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Catalytic Cyclization of *o*-Alkynylbenzaldehyde Acetals and Thioacetals. Unprecedented Activation of the Platinum Catalyst by Olefins. Scope and Mechanism of the Reaction

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Abstract: A general protocol for the synthesis of functionalized indenes from *o*-alkynylbenzaldehyde acetals and thioacetals has been elaborated. Acetals uniformly give cyclization products having the alkyl group from the starting acetylene migrated to the α-position, whereas the cyclization of the corresponding thioacetals proceeds without alkyl migration. Optimization of the catalytic system for the cyclization of *o*-alkynylbenzaldehyde acetals revealed an unknown activation effect: $PtCl_2$ was found to be a better catalyst for the cyclization of acetals in the presence of olefins than without. A similar catalytic system ($PtCl_2$/benzoquinone) has been found to be appropriate for the cyclization of cyclic acetals, whereas the optimal catalyst for the reaction of thioacetals is PdI_2. NMR monitoring of two reactions, acetal **3a** + $Pd(CH_3CN)Cl_2$ in CD_3CN and thioacetal **5j** + PdI_2 in CD_2Cl_2, revealed that in both reactions similar cationic species are formed at the early stage of the transformation. Computational data (B3LYP/SDD level of theory) suggest that the difference in the reaction pathways for acetals and thioacetals can be rationalized by taking into account the relative stabilities of the corresponding vinylpalladium intermediates (**22** vs **20** and **19** vs **21**), which suggests a reversible thermodynamically controlled alkyl migration in the intermediate vinylcationic species.

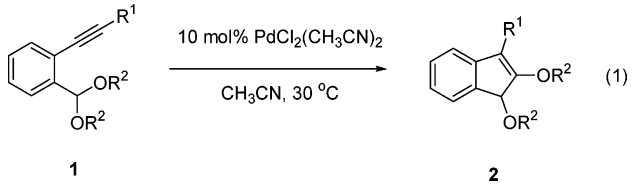
Introduction

Intramolecular palladium-catalyzed cyclization of alkynes is a useful tool for the synthesis of five-membered carbo- and heterocycles.[1] The heterocyclic products include unsaturated lactones,[2] furans,[3] pyrroles, and indoles,[4] whereas the carbocyclizations of this type provide a convenient approach to highly functionalized cyclopentanes[5] (Scheme 1). These reactions are usually thought to proceed via the initial formation of palladium−alkyne π-complexes, which undergo nucleophilic attack of G (C, N, O nucleophiles).[1]

The nature of the reaction product is considered to be defined by the properties of the resulting vinylpalladium intermediates and the nucleophiles present in the reaction mixture. The product can be formed directly via reductive elimination from the initially formed vinylpalladium intermediates, or the vinylpalladium intermediates can rearrange into further intermediate species, insert CO, or interact with other substrates present in the reaction mixture prior to the reductive elimination regenerating the catalyst.

Despite the large amount of synthetic studies for this type of the catalytic cycle, experimental evidence supporting the structure of the reactive intermediates is still lacking. Although several palladium−alkyne π-complexes of either Pd^0 or Pd^{II} have been characterized,[6] we are unaware of any experimental studies of the mechanism of the Pd-catalyzed cyclizations of alkynes.

Recently we have reported a palladium-catalyzed intramolecular carbalkoxylation reaction accompanied by an unprecedented 1,2-alkyl migration (eq 1).[7] It should be noted that such



1 2 (1)

(1) Recent review: Takacs, J. M.; Vayalakkada, S.; Jiang, X. *Science of Synthesis*; Thieme: Stuttgart, Germany, 2003; Vol. 1, pp 265−318.
(2) (a) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323. (b) Mandai, T.; Ohta, K.; Baba, N.; Kawada, M.; Tsuji, J. *Synlett* **1992**, 671. (c) Tsuda, T.; Ohashi, Y.; Nagahama, N.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 2650. (d) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976.
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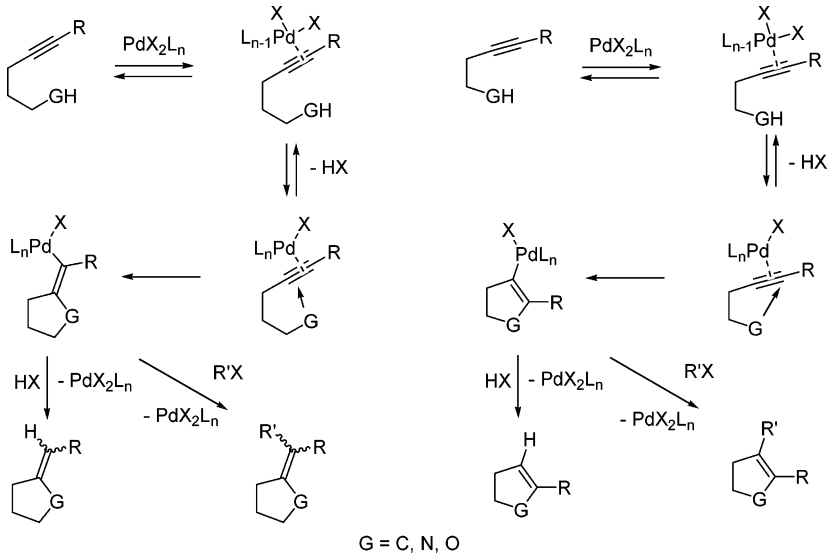
Scheme 1



type of alkyl migration is a quite rare phenomenon in transition-metal-catalyzed reactions. The only other alkyl migration example we are aware of occurs during the rhodium-catalyzed decomposition of some α-diazo esters.[8]

Here we report the scope of the catalytic carbocyclization with respect to the substrates and reagent structures, nature of the catalyst, and reaction conditions together with the mechanistic details revealed by NMR interception of intermediates and state-of-the-art DFT calculations.

