

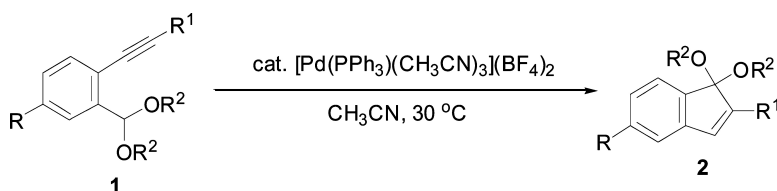
Article

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Stepwise Delivery of Two Methoxy Groups of Arylaldehyde Acetals across the Phenyl Ring. Vacant Site-Controlled Palladium Catalysis

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Abstract: A new catalytic cyclization of *o*-alkynylbenzaldehyde acetals **1** to the functionalized indenones **2** was found to be strictly controlled by the number of triphenylphosphine ligands on the Pd catalyst. Only complexes with three available coordination sites on Pd catalyze this reaction. Mechanistic study suggests that π -coordination of Pd to the benzene ring is a key step controlled by the number of vacant coordination sites.

Introduction

In many useful Pd-catalyzed reactions, previously it was not necessary to use specially designed ligands or to be concerned about the number of ligands on palladium.¹ Some Pd-catalyzed transformations reported recently use simple palladium salts as the source of catalytically active palladium species.² However, most of the recent remarkable progress in Pd-catalyzed transformations is due to the discovery of the ultimate importance of the size and structure of the ligands.³ The further development relies, therefore, on a deeper understanding of the Pd coordination chemistry. Here we report the striking effect of the number of phosphine ligands on a cationic Pd(II) complex on the outcome of the reaction catalyzed by this complex; the mechanistic investigation has revealed that exactly three vacant sites on Pd are essential for the unprecedented rearrangement of *o*-alkynylbenzaldehyde acetals **1** to the indene products **2**.

Results and Discussion

We found that the reaction of **1** was catalyzed by $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ in the presence of an equivalent amount of triphenylphosphine to give **2** in good yields (Scheme 1). The results are summarized in Table 1. The reaction of *o*-(1-octynyl)-benzaldehyde dimethyl acetal **1a** in the presence of 7.5 mol % of $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ and 7.5 mol % of PPh_3 in acetonitrile

Scheme 1. Cyclization of *o*-Alkynylbenzaldehyde Acetals Catalyzed by $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2 - \text{PPh}_3$

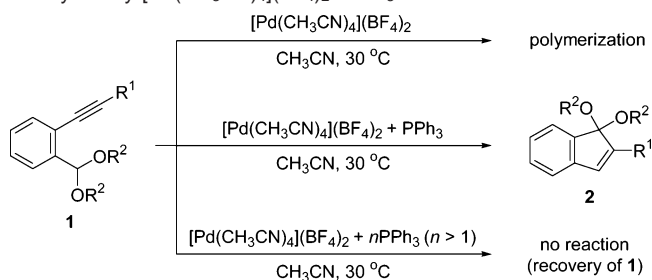


Table 1. Cyclization of *o*-Alkynylbenzaldehyde Acetals **1** Catalyzed by $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2 - \text{PPh}_3^a$

entry	1	R ¹	R ²	2	yield, % ^b
1	1a	Hex	Me	2a	60
2	1b	<i>n</i> -Pr	Me	2b	55
3	1c	Me	Me	2c	45
4	1d	(CH ₂) ₄ Cl	Me	2d	56
5	1e	Ph	Me	2e	65
6	1f	<i>p</i> -CF ₃ C ₆ H ₄	Me	2f	79
7	1g	<i>p</i> -MeC ₆ H ₄	Me	2g	53
8	1h	<i>p</i> -MeOC ₆ H ₄	Me	2h	44
9	1i	H	Me	—	nd ^c
10	1j	<i>n</i> -Pr	Et	2j	65
11	1k	<i>n</i> -Pr	Bu	2k	54

