DOI: 10.1002/ange.201308448

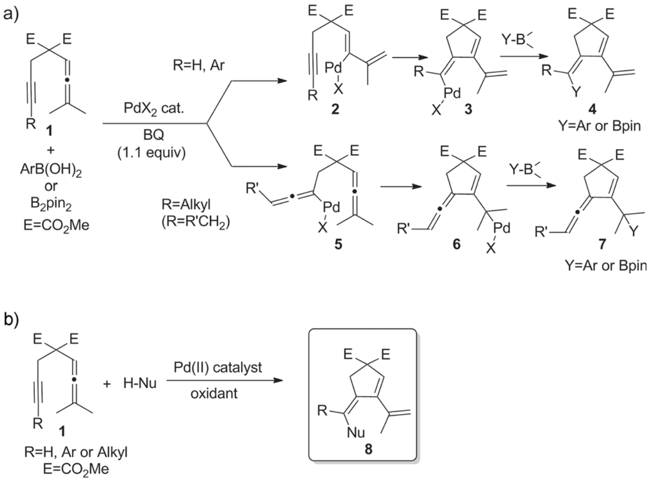
**Homogeneous Catalysis**

# Palladium-Catalyzed Aerobic Domino Oxidative Carbocyclization-Alkynylation of Allenynes**

*Chandra M. R. Volla and Jan-E. Bäckvall**

Transition-metal-catalyzed cycloisomerizations and carbocyclizations have become some of the most powerful methods for the construction of carbocyclic and heterocyclic compounds.[1] Metal-catalyzed carbocyclizations of unsaturated systems can be divided into oxidative and non-oxidative reactions, and have been extensively studied in recent years.[2]

In our group, we have a longstanding interest in the development of palladium-catalyzed oxidative carbocyclization reactions of enallenes, dienallenes, and enynes.[3] In recent studies on these carbocyclizations, we have shown that enallenes[4] and allenynes[5] **1** can be arylated or borylated by using catalytic amounts of a palladium(II) salt and an arylboronic acid or a bis(pinacolato)diboron ($B_2pin_2$), respectively. Allenyne **1** with R = H or aryl (Ar), led to triene **4** via the intermediacy of **2** and **3**. By contrast, allenyne **1** with aliphatic substitution (R = alkyl) afforded predominantly vinylallene product **7** through the corresponding intermediates **5** and **6**. More recently, we have addressed the selectivity issue of this carbocyclization-borylation reaction by using additives (Scheme 1 a).[5b]



**Scheme 1.** a) Oxidative Pd-catalyzed arylative/borylative carbocyclization (Previous work Ref. [5a]). b) Oxidative Pd-catalyzed carbocyclization with incorporation of a pronucleophile (H-Nu; this work).

The objective of the present study was to extend the synthetic potential of the carbocyclization of allenynes by quenching Pd intermediate **3** with a suitable pronucleophile (H-Nu; Scheme 1 b).

In Pd-catalyzed oxidative coupling reactions, the $Pd^{II}$ species couples two fragments to give the product and $Pd^0$.[6] The latter is oxidized back to $Pd^{II}$ by benzoquinone (BQ). Alternatively, the oxidation of $Pd^0$ to $Pd^{II}$ can also be performed under aerobic conditions by employing catalytic amounts of BQ, macrocyclic metal complex, and molecular oxygen.[7,8] For environmental reasons it would be desirable to employ the aerobic version with catalytic amounts of BQ. Herein, we report our studies on the oxidative carbocyclization-alkynylation of **1** (R = H, aryl, alkyl) by using molecular oxygen as the oxidant (Scheme 1 b).

Alkyne functionality exists in a wide range of molecular structures and its importance is demonstrated in various fields of synthesis ranging from biochemistry to materials science.[9] Alkynes serve as key intermediates in the preparation of a large variety of building blocks, and several research groups have recently studied palladium-catalyzed oxidative alkynylation reactions of terminal alkynes.[10,11] Although most of these studies involve oxidative coupling reactions between terminal alkynes and olefinic, aromatic, or heteroaromatic $C(sp^2)$–H bonds,[10] the use of palladium-catalyzed alkynylation as a termination step of insertion cascade reactions has remained largely unexplored. In 2005 Müller and co-workers reported a palladium(0)-catalyzed domino carbocyclization-alkynylation reaction for the synthesis of polycyclic compounds.[12] Zhu and co-workers recently developed an efficient route to 3-alkynylindoles by a palladium(II)-catalyzed coupling of *ortho*-alkynylanilines and terminal alkynes under aerobic conditions.[11] A similar heterocyclization followed by alkynylation to produce 2-alkynyl indoles was developed by Chan and co-workers by using silver triflate as a catalyst.[13]