Results and Discussion

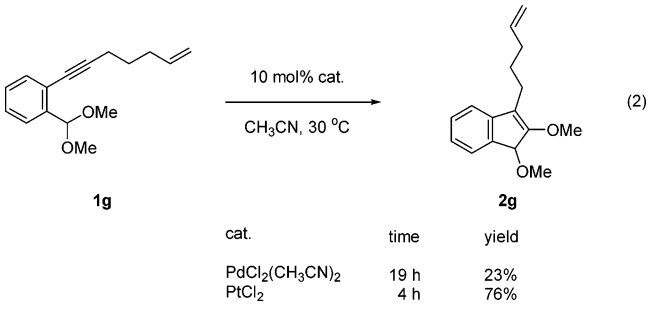
Scope of the Reaction and Modification of the Catalyst. We have found that the catalytic carbocyclization can be carried out for a wide range of the substrates, but in many cases modification of the catalyst is required. Thus, although the initially reported catalyst ($PdCl_2(CH_3CN)_2$) gave acceptable results with substrates **1a** (R^1 = *n*-Pr, R^2 = Me), **1b** (R^1 = *n*-Hex, R^2 = Me), **1j** (R^1 = *n*-Pr, R^2 = Et), and **1k** (R^1 = *n*-Pr, R^2 = Bu), the yields were only moderate to low when applied to the substrates **1c**−**i** (Table 2, eq 1). Moreover, our attempts to extend the scope of the reaction to the substrates containing a bulkier acetal group (**1l** and **1m**), various substituents on the benzene rings (**1n**−**r**), or cyclic acetals (**3a**−**g**) using the same catalyst system gave unsatisfactory results.

In our search for a better catalyst, we have tried several palladium and platinum compounds ($PdCl_2$, PdI_2, $PtCl_2$, $PtBr_2$, PtI_2, and $PtCl_4$). Despite these changes, the reaction either did not proceed at all or was very sluggish. However, quite unexpectedly it was discovered that the $PtCl_2$-catalyzed reaction of substrate **1g** afforded the desired carbocyclization product **2g** in 76% yield after 4 h at room temperature, compared to only 23% yield (and longer reaction times) with $PdCl_2(CH_3CN)_2$ (eq 2).

Table 1. Effect of the Olefin on the Reaction of **1a**[a]

entry	olefin	isolated yield, %
1	β-pinene	93
2	β-pinene[b]	93
3	β-pinene[c]	90
4	1,5-cyclooctadiene	75
5	2,3-dihydrofuran	69
6	cyclohexene	67
7	methylenecyclohexane	40
8	benzoquinone	24
9	maleic anhydride	12
10	α-pinene	11
11	2-ethyl-1-butene	9
12	1-octene	decomposition
13	none	no reaction

[a] The reaction of **1a** (0.4 mmol) was carried out in the presence of 10 mol % of $PtCl_2$ and 40 mol % of the olefin in acetonitrile at 30 °C. [b] 7 mol % of $PtCl_2$ and 28 mol % of β-pinene were used. [c] 7 mol % of $PtCl_2$ and 14 mol % of β-pinene were used.



Since the main structural feature distinguishing **1g** from all other substrates probed under the same conditions is the terminal olefin functionality, we argue that $PtCl_2$ might be activated in the presence of olefins. Indeed, as detailed in Table 1, a number of olefins are capable of promoting the catalytic carbocyclization of **1a** (eq 3). Moreover, when β-pinene was used as the

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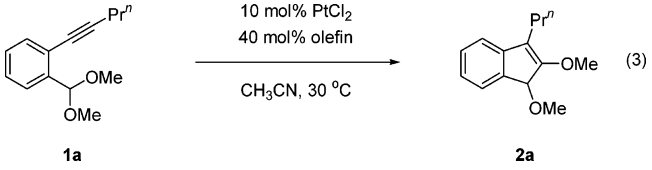


1a **2a**

activating agent, the yield of the product was significantly higher compared to our original reaction conditions ($PdCl_2(CH_3CN)_2$, entries 1−3). The reaction of **1a** in the presence of catalytic amounts of $PdCl_2(CH_3CN)_2$ and β-pinene proceeded sluggishly, affording **2a** in 16% yield.

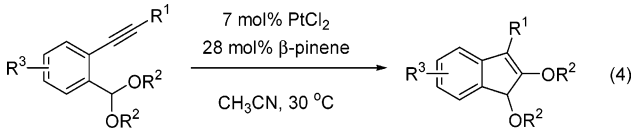
Encouraged by these results, we have carried out the carbocyclizations of the substrates **1a**−**r** with the newly designed and optimized catalytic conditions (eq 4, Table 2). The reaction of the substrates **1a**−**d**, which had an alkyl group at the alkynyl moiety, gave the products **2a**−**d** in good to excellent yields (entries 1−4). Various functional groups, such as bromo, ester, siloxy, alkenyl, phenyl, and nitro, were tolerated in this reaction (entries 5−8, 16). The substrate **1i** bearing a terminal alkynyl group was converted to the product **2i** in 81% yield (entry 9). Not only the substrates bearing di-*normal*-alkyl acetal group (**1j** and **1k**) but also **1l** and **1m**, which had a bulkier acetal group, reacted very smoothly (entries 10−13). The reaction of **1n**−**p** with an electron-withdrawing group on the aromatic ring proceeded in a similar manner, while the reaction of **1q** and **1r**, which had a methoxy group on the benzene ring, was sluggish (entries 14−18).