^a The reaction of **1** (0.5 mmol) was carried out in the presence of 7.5 mol % of $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ and 7.5 mol % of PPh_3 in acetonitrile at 30 °C. ^b Isolated yield. ^c A mixture of unidentified compounds was obtained.

proceeded at 30 °C, giving 1,1-dimethoxy-2-hexylindene **2a** in 60% yield (entry 1). The use of diphosphine ligands or greater amounts of triphenylphosphine and $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ did not promote the cyclization at all, and $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ itself caused rapid polymerization of **1** even at decreased temperatures (Scheme 1). The reactions of **1b**, **1c**, and **1d** afforded **2b**, **2c**, and **2d** in good yields (entries 2–4). The substrates **1e**, **1f**, **1g**, and **1h**, which each had an aromatic ring at the R¹ position, were converted to the corresponding 2-aryllindenone acetals **2e**,

- (1) Tsuji, J. *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*; John Wiley & Sons Ltd.: New York, 1995.
- (2) For example: (a) Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648. (b) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302. (c) Franzén, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2003**, *125*, 6056. (d) Zaitsev, V.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156. (e) Sirwardana, A. I.; Kathiraratchi, K. K. A. D. S.; Nakamura, I.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 13898. (f) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622.
- (3) (a) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719. (b) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (c) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953 and references therein. (d) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176. (e) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (f) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

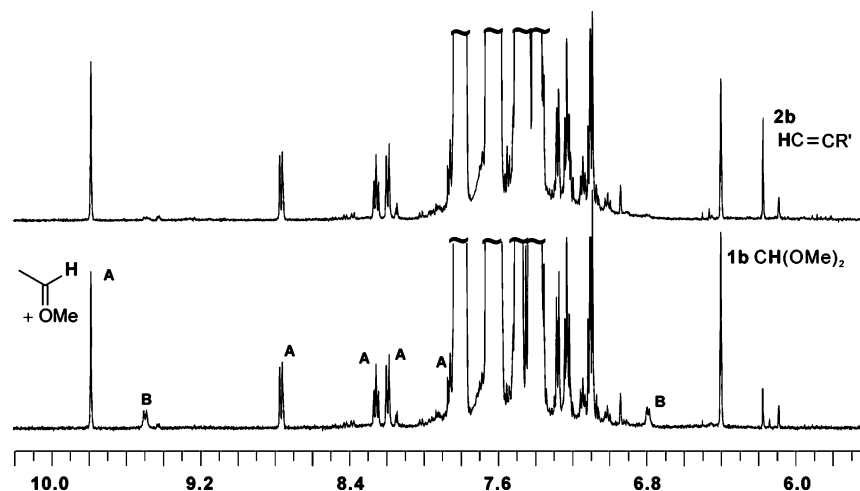
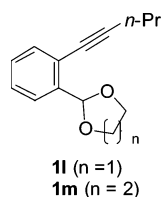


Figure 1. Section plots of the ^1H NMR spectra (600 MHz, CD_3CN , $50\text{ }^\circ\text{C}$) of the sample obtained by mixing deuterioacetonitrile solutions of **1b** and **3** at $-40\text{ }^\circ\text{C}$. Bottom: immediately after raising the temperature of the sample to $50\text{ }^\circ\text{C}$. Top: after 15 min at $50\text{ }^\circ\text{C}$.

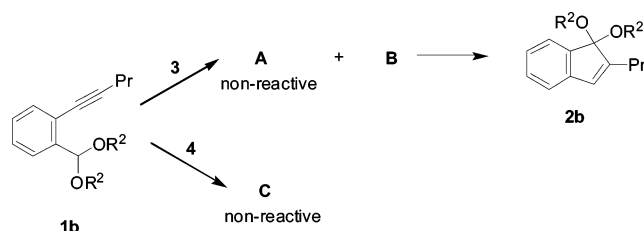
2f, **2g**, and **2h**, in 65, 79, 53, and 44% yield, respectively (entries 5–8). The reaction of the terminal alkyne **1i** gave a mixture of unidentified compounds (entry 9). The reactions of diethyl acetal **1j** and dibutyl acetal **1k** proceeded very smoothly (entries 10 and 11). The reactions of the cyclic acetals **1l** and **1m** did not proceed at all.