An initial challenge associated with the envisioned project was to reduce the tendency of terminal alkynes to undergo oxidative homocoupling under palladium catalysis.[14] An additional challenge would be to control the intrinsic reactivity of the substrate **1** when R = H. In this case, both reacting partners would be terminal alkynes and the possibility would exist for undesired heterocoupling of two alkynes under oxidative conditions.[15]

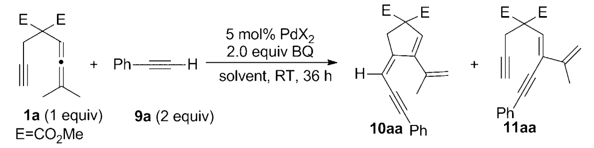
For the initial studies, we chose the reaction of **1a** and phenylacetylene (**9a**) in THF in the presence of 5 mol% of a $Pd^{II}$ catalyst and 2.0 equiv of benzoquinone. After screening various $Pd^{II}$ salts and temperatures, we realized that at elevated temperatures an Alder-ene type cyclization product predominates.[16] However, at room temperature the desired trienyne product **10aa** was obtained as a single regioisomer in

---

[*] Dr. C. M. R. Volla, Prof. Dr. J.-E. Bäckvall
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University
SE-106 91 Stockholm (Sweden)
E-mail: jeb@organ.su.se

[**] We would like to thank the Wenner-Gren Foundation for a postdoctoral fellowship to C.M.R.V.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201308448.

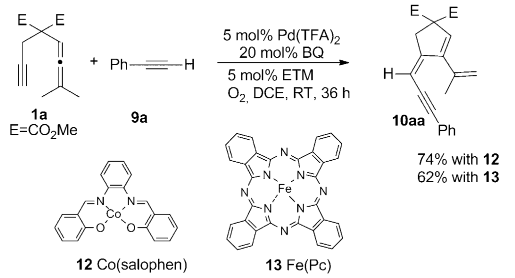


| PdX$_2$ Cat. | Solvent | 10aa | 11aa |
|---|---|---|---|
| Pd(OAc)$_2$ | THF | 39% | traces |
| Pd(OAc)$_2$ | DCE | 74% | 12% |
| Pd(TFA)$_2$ | DCE | 78% | 0% |
| Pd(OAc)$_2$ | toluene | 58% | 30% |
| Pd(OAc)$_2$ | benzene | 33% | 25% |
| Pd(OAc)$_2$ | pentane | 25% | 12% |