A similar catalytic system ($PtCl_2$/benzoquinone) was found to be effective for the carbocyclization of the cyclic acetals **3** (eq 5, Table 3). The reaction of the cyclic acetal **3a** in the presence of 20 mol % of $PtCl_2$ and 50 mol % of benzoquinone gave the corresponding tricyclic compound **4a** in 55% yield (entry 1). The reaction of **3a** using β-pinene instead of benzoquinone afforded **4a** in 29% yield. The tricyclic compounds **4b**−**g** were obtained from the corresponding cyclic acetals **3b**−**g** in good to acceptable yields (entries 2−7). Since cyclic acetals are generally more stable than acyclic acetals, the reaction of **3** would require much longer reaction times and more drastic conditions.

We have found that olefins activate platinum chloride as a catalyst in the carbocyclization of alkynylacetals. The origin of this effect is not clear, and we are not aware of other examples of such activation in the literature. A possible explanation could be formation of $PtCl_2(CH_3CN)_2$ and replacement of the acetonitrile ligands with the olefin. However, we have failed to find any indication of such coordination in the ^1H, ^{13}C, and ^{195}Pt NMR spectra of the samples containing either $PtCl_2$ and β-pinene or $PtCl_2(CH_3CN)_2$ and β-pinene in CD_3CN. Besides, the carbocyclization of **1a** in the presence of $PtCl_2(CH_3CN)_2$ occurred only very slowly. Addition of β-pinene accelerated the reaction but far beyond the rate range obtained by the use of the $PtCl_2$/β-pinene system. Since $PtCl_2$ is very insoluble in acetonitrile (it can be dissolved by prolonged heating, yielding $PtCl_2(CH_3CN)_2$), heterogeneous catalysis cannot be excluded.

To expand the synthetic scope of the catalytic carbocyclization, we carried out the reaction with the structurally similar thioacetals. Although $PdCl_2(CH_3CN)_2$ was not an appropriate catalyst, yielding complicated reaction mixtures after prolonged heating, when the $PtCl_2$/β-pinene system was applied to **5a** in acetonitrile a 55% yield of a new cyclization product (**6a**) resulted. The new cyclization product is isomeric to the one in the acetal case. Further variation of the catalyst showed that

Table 2. Catalytic Carbocyclization of Acyclic Acetals of *o*-Alkynylbenzaldehydes **1**[a]

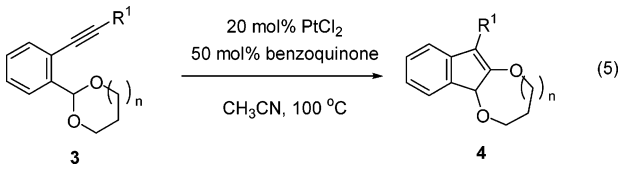


1 **2**

entry	1	R^1	R^2	R^3	2	isolated yield, % $PtCl_2$/β-pinene[a]	isolated yield, % $PdCl_2(CH_3CN)_2$[b]
1	**1a**	*n*-Pr	Me	H	**2a**	93	75
2	**1b**	*n*-Hex	Me	H	**2b**	96	65
3[c,d]	**1c**	cyclohexyl	Me	H	**2c**	87	52
4[c,d]	**1d**	Me	Me	H	**2d**	62	11
5	**1e**	$(CH_2)_3OCOAr$ (Ar = *p*-BrC_6H_4)	Me	H	**2e**	85	45
6	**1f**	$(CH_2)_3OTBS$	Me	H	**2f**	76	30
7	**1g**	$(CH_2)_3CH{=}CH_2$	Me	H	**2g**	81	23
8[d]	**1h**	Ph	Me	H	**2h**	92	40
9	**1i**	H	Me	H	**2i**	81	25
10	**1j**	*n*-Pr	Et	H	**2j**	85	87
11	**1k**	*n*-Pr	*n*-Bu	H	**2k**	91	80
12[d,e]	**1l**	*n*-Pr	*i*-Pr	H	**2l**	89	42
13[d,e]	**1m**	*n*-Pr	Bn	H	**2m**	69	25
14	**1n**	*n*-Pr	Me	4-CF_3	**2n**	76	57
15	**1o**	*n*-Pr	Me	5-CF_3	**2o**	87	52
16[f]	**1p**	*n*-Pr	Me	5-NO_2	**2p**	65	29
17	**1q**	*n*-Pr	Me	4-OMe	**2q**	12	no reaction
18	**1r**	*n*-Pr	Me	5-OMe	**2r**	trace	no reaction

[a] The reaction of **1** (0.4 mmol) was carried out in the presence of 7 mol % of $PtCl_2$ and 28 mol % of β-pinene in acetonitrile (1.6 mL) at 30 °C. [b] The reaction of **1** (0.5 mmol) was carried out in the presence of 10 mol % of $PdCl_2(CH_3CN)_2$ in acetonitrile (2 mL) at 30 °C. [c] The reaction was carried out at 60 °C. [d] 14 mol % of $PtCl_2$ and 56 mol % of β-pinene were used. [e] For 2 days. [f] For 20 h.

Table 3. Platinum-Catalyzed Carbocyclization of Cyclic Acetals of *o*-Alkynylbenzaldehydes **3**[a]



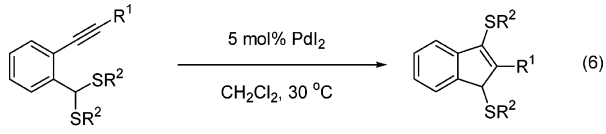
(5)

3 **4**

entry	**3**	*n*	R^1	**4**	isolated yield,%
1	**3a**	1	*n*-Pr	**4a**	55
2	**3b**	1	*n*-Bu	**4b**	50
3	**3c**	1	*n*-Hex	**4c**	55
4	**3d**	1	Ph	**4d**	38
5[b]	**3e**	2	*n*-Pr	**4e**	53
6[b]	**3f**	2	*n*-Bu	**4f**	43
7[b]	**3g**	2	*n*-Hex	**4g**	44

[a] The reaction of **3** (0.5 mmol) was carried out in the presence of 20 mol % of $PtCl_2$ and 50 mol % of benzoquinone in acetonitrile at 100 °C. [b] 10 mol % of $PtCl_2$ and 40 mol % of benzoquinone were used.