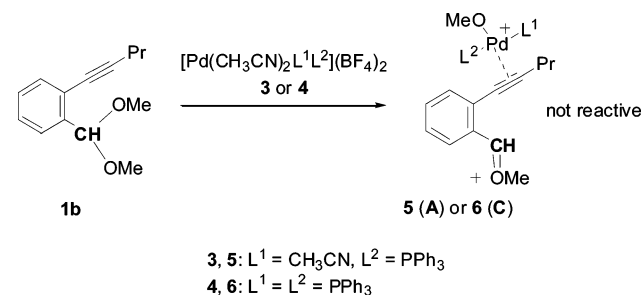
By performing multinuclear NMR experiments we found that the complexes of definite composition $[\text{Pd}(\text{Ph}_3\text{P})(\text{CH}_3\text{CN})_3](\text{BF}_4)_2$ (**3**, $\delta^{31}\text{P} = 27.6$) and $[\text{Pd}(\text{Ph}_3\text{P})_2(\text{CH}_3\text{CN})_2](\text{BF}_4)_2$ (**4**, $\delta^{31}\text{P} = 31.9$) were formed upon mixing $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ in deuterioacetonitrile with 1 and 2 equiv of triphenylphosphine, respectively. The bottom trace in Figure 1 displays the ^1H NMR spectrum of the sample obtained by mixing an equivalent amount of **1b** with **3** at $-40\text{ }^\circ\text{C}$,³ followed by quickly raising the temperature to $50\text{ }^\circ\text{C}$. Two kinds of low-concentration species (**A** and **B**) were detected (assignments verified by COSY spectrum). The intermediate **A** had all signals of the aromatic protons low-field shifted relative to the signals of **1b**, whereas the signals of the 1,2-disubstituted aromatic ring of the intermediate **B** were found in higher and lower field relative to the normal aromatic region. After 15 min at $50\text{ }^\circ\text{C}$, 50% conversion of **1b** to **2b** was achieved, and the signals of the intermediate **B** completely disappeared from the spectrum, whereas the intermediate **A** remained untouched (Figure 1, top; see more detailed information on the intermediates **A** and **B** in the Supporting Information, Figures S1–S3). This indicates that **B** must be an intermediate for the conversion of **1b** to **2b**, and **A** does not participate in the transformation of **1b** to **2b** (Scheme 2).

When **4** reacted with excess of **1b** at $0\text{ }^\circ\text{C}$, the clean formation of a single relatively high-concentration species (**C**) was observed. Its NMR spectra closely resembled those of the intermediate **A** (see Figures S5 and S6 in the Supporting Information). Even after prolonged storage of this sample at

Scheme 2. Intermediates Detected in the Reactions of **1b** with **3** and **4**



Scheme 3. Suggested Structures of the Nonreactive Species Observed in the Reactions of **1b** with **3** and **4**



	5		6	
	Exp	Calcd	Exp	Calcd
$\delta^1\text{H}$	9.8	9.2	9.8	8.1
$\delta^{13}\text{C}$	185.2	198.9	168.6	196.8

ambient temperature, no conversion of **1b** to **2b** was observed. Thus, both **3** and **4** can produce nonreactive species (**A** or **C**), but only **3** is capable of generating the reactive intermediate **B** (Scheme 2).