***Scheme 2.*** Palladium-catalyzed domino carbocyclization-alkynylation. DCE = 1,2-dichloroethane.

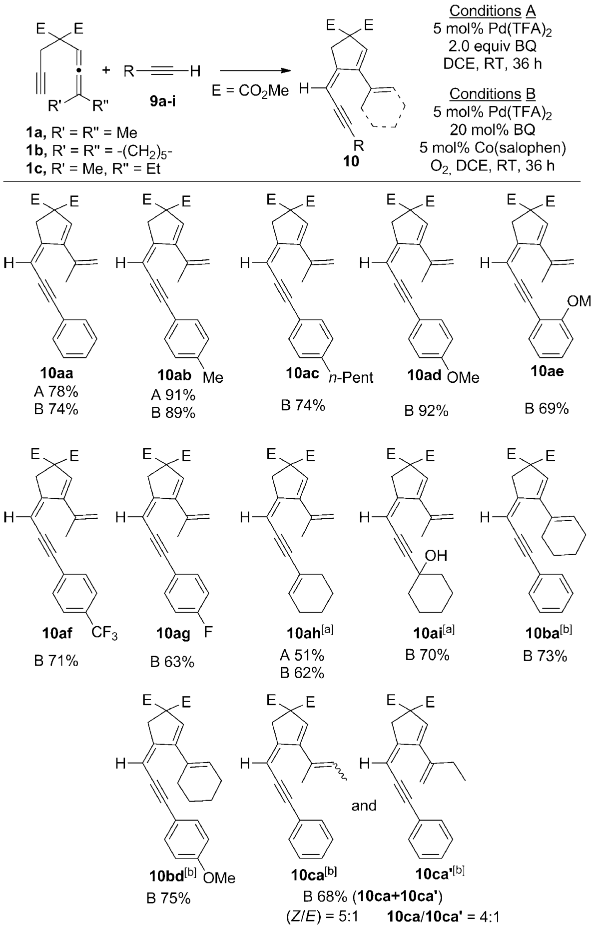
39 % yield (Scheme 2). The reaction was highly stereoselective and afforded the *Z* product exclusively. The high selectivity for the *Z* product is due to the stereospecific *cis*-carbopalladation of the alkyne by the dienylpalladium moiety in intermediate **2**. Various solvents were screened in the presence of a Pd(OAc)$_2$ catalyst, and it was found that the reaction has a strong dependence on the solvent (See the Supporting Information). In DCE, a clean reaction was observed to give the desired product **10aa** in 74 % yield of the isolated product (Scheme 2). An important point to note is that under these conditions, the acyclic alkyne product **11aa**, which results from the alkynylation of dienylpalladium intermediate **2**, was observed along with the desired product **10aa**. The relative amount of acyclic enyne **11aa** increases in nonpolar solvents such as toluene, benzene, and pentane. Although under these conditions the selectivity was impeded, it gave crucial information about the reaction mechanism (see below). In our previously developed palladium-catalyzed carbocyclization reactions of enallenes[4] or allenynes,[5] we proposed the formation of a dienylpalladium intermediate (cf. **2**). The formation of **11aa** thus provides convincing experimental support for a dienylpalladium intermediate in the carbocyclization of enallenes or allenynes.

Lower yields of the product were obtained in polar solvents such as methanol, DMSO, chloroform, acetone, and water. Polar solvents such as acetonitrile and DMF promoted the heterocoupling of phenylacetylene and **1a** to give a dialkynylative carbocyclization product in good yields (see the Supporting Information).[15] Interestingly, the use of 5 mol % of Pd(TFA)$_2$ (TFA = trifluoroacetate) in place of Pd(OAc)$_2$ in DCE completely suppressed the formation of side product **11aa** and furnished **10aa** in 78 % yield. When the anion is changed from acetate to trifluoroacetate, the palladium center will become more electrophilic, which apparently accelerates the carbocyclization and leads to the desired product without giving **11aa**. The use of excess alkyne (3.0–4.0 equiv) has no significant effect on the reaction. At this point, our attention turned to the aerobic oxidative carbocyclization-alkynylation process (Scheme 3). Replacing BQ by molecular oxygen as the oxidant did not lead to any reaction at room temperature, but led to decomposition of the starting material at higher temperatures. Stabilizing ligands for the palladium center (DMSO, BQ) did not improve the results. Fortunately, the use of 20 mol % of BQ and 5 mol % of a metal macrocyclic complex as electron-transfer mediators (ETMs)[7] under 1 atm of O$_2$ resulted in a productive reaction in DCE as the solvent at room temperature. Cobalt(salophen) as the ETM gave a higher yield of **10aa** (74 %) than iron(phthalocyanine) (62 %).