Table 4. Palladium-Catalyzed Carbocyclization of *o*-Alkynylbenzaldehyde Thioacetals **5**[a]



(6)

5 **6**

entry	**5**	R^1	R^2	**6**	isolated yield, %[a]
1	**5a**	*n*-Pr	Et	**6a**	95
2	**5b**	*n*-Bu	Et	**6b**	95
3	**5c**	*n*-Hex	Et	**6c**	97
4	**5d**	Me	Et	**6d**	80
5	**5e**	Ph	Et	**6e**	97
6[b]	**5f**	*p*-MeC_6H_4	Et	**6f**	95
7[b]	**5g**	*p*-$MeOC_6H_4$	Et	**6g**	98
8[b]	**5h**	*p*-$CF_3C_6H_4$	Et	**6h**	92
9	**5i**	H	Ph	**6i**	34
10	**5j**	*n*-Pr	Me	**6j**	93
11	**5k**	*n*-Pr	Ph	**6k**	70
12	**5l**	Ph	Ph	**6l**	85

[a] The reaction of **5** (0.5 mmol) was carried out in the presence of 5 mol % of PdI_2 in CH_2Cl_2 at 30 °C. [b] At 60 °C.

this transformation can be carried out most effectively using 5 mol % of PdI_2 in dichloromethane (eq 6). The results of the reaction of the *o*-alkynylbenzaldehyde thioacetals **5** are summarized in Table 4. The reaction of **5a**−**d**, which had an alkyl group at the alkynyl moiety, afforded **6a**−**d** in 95, 95, 97, and 80% yields, respectively (entries 1−4). The reaction of the dimethyl acetal of arylalkynylbenzaldehydes (**5e**−**h**), in which the aromatic ring was substituted by an electron-withdrawing group or electron-donating group at the para-position, proceeded very smoothly (entries 5−8). The reaction of **5i** having a terminal alkynyl group proceeded sluggishly, producing **6i** in 34% yield (entry 9). Dimethyl thioacetal **5j** and diphenyl thioacetals **5k** and **5l** were converted to **6j**−**l** in good to excellent yields (entries 10−12). The structures of **6** were explicitly confirmed by spectral data, and the structure of **6l** was unambiguously confirmed by the X-ray crystallographic analysis of **6l** (Figure 1).

NMR Search for the Reaction Intermediates. Several catalytic systems have been studied in the search for the appropriate conditions for the characterization of intermediates

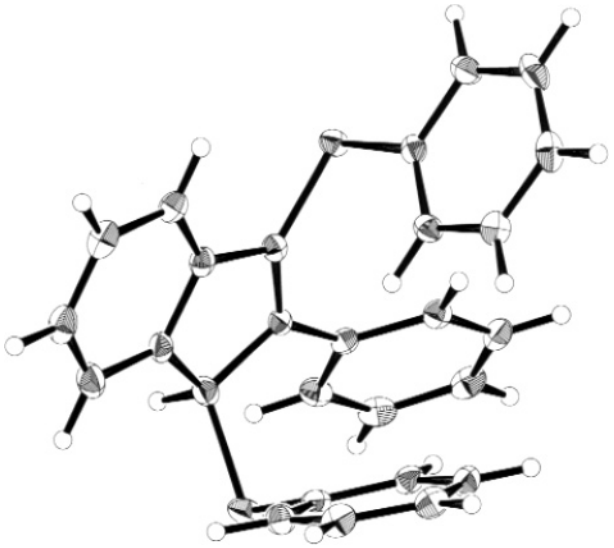


Figure 1. ORTEP drawing of **6l**.

in the carbocyclization of acetals and thioacetals. Minor intermediate species with similar NMR spectra have been observed in all reactions. Hence, our choice of the particular reactions for the detailed NMR and computational studies has been motivated rather by technical convenience than by the performance of the catalytic system. Thus, although the catalytic system $PtCl_2$/*β*-pinene provided the best synthetic results, we have failed so far to determine the nature of the active catalytic species (vide infra), so we leave this question open for further studies. On the other hand, when the carbocyclization of **1a** in the presence of $PdCl_2(CH_3CN)_2$ was monitored in CD_3CN, clean formation of a single intermediate was observed (vide supra), making this reaction an attractive goal for mechanistic studies. Furthermore, the reaction of the thioacetal **5a** catalyzed by PdI_2 in CD_2Cl_2 was also quite clean, and the intermediacy of the observed minor species was beyond any reasonable doubt. We therefore have chosen these two reactions catalyzed by the same metal for the comparative mechanistic study trying to reveal the origin of the difference in the structures of the final products.

The ^1H spectrum taken immediately after addition of substrate **1a** to a suspension of $PdCl_2(CH_3CN)_2$ in CD_3CN at room temperature showed the presence of a species with a characteristic low-field-shifted set of signals in the aromatic region (e.g., Figure 2). The concentration of this new species was 1−3% from the total sample concentration (substrate + product + intermediate). This concentration was found to be approximately constant during the whole transformation. After all the substrate had been consumed, the signals of the new species disappeared from the NMR spectra. We conclude on the basis of these observations that the observed low-concentration species is an intermediate in the catalytic interconversion of **1a** to **2a**. Its low concentration might be regulated by the relative rates of its formation and decay (stationary kinetics); however, the restricted solubility of the Pd complex might also be responsible for the impossibility to acquire high concentrations of the intermediate even if the reaction mixture was kept for a long time at low temperatures.