To get structural information about the reactive and non-reactive species observed in our experiments, we have studied their specific NMR properties. Thus, the extremely high chemical shifts of the benzylic protons and carbons in the nonreactive intermediates **A** and **C** can be qualitatively reproduced only for cationic species formed via the abstraction of one of the methoxy groups by palladium (Scheme 3). For various types of coordination complexes without abstraction of methoxy groups, the computed values $\Delta^1\text{H}$ (benzylic) do not exceed 6 ppm, and also the values of $\Delta^{13}\text{C}$ (benzylic) do not reach the values higher than 130 ppm. We have assigned,

therefore, for these nonreactive species the structures **5** (A) and **6** (C) (Scheme 3). Although the correspondence of the experimental and computed chemical shifts is not perfect, computations correctly reproduce extremely high values of both $\delta^1\text{H}$ and $\delta^{13}\text{C}$ characteristic for the cationic species. The reason for the complexes **5** and **6** being nonreactive can be understood by taking into account that both the coordinated acetylene and the oxonium group are positively charged and the cyclization of either **5** or **6** is retarded by electrostatic repulsion.

The reactive species **B** observed in the reaction of **1b** with **3** demonstrates specific features in its ^1H NMR spectrum. Thus, the signals of the aromatic ring are definitely split in two pairs: one pair appears over 8.0 ppm, whereas the other one resonates in the relatively high field (5.8–7.0 ppm). Such high-field shifted aromatic signals are characteristic for the species with π -coordination of Pd.⁵ Moreover, strong dynamic effects are observed in the aromatic region of the species **B** (see Figure S1 in the Supporting Information). Extensive broadening of the signals in the temperature interval from -40 to $+20$ °C, followed by the reappearance of the averaged signals at $+30$ °C and their sharpening at $+50$ °C, suggests that two or more species with strongly alternating chemical shifts exist in an equilibrium before being consumed in the further transformation.

To get further insight into the structure of the observed reactive intermediates, we looked for the different possible species computationally; DFT calculations of the real systems (using PPh_3) at the B3LYP/SDD level of theory were carried out, and an acetonitrile molecule was added to the structures to account partially for the solvent effects. The most important qualitative conclusion is that the experimentally observed specific chemical shifts of the aromatic ring can be reproduced only if the π -coordination of Pd to an aromatic ring is involved. Several structures of this kind with slightly different positions of Pd over the aromatic cycle were located. Two representative complexes (**7**, **8**) are shown in Figure 2, together with computed chemical shifts for their aromatic and oxonium protons. Noteworthy is the dramatic dependence of the chemical shift of each particular proton on the exact position of the coordinated Pd. Thus, if in the structure **7** the computed chemical shift of the proton in the ortho position relative to the triple bond is 8.32 ppm, the same proton in **8** has the computed chemical shift 6.09 ppm. If the structures **7** and **8** are in equilibrium, these two protons would produce an exchanging pair; the large difference in chemical shifts would lead to extensive broadening followed by the reappearance of the averaged signal. Thus, the computational results are in a good qualitative accordance with the experimentally observed dynamic effects and chemical shifts values in the ^1H NMR spectra of the intercepted intermediates.

We were unable to detect experimentally any intermediates of the later stages of the reaction; hence, we located them computationally (Scheme 4). The π -Pd intermediates **7** and **8** are most probably produced by abstraction of a methoxy group from the initial complex **9**. Cyclization and trapping of the unstable vinylic cation with the adjacent methoxy group in **8** may yield intermediate **10**. The transfer of the MeO group from

