Alkenes

Deutsche Ausgabe: DOI: 10.1002/ange.201602586
Internationale Ausgabe: DOI: 10.1002/anie.201602586

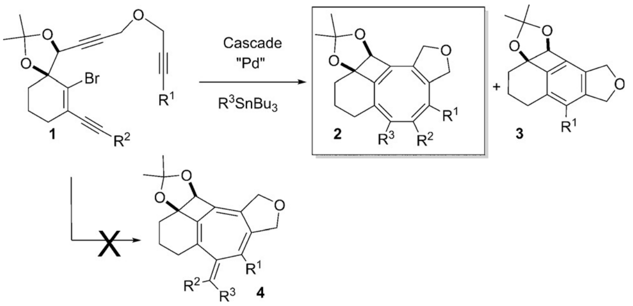
Synthesis of Cyclooctatetraenes through a Palladium-Catalyzed Cascade Reaction

Sarah Blouin, Vincent Gandon,* Gaëlle Blond,* and Jean Suffert*

Abstract: *Reported is a cascade reaction leading to fully substituted cyclooctatetraenes. This unexpected transformation likely proceeds through a unique 8π electrocyclization reaction of a ene triyne. DFT computations provide the mechanistic basis of this surprizing reaction.*

As a result of its unique structure, the cyclooctatetraene (COT) framework is particularly intriguing. This motif seems very rare in nature and only one natural product including a COT has been reported so far: caulerpin.[1] Nevertheless, COTs display very interesting properties and can be used to form new materials,[2] as new ligands in metal-catalyzed processes[3] or to construct molecules of structural or functional interest.[4] Different groups have examined, from a theoretical and synthetic perspective, these eight-membered ring derivatives containing four nonconjugated double bonds.[5] A one-step synthesis of COT consisting of the tetramerization of acetylene using the [Ni(CN)$_2$]/CaC catalyst was reported by Reppe in 1948.[6] Interest in the development of metal-mediated procedures to access highly substituted COTs has continually increased ever since.[7]

Our group and those of several others elegantly accomplished the construction of structurally complex scaffolds using cascade reactions.[8] We now report a cyclocarbopalladation cascade sequence which provides facile access to fully substituted COTs of type **2** directly from the alkenyl bromides **1** and a stannane as a coupling partner (Scheme 1). This reaction was discovered by serendipity since the polyunsaturated derivative **1** was initially designed to produce the polycyclic scaffold **4** which includes a seven-membered ring. In a preliminary experiment, classical conditions for palladium catalysis were applied simply using Pd(OAc)$_2$, PPh$_3$, and vinyltributylstannane as the trapping reagent of the final organopalladium species. The reaction was conducted under microwave irradiation at 100 °C in benzene. After full conversion of the starting compound **1a** (R^1 = SiMe$_3$, R^2 = C$_5$H$_{11}$), the COT **2aa** (R^3 = CH=CH$_2$) was isolated in 44 % yield. During this process, the side product **3a** (R^1 = SiMe$_3$) was also formed. It arises from a surprising elimination of the side chain, bearing the alkyl group, on the triple bond.[9] A 2:1 ratio (as determined by ^{1}H NMR spectroscopy) between **2aa** and **4a** was observed in the crude reaction mixture, thus indicating a possible competitive pathway during the reaction.



Scheme 1. A one-pot access to fully substituted COTs.

Considering the inherent interest in highly substituted COTs and the ease by which we could obtain this framework from simple precursors, we decided to optimize the reaction conditions to increase the selectivity for **2aa** (see Table S1 in the Supporting Information). Eventually, the use of Pd(OAc)$_2$ with DavePhos in acetonitrile under microwave irradiation proved to be the reaction conditions of choice to obtain **2aa** (Table 1, entry 1) in a 8:1 ratio relative to **3a**.

The scope and limitations of this reaction were next investigated. The starting compounds **1a–c** were prepared and tested under the optimized reaction conditions with various vinyl, allyl, alkenyl, and heteroaromatic stannanes [R^{3}SnBu$_3$, Pd(OAc)$_2$ (5 mol %), DavePhos (10 mol %), MeCN, MW, 100 °C]. Type **3** compounds were actually found in almost all reaction mixtures, yet they proved separable and their yield did not exceed 15 %. Yields of the desired type **2** compounds range from 18 to 53 % (Table 1), and can be considered good given the five-steps reaction and formation of four new C–C bonds.