***Scheme 3.*** Palladium-catalyzed domino carbocyclization-alkynylation under aerobic conditions.

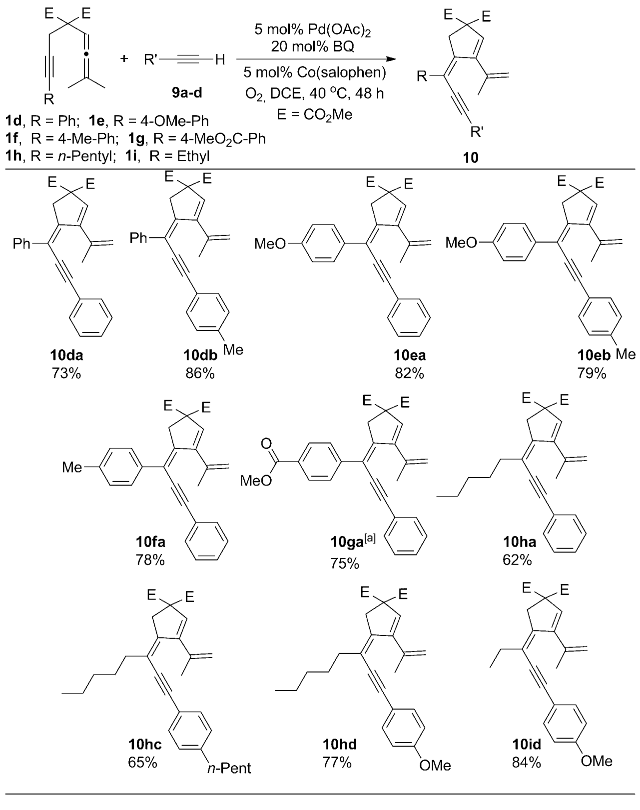
After having optimized the reaction conditions for the domino palladium(II)-catalyzed carbocyclization-alkynylation, the scope of the reaction was investigated by using terminal allenynes **1a–c** (Scheme 4). The use of either



***Scheme 4.*** Scope of the palladium-catalyzed carbocyclization-alkynylation with terminal allenynes. [a] Reaction was carried out at 40 °C instead of room temperature. [b] Reaction took 48 h to reach completion.

stoichiometric amounts of BQ (A) or the optimized aerobic conditions (B) gave similar results, as is clear from the examples **10aa**, **10ab**, and **10ah**. Aromatic and aliphatic terminal alkynes could all be used in the reaction with allenyne **1a**. Electron-donating substituents on the aromatic ring resulted in slightly higher yields compared to electron-withdrawing groups such as F or $CF_3$. Aliphatic alkynes having either an alkene or alcohol functionality also reacted nicely with **1a** to give high yields of the corresponding products **10ah** and **10ai**.[17] As expected, as a consequence of the lower reactivity of aliphatic alkynes, a slightly higher temperature (40 °C) was required for the reaction to reach completion. When the dimethyl groups of the allene moiety were replaced by more bulky groups, such as pentamethylene **1b** or ethylmethyl groups **1c**, the reaction gave the products **10ba** and **10ca**, respectively, in high yields.

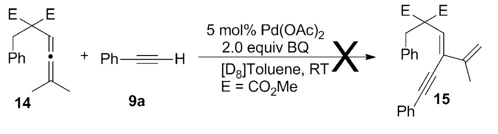
To extend the scope of this palladium(II)-catalyzed oxidative aerobic domino carbocyclization-alkynylation, internal allenynes **1d–g** having aromatic substituents were allowed to react with substituted phenylacetylenes (Scheme 5). As a result of the increased steric hindrance for the formation of tetrasubstituted enyne products **10da–ga**, these reactions did not go to completion under the conditions used in Scheme 4, even after extended reaction times. Increasing the temperature resulted in the formation of a large amount of thermal Alder-ene product as a side product.[16] Fortunately, we found that the use of $Pd(OAc)_2$ instead of $Pd(TFA)_2$ at 40 °C solved this problem and gave the products **10da–ga** in high to excellent yields. Next, we focused our attention towards the alkyl-substituted allenyne substrates **1h** and **1i**, where we previously observed that a mixture of triene product along with vinylallene product was obtained in the absence of any additives (Scheme 1a, Ref. [5]). However, we were pleased to find that only a single product **10** was formed under the alkynylation conditions. No allenic product **7** was observed in the NMR analysis of the crude reaction mixture.



*Scheme 5.* Scope of the palladium-catalyzed carbocyclization-alkynylation with internal allenynes. [a] Reaction was carried out at 50 °C instead of 40 °C.