The minor second isomer of the reaction intermediate is clearly seen in the ^1H NMR spectrum (Figure 2, see asterisks); the ratio of the isomers is 5:1 at 298 K. Dynamic effects

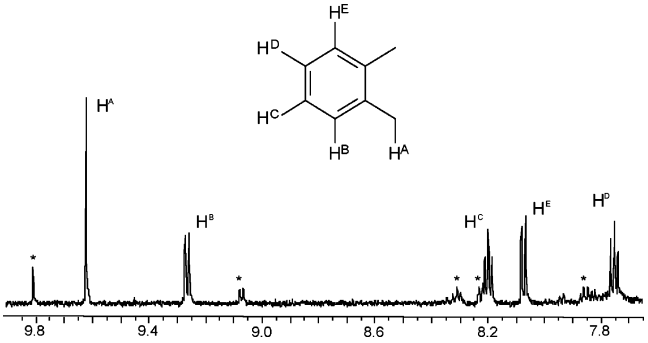


Figure 2. Section plot of the ^{1}H NMR spectrum (600 MHz, 298 K, CD_3CN) of the reaction mixture prepared by adding 10 mg of **1a** to a suspension of 8 mg of $PdCl_2(CH_3CN)_2$ in 0.75 mL of CD_3CN. The assignment of protons was made from the ^{1}H−^{1}H COSY spectrum. The signals of minor isomer are marked with asterisks.

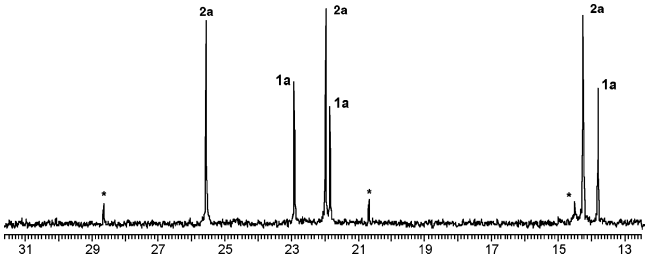


Figure 3. Section plot (signals of the propyl group) of the ^{13}C NMR spectrum (150 MHz, 298 K, CD_3CN) of the same reaction mixture as in Figure 2; the signals of the low-concentrated intermediate are marked with asterisk.

observed upon variation of the temperature suggest that these two isomers are interconverting reversibly in solution.

In the ^{13}C NMR spectrum, some signals of the observed intermediate were reliably detected by 2D C−H correlation experiments. For example, Figure 3 demonstrates the absence of any other species in the reaction mixture. Noteworthy was the extremely high chemical shift of the $CH(OMe)_2$ carbon (δ = 168.2) in the intermediate. The chemical shifts of the four CH carbons of the aromatic cycle were not remarkable (δ = 128.8, 125.9, 127.8, 130.5).

Addition of the thioacetal **5j** to a suspension of PdI_2 in CD_2Cl_2 at ambient temperature resulted in the formation of a low-concentration species with the characteristic low-field signals in the ^{1}H NMR spectrum (singlet at δ = 10.54 and doublet at δ = 9.66) quite similar to those of the intermediate in the catalytic cyclization of **1a**.

Computational Studies

Computational Assignment of the NMR-Detected Intermediates. Since the low concentration of the detected transient species precluded the unambiguous assignment of their structures solely by NMR, we approached this problem computationally using the available NMR data as a reference.

It is a generally accepted assumption that the Pd-catalyzed cyclizations begin from the coordination of Pd to the nucleophilic center (or centers) of the substrate. We therefore looked for the possible structures of such complexes. Figure 4 shows the optimized structures of four intermediates (**7**, **8**, and **9a**,**b**) corresponding to the initial coordination stage (Me-substituted compound **1d** has been used for the calculations).

The relative energies of the coordination complexes **7**, **8**, and **9a**,**b** are shown in Table 5. The least energetically demanding

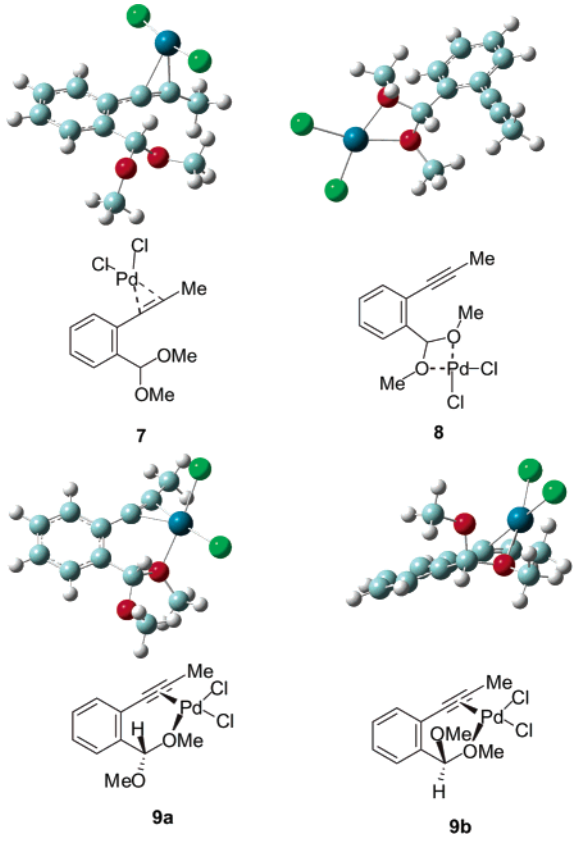


Figure 4. Molecular structures and optimized geometries (B3LYP/SDD) of the coordination complexes **7**, **8**, and **9a**,**b**.

mode of the initial coordination of $PdCl_2$ corresponds to the structure **9b**, which is approximately 5 kcal/mol more favorable than **8** or **9a** and 10 kcal/mol more stable than **7**. This finding illuminates the importance of the chelating coordination of palladium in the catalytic cyclizations of functionalized alkynes, which has often been suggested as a driving force of such reactions.[4f,9]

