3272.

[34] (a) Review: Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241−2290. (b) Hoberg, J. O.; Jennings, P. W. *Organometallics* **1996**, *15*, 3902−3904. (c) Beyer, J.; Skaanderup, P. R.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 9575−9583 and references therein.

[35] (a) Calculations at the same level on σ-alkenyl−Pt complexes show that the Pt−C distance lies around 2.01 Å. Experimental σ-alkenyl−Pt bond distances are around 2.01−2.04 Å: (b) Zhang, X.; Watson, E. J.; Dullagan, C. A.; Gorun, S. M.; Sweigart, D. A. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2206−2208. (c) Ackermann, M. N.; Ajmera, R. K.; Barnes, H. A. *Organometallics* **1999**, *18*, 787−792. (d) Allevi, C.; Garlaschelli, L.; Malataesta, M. C. *Organometallics* **1990**, *9*, 1383−1391.

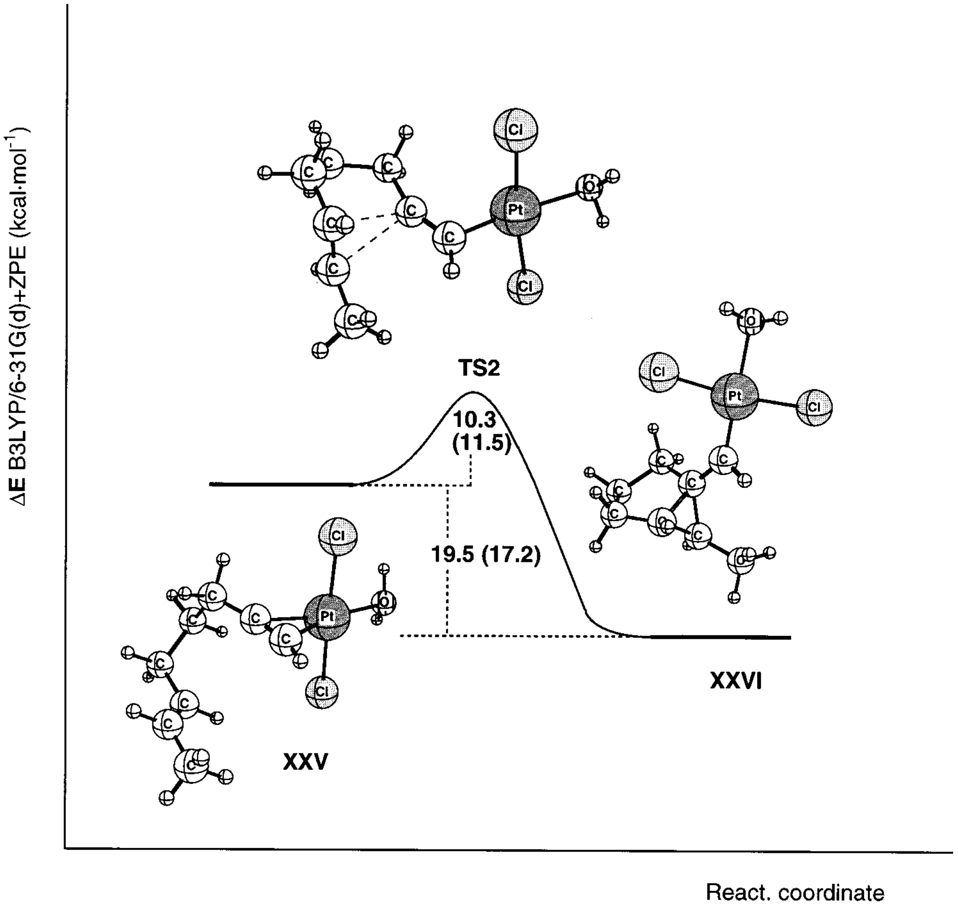
[36] The X-ray structure of a recently reported Fischer Pt carbene shows the coplanarity between the carbene and the coordination planes.[33]

[37] For a recent discussion on metal-stabilized vinyl cations, see: Müller, T.; Meyer, R.; Lennartz, D.; Siehl, H.-U. *Angew. Chem., Int. Ed.* **2000**, *39*, 3074−3077.