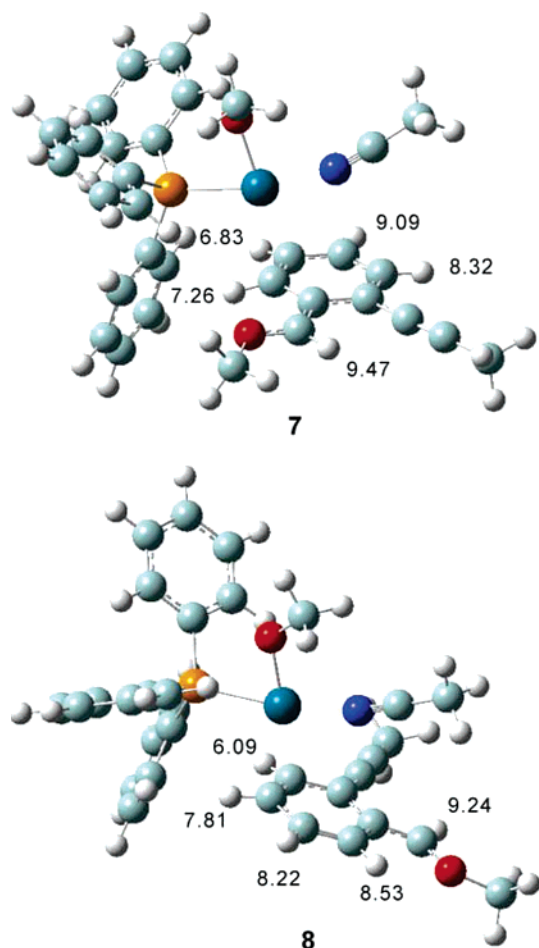


Figure 2. Representative structures of π -Pd intermediates **7** and **8** (B3LYP/SDD) and computed ^1H NMR chemical shifts (GIAO).

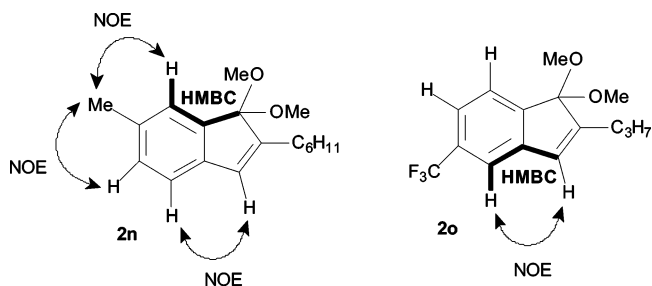
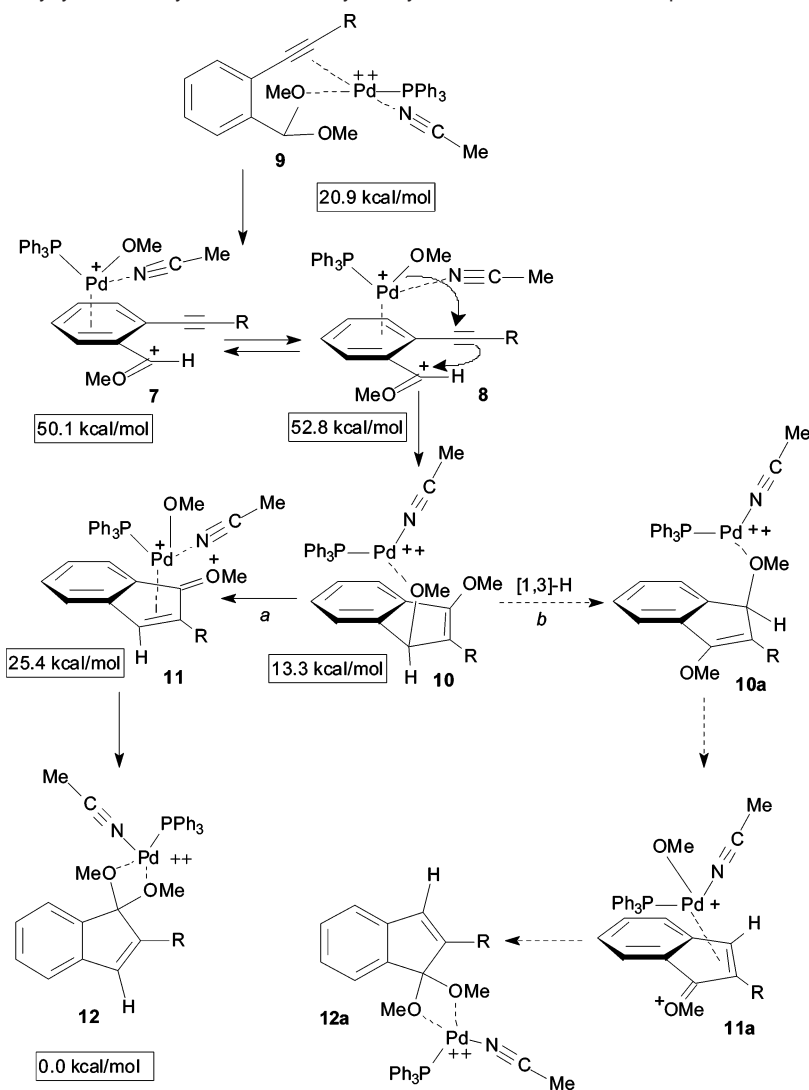
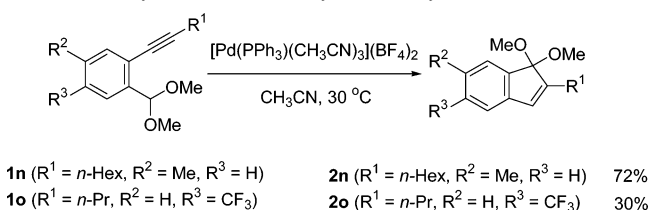