NMR data and other analytical analyses were consistent with the presence of the COT core in these products, and a structural confirmation was obtained by X-ray crystallographic analysis of **2ba** (Figure 1). The COT framework adopts a boatlike geometry, which minimizes the steric congestion between the dimethyldioxolane, dihydrofuran moiety, and trimethylsilyl groups, and avoids the antiaromaticity which would result from planarity. The rigidity conferred by the cyclobutene ring actually precludes the inver-

---

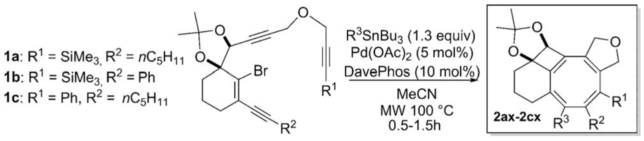
[*] S. Blouin, Dr. G. Blond, Dr. J. Suffert
Université de Strasbourg, Faculté de Pharmacie, UMR 7200 CNRS/UDS, 74 Route du Rhin, 67401 Illkirch-Graffenstaden (France)
E-mail: gaelle.blond@unistra.fr
jean.suffert@unistra.fr

Prof. V. Gandon
ICMMO, CNRS UMR 8182, Univ. Paris-Sud, Université Paris-Saclay bâtiment 420, 91405 Orsay cedex (France)
E-mail: vincent.gandon@u-psud.fr

Prof. V. Gandon
ICSN, CNRS UPR 2301, Univ. Paris-Sud, Université Paris-Saclay
91198 Gif-sur-Yvette (France)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201602586.

Table 1: Scope of the reaction



Entry	R^1	R^2	R^3	**2**	Yield [%][a]
1	SiMe$_3$	nC$_5$H$_{11}$	CH=CH$_2$	**2aa**	53
2	SiMe$_3$	nC$_5$H$_{11}$	CH=CHCH$_2$OH	**2ab**	25
3	SiMe$_3$	nC$_5$H$_{11}$	CH=CHSiMe$_3$	**2ac**	20
4	SiMe$_3$	nC$_5$H$_{11}$	CH$_2$CH=CH$_2$	**2ad**	23
5	SiMe$_3$	nC$_5$H$_{11}$	2-furanyl	**2ae**	34
6	SiMe$_3$	nC$_5$H$_{11}$	2-thienyl	**2af**	22
7	SiMe$_3$	nC$_5$H$_{11}$	C≡CPh	**2ag**	18[b]
8	SiMe$_3$	Ph	CH=CH$_2$	**2ba**	47
9	SiMe$_3$	Ph	CH=CHCH$_2$OH	**2bb**	35
10	SiMe$_3$	Ph	CH=CHSiMe$_3$	**2bc**	25
11	SiMe$_3$	Ph	CH=CHPh	**2bh**	30
12	SiMe$_3$	Ph	CH=CH(p-MeOC$_6$H$_4$)	**2bi**	30
13	SiMe$_3$	Ph	CH$_2$CH=CH$_2$	**2bd**	33
14	SiMe$_3$	Ph	2-furanyl	**2be**	40
15	SiMe$_3$	Ph	2-thienyl	**2bf**	36
16	Ph	nC$_5$H$_{11}$	CH=CH$_2$	**2ca**	42

[a] Yield of the isolated product. [b] 39% of **1a** was recovered. DavePhos = 2-dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl.