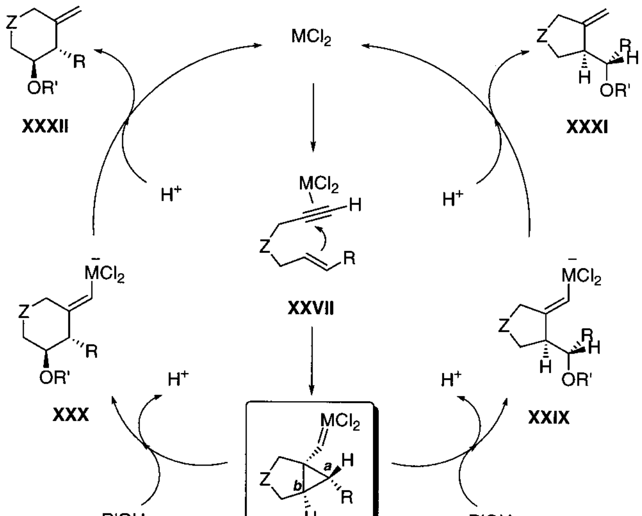
[38] An alternative mechanism proceeding by a metalacyclopentene has been favored by Trost.[2,8,11]

[39] 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 15. Reaction Coordinate for the Cycloisomerization of Enynes; Δ*G* (kcal·mol^{-1}) Energies Are Given in Parentheses



Scheme 16



alkyne)metal species.[15] A similar scheme could be drawn for the reaction catalyzed by $AuCl_3$. Intramolecular electrophilic attack on the alkene might form the key cyclopropylmetal carbene intermediate **XXVIII**. This species could also be viewed as the metal stabilized homoallyl−methylcyclopropyl−cyclobutyl cation.[40] Stereoselective attack at the cyclopropane carbons labeled as *a* and *b* of intermediate **XXVIII** by the alcohol or water could give either the five- (**XXIX**) or six-membered ring (**XXX**) derivatives, respectively. Finally, protonolysis (or deuteriolysis) of the alkenylmetal bond by the alcohol or water would give cycles **XXXI** or **XXXII**.

The regioselectivity in the nucleophilic attack is controlled by the electronegativity of substituent Z. Thus, the strong electron-withdrawing disulfone substituents of **38** led to five-membered ring carbocycle **39** (Scheme 8), while malonate **15** gave a mixture of **51** and **52** (Scheme 9). Accordingly, enyne **53** with less electron-withdrawing acetoxymethyl groups at C5 afforded exclusively six-membered ring carbocycles **54** (Scheme 9). On the other hand, attack at the C1 of cinnamyl derivatives **41**, **45**, **48** as well as at the more substituted carbon of the alkene of **55** suggests that a substantial positive charge evolves in the transition state in the nucleophilic opening of intermediate **XXVIII**.

Although the cycloisomerization and alkoxy- and hydroxycyclization final processes are mechanistically distinct, an equilibrium probably exists between complexes of type **XIX** and **XXV** in solution (Scheme 17). In the model system, displacement of the alkene ligand of **XIX** by H_2O to give **XXV** is exothermic, $\Delta G = -11.1$ kcal·mol^{-1} [ΔE(B3LYP+ZPE) $= -17.4$ kcal·mol^{-1}]. Because all the intermediates are neutral, the dielectric constant is not expected to have a significant influence on the reactions energetics, although, as has been discussed previously, interaction of the solvent might be not negligible for **TS1** (Scheme 13) because of the presence of vacant coordination sites. The favorable equilibrium shown in Scheme 17 and the lower activation energy for the formation of the key intermediate in the alkoxy- and hydroxycyclization reactions (Scheme 15) are in agreement with the experimental results (Tables 2 and 3).