To check if either of the coordination complexes can be associated with the observed intermediate, we have computed the ^{1}H and ^{13}C NMR chemical shifts (GIAO) for **7**, **8**, and **9a**,**b** and compared them with the experimentally observed values (Table 5). The most characteristic chemical shifts of the observed intermediate are $\delta(^1H)$ and $\delta(^{13}C)$ of the CH unit of the acetal group (9.62 and 168.2 respectively), and $\delta(^1H)$ of the aromatic proton at the ortho-position to the acetal group (9.26). As can be seen from Table 5, the computed chemical shifts of compounds **7**, **8**, and **9a**,**b** are quite different from those of the experimentally observed intermediate species. In particular, the experimental chemical shifts are significantly more strongly low-field-shifted, hinting at the more cationic character of the observed intermediate. This conclusion prompted us to look for intermediates with more clearly defined cationic centers, such as **10a**,**b** (Figure 5).

The computed chemical shifts for the structures **10a** and **10b** (Table 5) are in a reasonable accordance with the experimentally observed intermediate species, reproducing well the significant low-field shifts of the protons and carbon atom in the close

(9) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto Y. *J. Am. Chem. Soc.* **2002**, *124*, 764.

Table 5. Computed Relative Energies,[a] NMR Chemical Shifts (GIAO) of the Intermediates **7**−**10**, and Experimental NMR Chemical Shifts for the Transient Species Observed in the Reaction of **1a** with $PdCl_2(CH_3CN)_2$

	compound						experimental	
	7	**8**	**9a**	**9b**	**10a**	**10b**	major	minor
relative energy, kcal/mol	30.3	26.1	25.5	21.0	48.4	46.5		
$\delta(^1H)$ acetal C−H	6.03	6.18	7.58	4.75	10.19	10.86	9.62	9.92
$\delta(^{13}C)$ acetal C−H	113.7	128.8	119.6	123.2	168.6	146.2	168.2	-[b]
$\delta(^1H)$ *o*-H of Ar group	8.77	8.92	8.06	7.28	8.83	8.69	9.26	9.18

[a] The geometries were optimized at the B3LYP/SDD level of theory; all relative energies are referred to **1a** + $PdCl_2(CH_3CN)_2$. [b] Not detected.

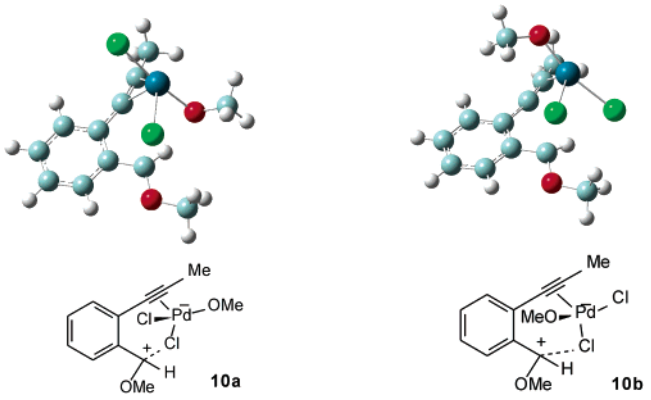


Figure 5. Molecular structures and optimized geometries (B3LYP/SDD) of the cationic complexes **10a**,**b**.

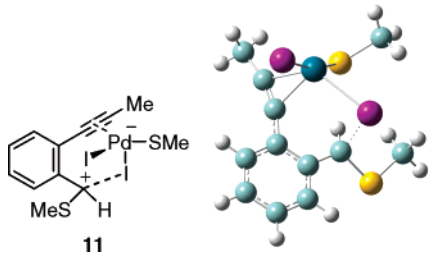


Figure 6. Structure of cationic intermediate **11** optimized at the B3LYP/SDD level of theory.

vicinity of the carbocationic center. We consider that this is a sufficient reason to suggest that two isomers of the interconverting intermediates detected in the NMR spectra of the reaction mixture have the corresponding structures.

Similarly, the low-field chemical shifts for the H(acetal) and H(ortho) protons of the transient species observed in the course of the reaction of thioacetal **5a** catalyzed by PdI_2 were in accordance with cationic intermediate of type **11** (Figure 6).

Thus, we conclude that generation of cationic intermediates **10** or **11** is an essential condition for the occurrence of the carbocyclization of *o*-alkynylbenzaldehyde acetals and thioacetals. This conclusion helps to explain the difference in outcomes for the various catalytic systems. Thus, the cyclization of acetals is catalyzed by the chloride derivatives of Pd or Pt, whereas the cyclization of thioacetals requires palladium iodide as a catalyst. If the oxygen atoms in the optimized structure of the cationic intermediate **10a** were replaced with sulfur atoms and the resulting structure (**12**) was then used as an input for the computations, compound **13** containing the covalent C−Cl bond was obtained after the optimization (Scheme 2). This result can be explained by stronger binding of Pd with sulfur (Pd−S bond is stronger than the Pd−O bond), making the intermediate cationic structure collapse into **13**, thus stopping the catalytic cycle.

If, on the other hand, not only the oxygen atoms in the compound **10a** were replaced with sulfur atoms, but simultaneously both chlorines were replaced with iodine atoms (yielding a sulfur−PdI_2 analogue **14**), the optimization would predict compound **11** (Scheme 2). Apparently, the larger size and polarizability of the iodine compared to chlorine prevents the occurrence of the irreversible exchange reaction similar to that leading to the formation of **13**.