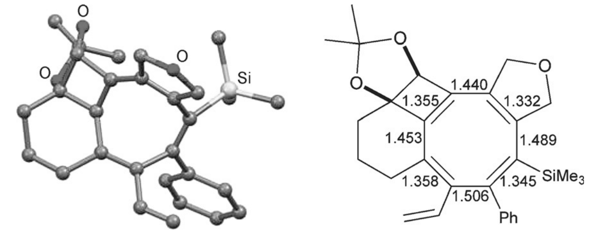
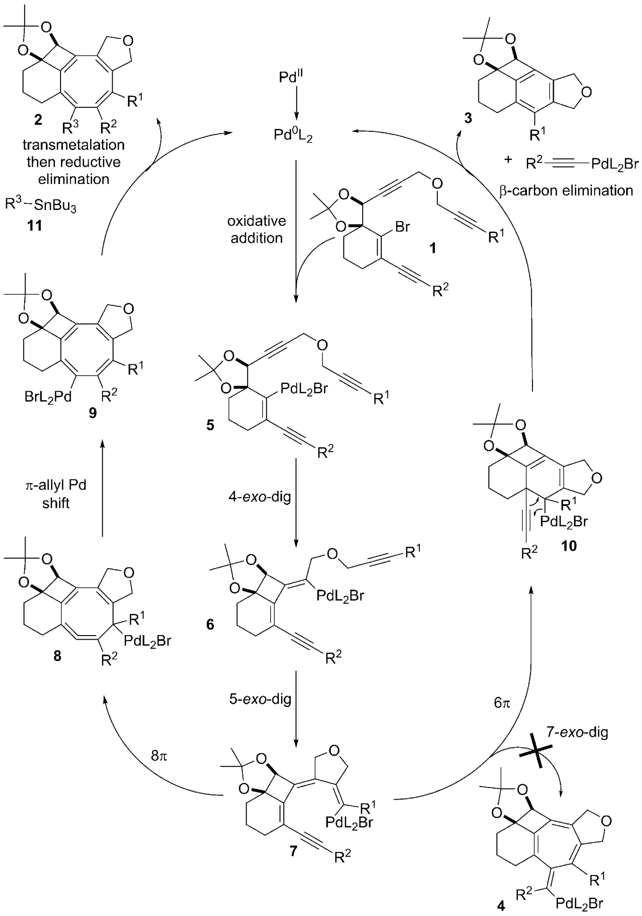


Figure 1. X-ray crystal analysis of the COT derivative **2ba** and COT bonds length. Hydrogen atoms are omitted for clarity.

sion of the COT. Moreover, this X-ray crystal analysis allowed determination of the location of the four double bonds. It indicates a complete shift of all unsaturations of the starting material during the reaction. The lengths of the single bonds are around 1.47 Å, whereas the double bonds are around 1.34 Å (Figure 1). By comparison, in a nonsubstituted COT, the single bonds are longer (1.54 Å) while the double bonds are identical in length (1.34 Å).[10]

We propose the following mechanism to account for the experimental results (Scheme 2). After oxidative addition of the active palladium species into the C−Br bond of **1**, a 4-*exo*-dig cyclocarbopalladation gives rise to the intermediate **6** which undergoes a 5-*exo*-dig cyclocarbopalladation giving **7**. A 8π electrocyclization pathway then gives **8**. A 1,3 π-allyl palladium shift takes place to provide **9** followed by a Stille cross coupling leading to the final COT **2**. The complex **7** is supposed to be a common intermediate on the way to **2** and the side product **3**. To generate **3**, it undergoes a 6π electrocyclization to give the intermediate **10**. This complex finally undergoes a β-carbon atom elimination. As mentioned above, no traces of the *syn* addition of the palladium to the remaining triple bond through a 7-*exo*-dig cyclocarbopalladation to form **4** were observed. If valid, the transformation of **7** into **8** would be unique so DFT computations were carried out to corroborate this hypothesis. Only the most important features are presented in Figure 2, and the full mechanism can be found in the Supporting Information. To limit the number of atoms in the system, the calculated complexes are unsubstituted at the alkyne termini and lack two methyl groups at the dioxolane ring. The phosphine ligand L has been used as a simplified model for DavePhos. The chosen computational method[11] was recently used by Wang et al. to investigate the palladium-catalyzed cyclization of polyunsaturated substrates.[12] The complex **A** has been taken as reference for the Gibbs free energies. Two complexes, $\mathbf{C'}_{trans}$ and $\mathbf{C'}_{cis}$, were actually found to be precursors to the eight-membered ring. The descriptors *trans* and *cis* are used here to highlight the relative disposition of the dioxolane ring and the metal fragment. A transition state connecting $\mathbf{C'}_{trans}$ to the bent allene complex[13] $\mathbf{E}_{trans}$ was located only 8.3 kcal mol^{-1} above the former. The transformation is appreciably exergonic by 28.6 kcal mol^{-1}. The main geometrical change to reach the transition state concerns the terminal carbon atoms of the ene triyne system, and they move closer together (from 3.00 Å to 2.20 Å; see Figure 3 for the geometry of $\mathbf{TS}_{\mathbf{C'E}\text{-}trans}$). HOMOs of $\mathbf{C'}_{trans}$ and $\mathbf{TS}_{\mathbf{C'E}\text{-}trans}$ have the ideal symmetry for a conrotatory ring closure (see Figure S3).



Scheme 2. Proposed catalytic cycle for the formation of COTs.