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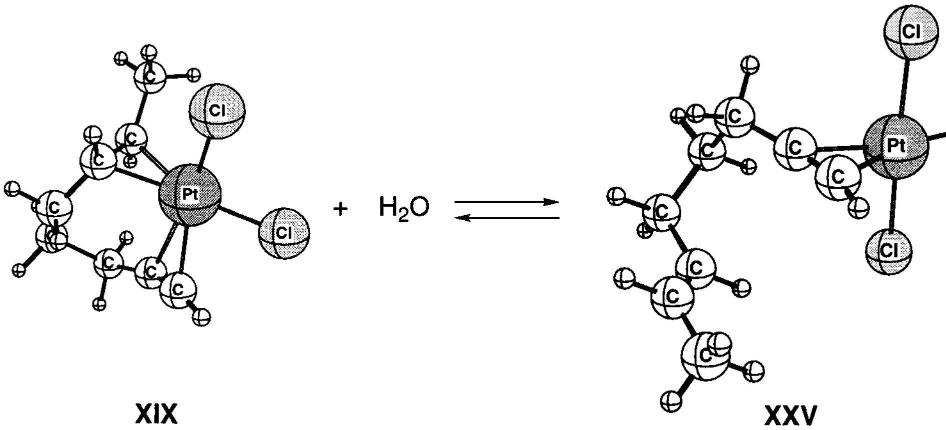
(40) Schleyer, P. v. R. In *The Nonclassical Ion Problem*; Brown, H. C., Ed.; Plenum: New York, 1977; pp 79−82.

Scheme 17



XIX **XXV**

Conclusions

This work demonstrates that $PtCl_2$, a catalyst for metathesis-type rearrangements of enynes in nonpolar solvents such as toluene,[9b,10,11] also catalyzes the alkoxy- and hydroxycyclization or the cycloisomerization reaction in polar solvents. Enynes containing disubstituted alkenes also undergo cycloisomerization by using $RuCl_3$ or $Ru(AsPh_3)_4Cl_2$ in MeOH. However, trisubstitution on the alkene favors Ru(II)-catalyzed alkoxycyclization. This reaction could also be carried out with $AuCl_3$ or Pd(II) complexes, although these reactions are more limited in scope.

Mechanistic studies and DFT calculations support the involvement of intermediates such as **XXVIII** in the alkoxy- and hydroxycyclization reactions. This complex might be also the key intermediate in the formation of rearrangement products **IV** (Scheme 1).

These cyclization reactions proceed with a maximum atom economy under neutral and relatively mild conditions and are environmentally benign. The alkoxy- and hydroxycyclization reactions catalyzed by Pt(II) are of particular interest, because these transformations allow for the simultaneous formation of a C−C and a C−O bond from enynes. Additionally, the reactions are stereospecific. Interestingly, in contrast with cationic polyenyne cyclizations, in which alkynes have been used as the terminators, this cyclization is initiated at the alkyne terminus of the enyne.[41] This method offers an alternative to current methodologies for the synthesis of carbocycles based on the intramolecular attack of silyl enol ethers to alkynes promoted by $Pd(OAc)_2$ or $HgCl_2$.[42,43] It is expected that increasing the reactivity of the alkene by substitution of alkoxy, trialkylsilyloxy, or amine substituents should lead to new transition metal-catalyzed cyclization reactions under mild conditions. Additionally, trapping of intermediates with carbon nucleophiles should allow for the formation of an additional C−C bond. Work along these lines is in progress.

Computational Methods

The calculations were performed with the GAUSSIAN 98 series of programs.[44] The geometries of all complexes were optimized at the HF level to obtain starting structures for subsequent optimizations applying density functional theory (DFT) at the generalized gradient approximation using the B3LYP[45] 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 geometry for the transition state (TS) was located graphically. Intrinsic reaction coordinate (IRC) calculations showed that the TS found actually connects the reagent and the product. Natural charges were obtained from the natural bonding orbitals (NBO) analysis.

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Supporting Information Available: Experimental details, characterization data for new carbocycles, and atomic coordinated for structures of Schemes 13 and 15 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[41] For reviews, see: (a) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, chapter 1.9. (b) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812−2833.

[42] (a) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916−4925. (b) Toyota, M.; Odashima, T.; Wada, T.; Ihara, M. *J. Am. Chem. Soc.* **2000**, *122*, 9036−9037.

[43] See: Frontier, A. J.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6151−6159 and references therein.

[44] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O. J.; 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.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, R.; Gomperts, R. L.; Martin, D. J.; Fox, T.; Keith, M. A.; Al-Laham, C. Y.; Peng, I.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

[45] (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*, 12974−12980.