Figure 3. NMR determination of the structures **2n** and **2o**.

the benzylic carbon of **10**, concomitant migration of the olefinic bond, and subsequent coordination of the olefin to palladium would lead to **11** (path a). The migration of the MeO group from palladium to the benzylic carbon produces the indenone acetal–palladium complex **12**, which gives the product **2** through decomplexation of palladium. Alternatively, the 1,3-hydrogen shift in **10** may lead to **10a** (path b); **10a** is an enantiomer of **10**. In a manner similar to path a, **10a** gives **11a**, which affords **12a**. To distinguish the two possible pathways, we studied the cyclization of the non-symmetrically substituted acetals **1n** and **1o**, which yielded selectively **2n** and **2o**, respectively (Scheme 5). The regioisomers of **2n** and **2o** were not detected. The structures of **2n** and **2o** were unambiguously determined by collateral evidence of NOE and HMBC spectra (Figure 3; see also Supporting Information). Thus, the two methoxy groups from **1** are being consequently transferred by

(4) At -40 °C, two rapidly interconverting species of type **A** and three of type **B** were detected (see Supporting Information); at 50 °C, averaged NMR spectra for **A** and **B** were observed.

(5) Dotta, P.; Kumar, P. G. A.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2004**, *23*, 4247.

Scheme 4. Cyclization of *o*-Alkynylbenzaldehyde Acetals Catalyzed by Dicationic Palladium Complexes**Scheme 5.** Cyclization of Non-Symmetrically Substituted Acetals

Pd catalyst to their new position (path a). To the best of our knowledge, this is the first example of such stepwise delivery of the functional group by the Pd catalyst.

In conclusion, we have found a new cyclization reaction of *o*-alkynylbenzaldehyde acetals accompanied by a stepwise

delivery of two methoxy groups via the palladium cationic center coordinated to the aromatic ring.⁶ This type of coordination can be realized only when *three vacant sites* are available in the palladium catalyst. We are now in a position to understand why many useful transformations of *o*-alkynylaryl amines, aldehydes, imines, etc. take place readily with Pd catalyst, but those of the corresponding *aliphatic analogues* do not occur easily.

Acknowledgment. This work was financially supported by the Chemistry COE Program of Tohoku University. The computational results in this research were obtained using supercomputing resources at Information Synergy Center, Tohoku University.

Supporting Information Available: Experimental details, NMR charts for all new compounds and intermediates, and Cartesian coordinates of the optimized structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(6) Completely different cyclization of **1** has been previously reported when a neutral Pd(II) complex, $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, was used as a catalyst: (a) Nakamura, I.; Bajracharya, G. B.; Mizushima, Y.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4328. (b) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423.