Carbocycles

Deutsche Ausgabe: DOI: 10.1002/ange.201608247
Internationale Ausgabe: DOI: 10.1002/anie.201608247

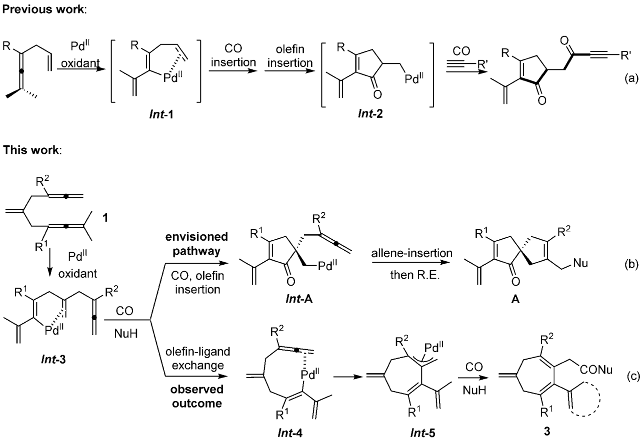
Highly Selective Construction of Seven-Membered Carbocycles by Olefin-Assisted Palladium-Catalyzed Oxidative Carbocyclization–Alkoxycarbonylation of Bisallenes

Can Zhu[+], Bin Yang[+], Youai Qiu, and Jan-E. Bäckvall**

***Abstract:** An olefin-assisted palladium-catalyzed oxidative carbocyclization–alkoxycarbonylation of bisallenes to afford seven-membered carbocycles has been established. This dehydrogenative coupling reaction showed excellent substrate scope and functional group compatibility. The reaction exhibited high chemo- and regioselectivity, and ester **3** was the only product obtained. The olefin unit has been proven to be indispensable during the reaction. Moreover, intramolecular oxidative coupling suggests that the reaction proceeds via a (π-allyl)palladium intermediate.*

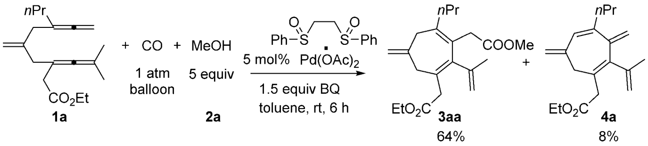
The construction of medium-sized (seven- and eight-membered) carbocycles has been an attractive area of research, owing to their broad occurrence as the core structure in various natural products as well as pharmacologically active substances.[1,2] Such units have been widely found in hydroazulene, guaiane, and pseudoguaiane sesquiterpenes.[3] However, to date, the efficient and selective annulation for medium-sized rings is still highly challenging, due to their unfavorable transannular interactions and entropic factors.[4] In this regard, only few methods focusing on the formation of seven-membered rings have been developed. Therefore, the development of novel approaches for the efficient catalytic construction of medium-sized carbocyclic compounds is highly desirable.

Bisallenes have been demonstrated as powerful building blocks in synthetic chemistry,[5] and transition metal-catalyzed cyclizations of bisallenes have emerged as effective strategies for preparing complicated skeletons.[6] In 2005, Ma and coworkers developed an efficient Rh^I-catalyzed route to steroid scaffolds from bisallenes, which showed the unique advantages of bisallenes.[7] However, the challenge will be the control of selectivity during the reaction, considering the fact that skeletons of bisallenes are highly unsaturated structures ($UN \geq 4$, UN = unsaturated number). Recently, we reported an efficient cascade reaction of enallenes via carbonylation–carbocyclization–carbonylation–alkynylation, in which four new carbon–carbon (C−C) bonds were formed (Scheme 1 a).[8] The additional coordination of the olefin unit to Pd^{II} was an essential element for the subsequent allene[9] attack to afford ***Int*-1**,[10] which on sequential insertion of carbon monoxide (CO) and olefin would give ***Int*-2**. On the basis of these results, we envisioned that, when an additional allene unit was introduced, ***Int*-A** would be formed (Scheme 1 b). Therefore, the further insertion of an allene moiety and nucleophilic quenching might produce spiro-type product **A**.