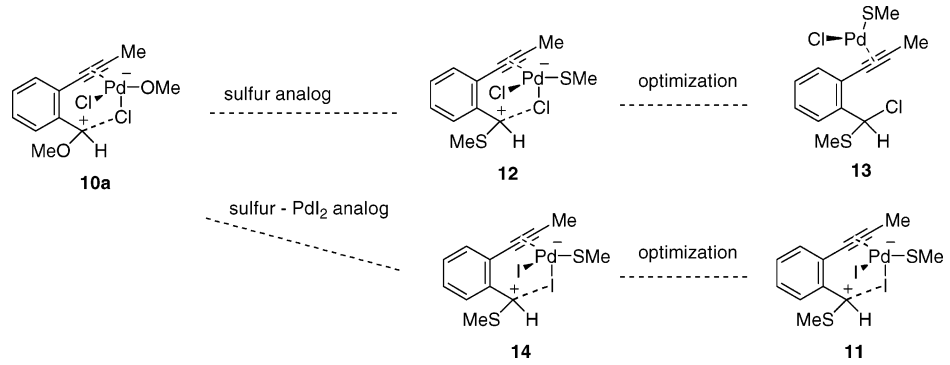
Thus, the combined NMR data and computational results suggest that both the carbocyclization of acetals accompanied by 1,2-alkyl migration catalyzed by $PdCl_2(CH_3CN)_2$ and the carbocyclization of thioacetals proceeding without rearrangement have common early intermediates (cationic species **10** and **11**). Hence, the origin of the different structures of the reaction products must be searched at the later stages of the reaction.

Computation of the Later Intermediates: Vinylpalladium Species. Apparently, the next transformation of the cationic species **10** (or **11**) is the electrophilic attack by the cationic center on the triple bond, formally yielding a vinyl cation, which is further stabilized via the vinylpalladium intermediate. Facile alkyl migrations are a well-known feature of vinyl cations.[10] We argue, therefore, that the alkyl migration accompanying the carbocyclization of acetals can occur at this stage of the reaction (Scheme 3). If this is the case, the formation of different vinylpalladium species **19** (from thioacetals) or **20** (from acetals) can be explained by selective trapping of equilibrating vinyl cations **16** and **18** or **15** and **17**, respectively (Scheme 3). To support this assumption, we optimized geometries of four vinylpalladium species **19**−**22** (Figure 7). As can be seen from Figure 7, the relative stabilities of vinylpalladium species **19**−**22** are different for the two reactions: the vinylpalladium intermediate **19** is 13.4 kcal/mol more stable than **21**, which could form by trapping of the rearranged vinyl cation **18** (Scheme 3). On the other hand, in the acetal case, the vinylpalladium species **20**, originating from the rearranged vinyl cation **17**, is 6.8 kcal/mol more stable than **22** produced directly from **15**. These data are in accord with the experimental outcome of both reactions.

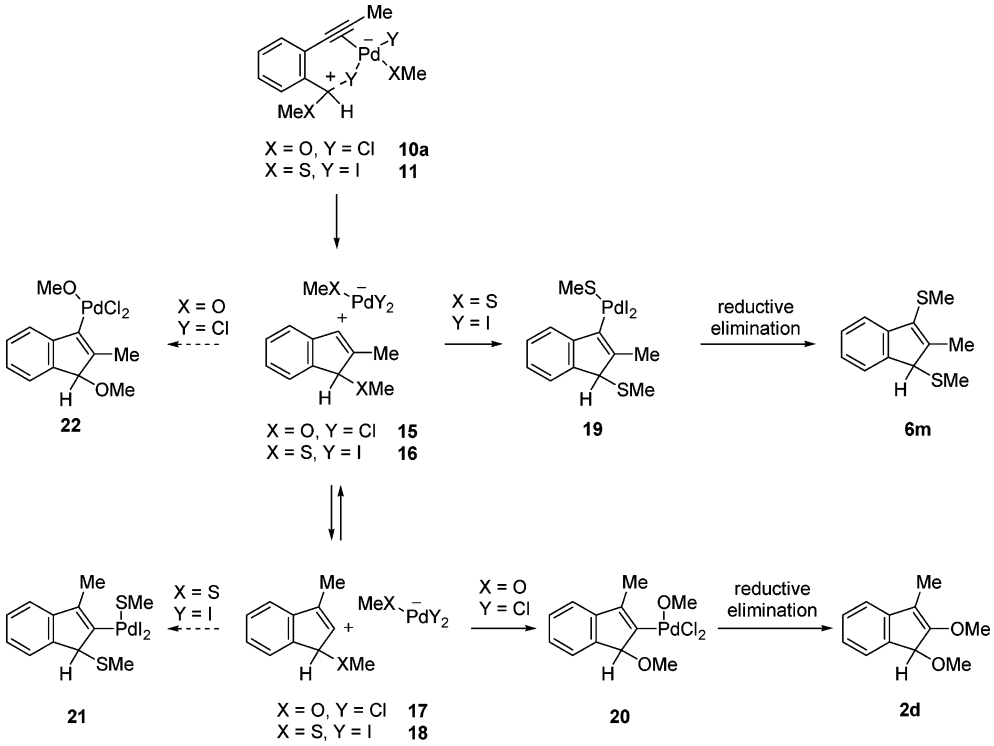
Thus, the mechanistic study of the Pd-catalyzed carbocyclizations of alkynylacetals and thioacetals suggests that both reactions proceed via cationic intermediates formed at the early stage of the reaction from the Pd coordination complexes, in which the triple bond and the acetal (or thioacetal) group are both bonded to the metal. Ring closure of the cationic intermediates leads to cyclic vinyl cations, which are further stabilized via the vinylpalladium intermediates. The particular structure of the products can be regulated by the relative

(10) For recent references, see: (a) Gronheid, R.; Lodder, G.; Ochiai, M.; Sueda, T.; Okuyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 8760. (b) Gronheid, R.; Lodder, G.; Okuyama, T. *J. Org. Chem.* **2002**, *67*, 693.