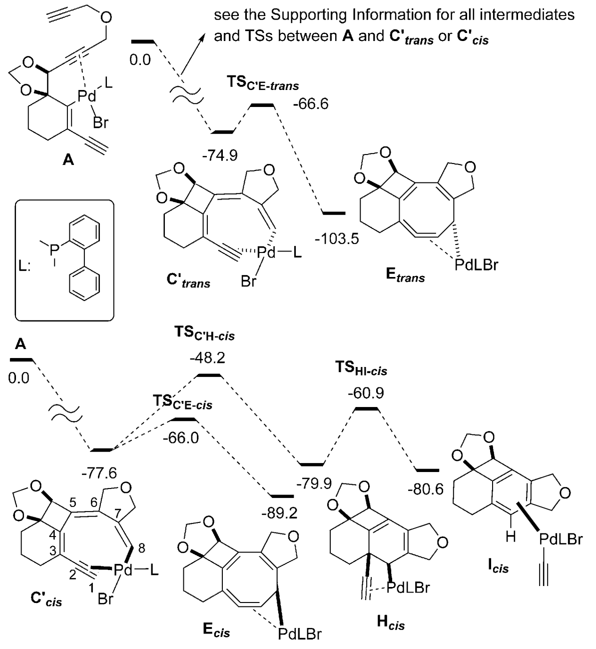
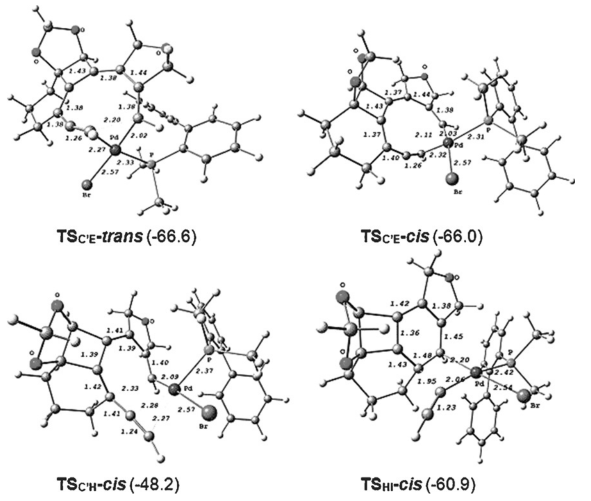


Figure 2. Selected part of the computed reaction profile (ΔG_{298}, kcal mol^{-1}).


TS$_{C'E}$-*trans* (-66.6) TS$_{C'E}$-*cis* (-66.0)

TS$_{C'H}$-*cis* (-48.2) TS$_{HI}$-*cis* (-60.9)

Figure 3. Geometries of selected transition states (selected distances in Å, the free energy relative to **A** is indicated within parentheses in kcal mol^{-1}).

Thus, the cyclization of **C′**$_{trans}$ to **E**$_{trans}$ can be referred to as a 8π electrocyclization of a polyunsaturated open chain containing three conjugated double bonds, a triple bond, and bearing a palladium on the terminal position of one double bond. This cyclization has no precedent. The result of this reaction is the formation of an eight-membered ring including two conjugated double bonds and an allenyl palladium species.