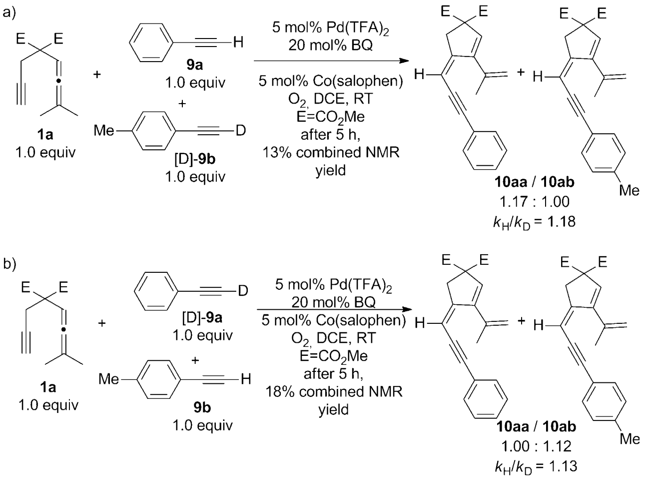
From the isolation of the acyclic alkynylation side product **11aa** (Scheme 2), it is clear that the reaction proceeds through the formation of dienylpalladium intermediate **2**, which can be formed by the nucleophilic attack of the allene moiety on the palladium center. Several control experiments were carried out to obtain more details concerning the mechanism of the reaction. Firstly, when 1.0 equiv of allenyne **1a**, 1.0 equiv of $Pd(OAc)_2$, and 2.0 equiv of phenylacetylene were mixed in an NMR tube, no reaction was observed even after 3 h, and only starting material was detected. The addition of 20 mol % BQ immediately triggered the reaction, which suggests that BQ not only acts as an oxidant but also plays a role as a ligand. Secondly, 1.0 equiv of allenyne **1a** was mixed with 1.0 equiv of $Pd(OAc)_2$ and 20 mol % of BQ. In the absence of phenylacetylene, no carbocyclization product was observed even after 3 h and only starting material was seen in the crude NMR spectrum. The addition of phenylacetylene then "kick-starts" the reaction. These experiments clearly indicate that the presence of both BQ and phenylacetylene is crucial for the carbocyclization reaction to occur.

Moreover, the conditions that favored the formation of acyclic enyne **11aa** (Scheme 2) by alkynylation of dienylpalladium intermediate **2** did not give the corresponding product **15** from the reaction of allene **14** with phenylacetylene (**9a**; Scheme 6). This result suggests that the formation of a π complex between the palladium(II) center and the alkyne unit of allenyne **1** is important for the nucleophilic addition of the allene moiety to the palladium center.



*Scheme 6.* Attempted palladium-catalyzed allene alkynylation.

To investigate whether there is a kinetic deuterium isotope effect in the reaction, allenyne **1a** was allowed to react with phenylacetylene (**9a**) and 1-deuteriophenylacetylene ([D]-**9a**) in separate experiments under the optimized reaction conditions for the carbocyclizations (see the Supporting Information). The rate of both reactions was monitored for the initial stage of the reaction. Aliquots of the reaction mixture were filtered and subjected to NMR spectroscopy at different time intervals. No difference in the rate of the reaction was observed between the two alkynes. This finding indicates that the alkynylation of palladium is not the rate-determining step in the catalytic reaction.

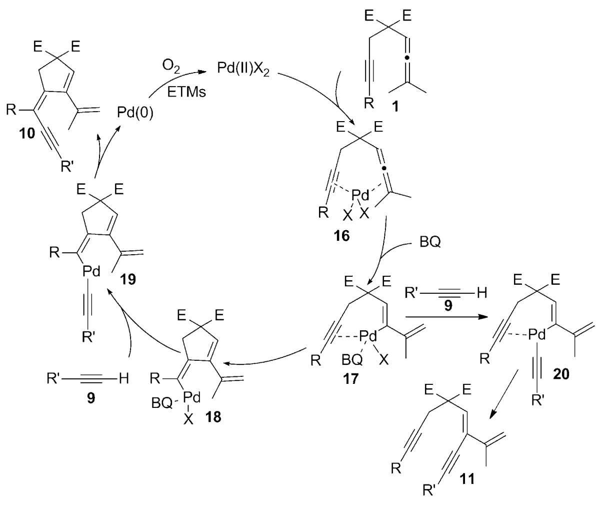


***Scheme 7.*** Palladium-catalyzed kinetic experiments of the intrinsic kinetic isotope effect.

To gain more details about the presence of an intrinsic kinetic isotopic effect, substrate **1a** was treated with a 1:1 mixture of phenylacetylene (**9a**) and 1-deuteriotolylacetylene ([D]-**9b**) under the optimized reaction conditions for the carbocyclization (Scheme 7a). A ratio of 1.17:1.00 between **10aa** and **10ab** was obtained, which gives an intrinsic deuterium isotopic effect ($k_H/k_D$) of 1.18.[18]