Scheme 2



Scheme 3



thermodynamic stabilities of the vinylpalladium intermediates formed from rearranged and non-rearranged cyclic vinyl cations.

Conclusions

The synthetic results presented in this study demonstrate a general strategy for building polycyclic molecules via transition-metal-catalyzed cyclizations of ortho-functionalized phenylacetylenes. A representative series of substrates has been transformed into the corresponding functionalized indenes via mild catalytic conditions. Moreover, using either acetals or thioacetals as substrates allowed us to obtain selectively indenes with alkyl substituents in different position. This observation should find use in constructing various indenyl building blocks for organic synthesis.

Mechanistic results obtained in the NMR and computational studies confirm some long-existing assumptions but also bring up previously unknown aspects of the mechanisms of Pd-catalyzed reactions. Thus, we have demonstrated the importance of the chelate coordination of palladium involving both the triple bond and the acetal group for the occurrence of the reaction. Furthermore, our NMR and computational data put forward the formation of a real carbocationic center and palladate anion in the course of the cyclizations reactions studied in this work. Although the possibility of such charge separation in the Pd(II)-catalyzed reactions was suggested quite early,[11] we are unaware of any published data supporting this possibility. Further synthetic applications of Pd-catalyzed reactions involving the carbocationic centers are being actively investigated in our laboratory.

Experimental Section

General Procedure of Carbocyclization of Acyclic Acetals 1. To $PtCl_2$ (7.4 mg, 0.028 mmol) and β-pinene (17 μL, 0.112 mmol) in 1.6 mL of acetonitrile was added the *o*-alkynylbenzaldehyde dialkyl acetal **1** (0.5 mmol) in 1 mL of acetonitrile under an Ar atmosphere in a pressure vial. After being heated at 30 °C for 15 h, the reaction mixture was filtered through a short silica gel column using ethyl acetate as an eluent. Separation by silica gel column chromatography using hexane/EtOAc (30/1) as an eluent afforded the products **2**.

General Procedure of Carbocyclization of Cyclic Acetals 3. To a mixture of $PtCl_2$ (26.6 mg, 0.1 mmol), 1,4-benzoquinone (27.0 mg,

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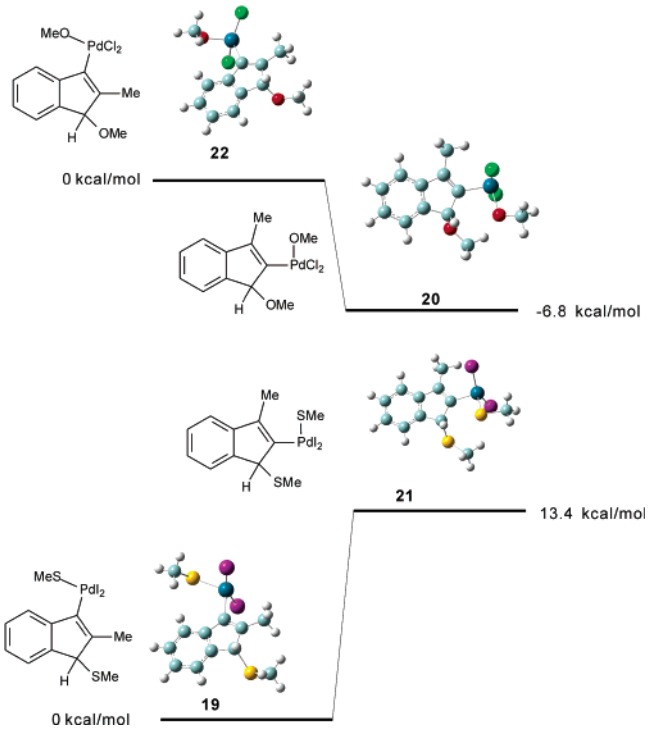

Figure 7. Molecular structures, optimized geometries (B3LYP/SDD), and relative energies of the vinylpalladium intermediates **19**−**22**.

0.25 mmol), and *o*-alkynylbenzaldehyde cyclic acetal **3** (0.5 mmol)was added 2 mL of acetonitrile under an Ar atmosphere in a pressure vial. After being heated at 100 °C for 1−7 days, the reaction mixture was filtered through a short alumina column to remove catalyst from the reaction mixture by using ethyl acetate as an eluent. The mixture was then purified by silica gel column chromatography using a hexane/ethyl acetate mixture as an eluent to afford the products **4**.

General Procedure of Carbocyclization of Thioacetals 5. To PdI_2 (9.0 mg, 0.025 mmol) in 1 mL of CH_2Cl_2 was added the *o*-alkynylbenzaldehyde dialkyl thioacetal **5** (0.5 mmol) under an Ar atmosphere in a pressure vial. After being heated at 30 °C for 2 h, the reaction mixture was filtered through a short silica gel column using ethyl acetate as an eluent. Separation by silica gel column chromatography using hexane/EtOAc (100/1) as an eluent afforded the products **6**.

Computational Details. Geometries of all stationary points were optimized using analytical energy gradients of self-consistent-field[12] and density functional theory (DFT).[13] The latter utilized Becke's three-parameter exchange-correlation functional[14] including the nonlocal gradient corrections described by Lee, Yang, and Parr (LYP),[15] as implemented in the Gaussian 98 program package.[16] All geometry optimizations were performed using the SDD basis set.[17]

NMR chemical shifts were computed with the gauge-invariant atomic orbital (GIAO) approach[17] in conjunction with the B3LYP functional.[15,16] The absolute shifts (σ) of tetramethylsilane (TMS) were used to compute the relative chemical shifts $\delta^{\dagger} = \sigma_{\text{reference}} - \sigma_{\text{compound}}$.

Supporting Information Available: Characterization data of the products **2**, **4**, and **6** and Cartesian coordinates for the intermediates **7**−**11** and **19**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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