Having deciphered the formation of the eight-membered ring products, we next aimed at finding a rationale for the type **I** benzene derivatives (Figure 2). Scanning the potential energy surface (PES) from **C**$_{trans}$ or **C′**$_{trans}$ did not lead to any transition state. Thus, we decided to turn our attention to the *cis* series. Apart from the absolute configuration of the helix, **C′**$_{cis}$ displays bond lengths very similar to those found in **C′**$_{trans}$. The 8π electrocyclization is also possible from **C′**$_{cis}$. The corresponding transition state **TS**$_{C'E\text{-}cis}$ lies virtually at the same free energy as **TS**$_{C'E\text{-}trans}$ ($\Delta\Delta G^{\neq}_{298} = 0.6$ kcal mol^{-1}). However, **E**$_{cis}$ is markedly less stable than **E**$_{trans}$ ($\Delta\Delta G_{298} = 14.3$ kcal mol^{-1}). This time, it was possible to rationalize the formation of the benzene type of products **I**. A transition state connecting **C′**$_{cis}$ with the cyclohexadiene complex **H**$_{cis}$ could be located, and it lies 29.4 kcal mol^{-1} above **C′**$_{cis}$. Interestingly, in **TS**$_{C'H\text{-}cis}$, which corresponds to the formation of the central six-membered ring, the metal center remains coordinated to the alkyne terminus. This arrangement means that the rotations around the C3−C4 and C7−C8 bonds both occurred in an outward fashion. Thus, this process can be described as a disrotatory 6π electrocyclization. Complex **H**$_{cis}$ is more stable than **C′**$_{cis}$ by 2.3 kcal mol^{-1}. The formation of the aromatic system could be achieved through **TS**$_{HI\text{-}cis}$, which lies 19.0 kcal mol^{-1} above **H**$_{cis}$. Its geometry and transition vector show the rotation of the H-C1≡C2 fragment around C1. The breaking C−C bond and the forming C−Pd bond are close in length (1.95 Å vs. 2.06 Å respectively). This step can be referred to as a β-carbon atom elimination, a process which remains relatively rare in organometallic chemistry, especially if the α-atom is a carbon atom and not an oxygen atom.[14] We are not aware of any example of β-alkyne elimination when the α-atom is a carbon atom.[15] The benzene η^1-complex **I**$_{cis}$ is more stable than **H**$_{cis}$ by only 0.7 kcal mol^{-1}. Since **TS**$_{C'H\text{-}cis}$ lies at 17.8 kcal mol^{-1} above **TS**$_{C'E\text{-}cis}$, this cyclization pathway is unlikely to occur at room temperature. However, the reaction is carried out at 100 °C under microwave irradiation. Therefore, the formation of side products through **H**$_{cis}$ and **I**$_{cis}$ is conceivable. That the reactivity can be funnelled towards **I**$_{cis}$ could also be due to a relatively slow cross coupling of **E** with the stannane, which would allow reversibility of **E**$_{cis}$ to **C′**$_{cis}$, and rapid consumption of **I**$_{cis}$, presumably by cross-coupling as well. Overall, the 8π electrocyclization pathway remains the most favorable and is likely to take place in both *cis* and *trans* series.

The 6π electrocyclization/β-carbon atom elimination route could only be modelled in the *cis* series. The 6π electrocyclization in the *trans* series would lead to a complex in which the alkyne and the dioxolane moiety would display a *trans* relationship, which seems geometrically impossible. It is also worthy of note that the 7-*exo*-dig pathway, which was the original target of this work, could not be modelled from either **C′**$_{trans}$ or **C′**$_{cis}$.

In summary, we have discovered a remarkable route for the expedient preparation of fully substituted COTs through a new mechanistic pathway. This transformation is unique in several points: 1) the formation of a COT scaffold in a one-pot cascade reaction; 2) a 8π electrocyclization of an ene triyne; 3) a 1,3 π-allyl palladium shift on a cyclooctadienallene; and 4) an unprecedented β-carbon atom elimination of a triple bond leading to a very strained aromatic polycycle. DFT calculations nicely corroborate the results observed for this transformation. These results open the route for a series of polysubstituted COTs potentially useful in the development of new materials or the design of original ligands.

Acknowledgments

We thank the MNERT (S.B.) for fellowship, and Prof. Michael Harmata (University of Missouri-Columbia) and Prof. Dr Armin de Meijere (University of Göttingen) for helpful discussions. We used the computing facility of the CRIANN – Centre Régional Informatique et d'Applications Numériques de Normandie (project 2006-03).

Keywords: alkenes · density functional calculations · electrocyclizations · palladium · reaction mechanisms

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 7208–7211
Angew. Chem. **2016**, *128*, 7324–7327

---

[1] B. C. Maiti, R. H. Thomson, M. Mahendran, *J. Chem. Res. Miniprint* **1978**, 1682.

[2] a) M. J. Marsella, R. J. Reid, *Macromolecules* **1999**, *32*, 5982; b) R. Gleiter, B. Esser, S. C. Kornmayer, O. I. Universita, *Acc. Chem. Res.* **2009**, *42*, 1108; c) T. Nishiuchi, Y. Kuwatani, T. Nishinaga, M. Iyoda, *Chem. Eur. J.* **2009**, *15*, 6838.

[3] a) F. Schager, K. Haack, R. Mynott, A. Rufinska, K.-R. Pörschke, *Organometallics* **1998**, *17*, 807; b) P. W. Roesky, *Eur. J. Inorg. Chem.* **2001**, *2001*, 1653; c) T. Murahashi, N. Kato, S. Ogoshi, H. Kurosawa, *J. Organomet. Chem.* **2008**, *693*, 894; d) T. Murahashi, S. Kimura, K. Takase, T. Uemura, S. Ogoshi, K. Yamamoto, *Chem. Commun.* **2014**, *50*, 820.

[4] K. W. Glaeske, W. A. Donaldson, *Mini. Rev. Org. Chem.* **2012**, *9*, 31.