To eliminate the effect of the tolyl group, experiments using a 1:1 mixture of [D]-**9a** and **9b** were carried out (Scheme 7b). A **10aa**/**10ab** ratio of 1.00:1.12 was obtained, which gives a value of 1.13 for $k_H/k_D$.[18] From these experiments we conclude that there is a small intrinsic deuterium isotope effect of $k_H/k_D = 1.15$. The small difference in $k_H/k_D$ between the two experiments might be due to the 4-methyl group.

On the basis of the above results, we propose the mechanism shown in Scheme 8 for the domino carbocyclization-alkynylation. Formation of π complex **16** followed by the nucleophilic attack of the allene moiety on the palladium center would produce dienylpalladium species **17**. *cis*-Insertion of the alkyne into the palladium–vinyl bond of **17** will give vinylpalladium complex **18**. Subsequent reaction of terminal alkyne **9** with Pd will generate **19**, from which the product **10** is formed after reductive elimination. Quenching of dienylpalladium intermediate **17** gives side product **11** via intermediate **20**. Oxidation of $Pd^0$ to $Pd^{II}$ by $O_2$ catalyzed by the ETMs (BQ and Co(salophen)) completes the catalytic cycle.



***Scheme 8.*** Proposed mechanism for the palladium-catalyzed domino carbocyclization-alkynylation.

In conclusion, we have developed an efficient palladium(II)-catalyzed aerobic oxidative domino carbocyclization-alkynylation of allenynes and terminal alkynes. The reactions proceed under aerobic conditions consisting of 20 mol% of BQ, 5 mol% of cobalt(salophen), and 1 atm of $O_2$ for the reoxidation of palladium(0) to palladium(II). A wide range of aromatic and aliphatic terminal alkynes with various functional groups are tolerated under the reaction conditions. Furthermore, in contrast to our previously developed carbocyclization of allenynes involving arylation/borylation, the reaction selectively gave a single product with alkyl-substituted allenynes. A key intermediate was quenched as an isolated side product, which supports the proposed mechanism. Further studies to extend the carbocyclization chemistry and detailed mechanistic studies are underway in our laboratory.

Received: September 27, 2013

**Keywords:** alkynylation · biomimetic oxidation · carbocyclization · homogeneous catalysis · palladium

---

[1] a) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635; b) for an excellent review on the metal-catalyzed cycloisomerization reactions of allenes, see C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954; c) E.-I. Negishi, C. Copéret, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365.

[2] a) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; b) for a recent review on palladium-catalyzed oxidative carbocyclizations, see Y. Deng, A. K. Å. Persson, J.-E. Bäckvall, *Chem. Eur. J.* **2012**, *18*, 11498.

[3] a) J. Franzén, J. Löfstedt, I. Dorange, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2002**, *124*, 11246; b) J. Franzén, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2003**, *125*, 6056; c) J. Franzén, J. Löfstedt, J. Falk, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2003**, *125*, 14140; d) J. Piera, K. Närhi, J.-E. Bäckvall, *Angew. Chem.* **2006**, *118*, 7068; *Angew. Chem. Int. Ed.* **2006**, *45*, 6914; e) J. Piera, A. Persson, X. Caldentey, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2007**, *129*, 14120; f) E. V. Johnston, E. A. Karlsson, S. A. Lindberg, B. Åkermark, J.-E. Bäckvall, *Chem. Eur. J.* **2009**, *15*, 6799; g) A. K. Å. Persson, J.-E. Bäckvall, *Angew. Chem.* **2010**, *122*, 4728; *Angew. Chem. Int. Ed.* **2010**, *49*, 4624; h) M. Jiang, T. Jiang, J.-E. Bäckvall, *Org. Lett.* **2012**, *14*, 3538; i) M. Jiang, J.-E. Bäckvall, *Chem. Eur. J.* **2013**, *19*, 6571.

[4] a) A. K. Å. Persson, T. Jiang, M. T. Johnson, J.-E. Bäckvall, *Angew. Chem.* **2011**, *123*, 6279; *Angew. Chem. Int. Ed.* **2011**, *50*, 6155; b) T. Jiang, A. K. Å. Persson, J.-E. Bäckvall, *Org. Lett.* **2011**, *13*, 5838.