[5] a) S. M. Bachrach, *J. Org. Chem.* **2009**, *74*, 3609; b) L. A. Paquette, T. Z. Wang, C. E. Cottrell, *J. Am. Chem. Soc.* **1987**, *109*, 3730; c) L. A. Paquette, *Pure Appl. Chem.* **1982**, *54*, 987; d) L. A. Paquette, *Acc. Chem. Res.* **1993**, *26*, 57; e) P. Wenthold, D. Hrovat, W. Borden, W. Lineberger, *Science* **1996**, *272*, 1456; f) D. M. Neumark, *Phys. Chem. Chem. Phys.* **2005**, *7*, 433.

[6] W. Reppe, O. Schlichting, K. Klager, T. Toepel, *Justus Liebigs Ann. Chem.* **1948**, *560*, 1.

[7] a) C. Wang, Z. Xi, *Chem. Commun.* **2007**, 5119; b) P. A. Wender, J. P. Christy, A. B. Lesser, M. T. Gieseler, *Angew. Chem. Int. Ed.* **2009**, *48*, 7687; *Angew. Chem.* **2009**, *121*, 7823; c) H. J. Zhang, J. Wie, F. Zhao, Y. Liang, Z. Wang, Z. Xi, *Chem. Commun.* **2010**, *46*, 7439.

[8] a) J. Pétrignet, A. Boudhar, G. Blond, J. Suffert, *Angew. Chem. Int. Ed.* **2011**, *50*, 3285; *Angew. Chem.* **2011**, *123*, 3343; b) C. Hulot, G. Blond, J. Suffert, *J. Am. Chem. Soc.* **2008**, *130*, 5046; c) M. Charpenay, A. Boudhar, G. Blond, J. Suffert, *Angew. Chem. Int. Ed.* **2012**, *51*, 4379; *Angew. Chem.* **2012**, *124*, 4455; d) C. Hulot, S. Amiri, G. Blond, P. Schreiner, J. Suffert, *J. Am. Chem. Soc.* **2009**, *131*, 13387; e) M. Charpenay, A. Boudhar, C. Hulot, G. Blond, J. Suffert, *Tetrahedron* **2013**, *69*, 7568. For excellent reviews in the field of cascade reactions see: f) A. de Meijere, F. E. Meyer, *Angew. Chem. Int. Ed. Engl.* **1995**, *33*, 2379; *Angew. Chem.* **1994**, *106*, 2473 and references inside g) A. de Meijere, S. Bräse, *J. Organomet. Chem.* **1999**, *576*, 88; h) T. Vlaar, E. Ruijter, R. V. A. Orru, *Adv. Synth. Catal.* **2011**, *353*, 809; i) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; *Angew. Chem.* **2006**, *118*, 7292; j) L. Tietze, *Chem. Rev.* **1996**, *96*, 115.

[9] The compound **3a** was already obtained in an alternative way: G. Blond, C. Bour, B. Salem, J. Suffert, *Org. Lett.* **2008**, *10*, 1075.

[10] H. S. Kaufman, I. Fankuchen, H. Mark, *Nature* **1948**, *161*, 165.

[11] We used the Gaussian 09 software package. All the structures were optimized and characterized to be energy minima or transition states at the B3LYP/BSI level, where BSI denotes a basis set of LANL2DZ for palladium and 6-31G(d) for nonmetal atoms. The energies were then improved by M06/BSII single-point calculations with the solvent effects accounted by SMD solvent model (CH_3CN) where BSII denotes a basis set of SDD for palladium and 6-311++G(d,p) for nonmetal atoms. The thermal corrections to the Gibbs free energies were carried out at 298.15 K under 1 atm, using B3LYP/BSI harmonic frequencies. The solvent-corrected M06 Gibbs free energies at 298.15 K are discussed (ΔG_{298}).

[12] Y. Xia, S. Qu, Q. Xiao, Z.-Y. Wang, P. Qu, L. Chen, Z. Liu, L. Tian, Z. Huang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 13502.

[13] M. Melaimi, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2010**, *49*, 8810; *Angew. Chem.* **2010**, *122*, 8992.

[14] T. Satoh, M. Miura, *Top. Organomet. Chem.* **2005**, *14*, 1.

[15] For examples of β-alkyne elimination when the α-atom is an O, see: T. Nishimura, H. Araki, Y. Maeda, S. Uemura, *Org. Lett.* **2003**, *5*, 2997.

Received: March 14, 2016