[5] a) Y. Deng, T. Bartholomeyzik, A. K. Å. Persson, J. Sun, J.-E. Bäckvall, *Angew. Chem.* **2012**, *124*, 2757; *Angew. Chem. Int. Ed.* **2012**, *51*, 2703; b) Y. Deng, T. Bartholomeyzik, J.-E. Bäckvall,

*Angew. Chem.* **2013**, *125*, 6403; *Angew. Chem. Int. Ed.* **2013**, *52*, 6283; c) for palladium-catalyzed oxidative carbocyclization-acyloxylation of alkyl-susbstituted allenynes, see Y. Deng, J.-E. Bäckvall, *Angew. Chem.* **2013**, *125*, 3299; *Angew. Chem. Int. Ed.* **2013**, *52*, 3217.

[6] For reviews, see a) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; b) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780.

[7] a) For a review on the use of a biomimetic approach in catalytic oxidation, see J. Piera, J.-E. Bäckvall, *Angew. Chem.* **2008**, *120*, 3558; *Angew. Chem. Int. Ed.* **2008**, *47*, 3506.

[8] a) B. P. Babu, J.-E. Bäckvall, *Chem. Eur. J.* **2013**, *19*, 4140; b) N. Gigant, J.-E. Bäckvall, *Chem. Eur. J.* **2013**, *19*, 10799.

[9] a) *Modern Acetylene Chemistry* (Ed.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim, **1995**; b) *Acetylene Chemistry* (Ed.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, **2005**; c) for a recent review about the importance of alkynes in the preparation of chemicals under palladium catalysis, see R. Chinchilla, C. Nájera, *Chem. Rev.* **2013**, DOI: 10.1021/cr400133p.

[10] a) X. Jie, Y. Shang, P. Hu, W. Su, *Angew. Chem.* **2013**, *125*, 3718; *Angew. Chem. Int. Ed.* **2013**, *52*, 3630; b) S. H. Kim, J. Yoon, S. Chang, *Org. Lett.* **2011**, *13*, 1474; c) F. Shibahara, Y. Dohke, T. Murai, *J. Org. Chem.* **2012**, *77*, 5381; d) L. Yang, L. Zhao, C.-J. Li, *Chem. Commun.* **2010**, *46*, 4184.

[11] B. Yao, Q. Wang, J. Zhu, *Angew. Chem.* **2012**, *124*, 12477; *Angew. Chem. Int. Ed.* **2012**, *51*, 12311.

[12] a) D. M. D'Souza, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2005**, *117*, 156; *Angew. Chem. Int. Ed.* **2005**, *44*, 153; b) T. J. J. Müller, D. M. D'Souza, *Pure Appl. Chem.* **2008**, *80*, 609; c) D. M. D'Souza, A. Kiel, D.-P. Herten, F. Rominger, T. J. J. Müller, *Chem. Eur. J.* **2008**, *14*, 529.

[13] S. R. Mothe, P. Kothandaraman, S. J. L. Lauw, S. M. W. Chin, P. W. H. Chan, *Chem. Eur. J.* **2012**, *18*, 6133.

[14] J.-H. Li, Y. Liang, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 4393.

[15] For an aerobic oxidative coupling of two different alkynes, see W. Yin, C. He, M. Chen, H. Zhang, A. Lei, *Org. Lett.* **2009**, *11*, 709.

[16] a) K. Närhi, J. Franzén, J.-E. Bäckvall, *J. Org. Chem.* **2006**, *71*, 2914; b) P. H.-Y. Cheong, P. Morganelli, M. R. Luzung, K. N. Houk, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 4517.

[17] Under the standard conditions with 1-pentyne or 3,3-dimethyl-1-butyne, the carbocyclization product was isolated as an inseparable mixture with the thermal-ene product.

[18] The value of 1.18 was calculated based on the distribution of the two products **10aa**/**10ab** (1.17:1.00) and the conversion (13%), by taking into account the slight change in the ratio of **9a** and [D]-**9b**. The value of 1.13 from the experiment with [D]-**9a** and **9b** was obtained in the same way (see the Supporting Information).