Scheme 1. Previous work and proposal for this work. Nu = nucleophilic unit, R.E. = reductive elimination.

Based on this concept, we initially chose bisallene **1a** as the standard substrate. When bisallene **1a** was treated with bis-sulfoxide–$Pd(OAc)_2$ (White catalyst, 5 mol%),[11] MeOH (5 equiv), and BQ (1.5 equiv) in the presence of CO (balloon, approx. 1 atm) in toluene at rt (room temperature) for 6 h, the envisioned spiro-type product **A** was not observed (Scheme 2). Surprisingly, seven-membered carbocycle **3aa** was obtained in 64% yield instead, along with **4a** in 8% yield. Obviously, vinylpalladium complex ***Int*-3** reacts via ligand exchange and allene insertion to form ***Int*-5** via ***Int*-4**, instead of a sequential CO and olefin insertion to give ***Int*-A** (Scheme 1 b and c). As a result, seven-membered carbocycle **3aa** was produced by quenching ***Int*-5** with MeOH in the presence of CO, while **4a** was formed via direct β-H elimination from ***Int*-5**. To the best of our knowledge, this



Scheme 2. Initial attempt using bisallene **1a**. BQ = 1,4-benzoquinone.

---

[*] Dr. C. Zhu,[+] B. Yang,[+] Dr. Y. Qiu, Prof. Dr. J.-E. Bäckvall
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University
Stockholm, SE-106 91 (Sweden)
E-mail: zhucaner@gmail.com
jeb@organ.su.se

[+] These authors contributed equally to this work.

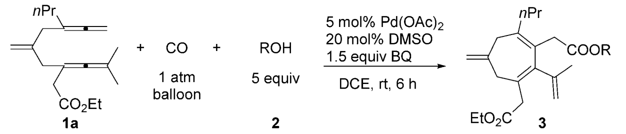
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201608247.

reaction is the first example for the construction of seven-membered carbocycles from bisallenes in a dehydrogenative manner.[12]

With these results in hand, we set out to optimize the reaction conditions (see Table S1 in the Supporting Information). Catalyst screening showed that $Pd(OOCCF_3)_2$ gave a higher yield of **3aa** compared to the White catalyst, while $Pd(OAc)_2$ increased the yield to 71 % with the best selectivity. $[Pd(PPh_3)_2Cl_2]$ and $[Pd(MeCN)_2Cl_2]$ failed to realize such a transformation. To our delight, the addition of DMSO (20 mol %) as the ligand improved the yield of **3aa** further to 77 % without formation of side-product **4a**. Solvent screening revealed that DCE (1,2-dichloroethane) was the best solvent, in which carbocycle **3aa** was produced in 84 % yield as the only product.[13] It is noteworthy that the reaction could also proceed well with MeOH as the solvent, although the yield is slightly lower (80 %). Therefore, the use of CO, $Pd(OAc)_2$ (5 mol %), DMSO (20 mol %), and BQ (1.5 equiv) in DCE at rt defined the optimized reaction conditions for additional studies.

Under the optimal reaction conditions, we next studied the scope of alcohols **2** in the reacton with bisallene **1a** (Table 1). Both benzyl alcohol and *p*-bromobenzyl alcohol worked well and afforded the corresponding products **3ab** and **3ac** in 80 and 70 % yield, respectively (Table 1, entries 2 and 3). A range of secondary alcohols were examined as well: along with *i*PrOH, alcohols with cyclic substituents, such as *c*-butyl, *c*-pentyl, and *c*-hexyl groups all reacted smoothly and produced the corresponding products **3ad**–**3ag** in good yields (Table 1, entries 4–7). Moreover, this dehydrogenative coupling reaction worked equally well using allyl alcohol (Table 1, entry 8). It is noteworthy that both olefinic and acetylenic alcohols were compatible with the standard reaction conditions (Table 1, entries 8–10). Finally, functional groups, such as TMS (trimethylsilyl), could be introduced on the terminal alkyne position of the acetylenic alcohols, thus leading to the corresponding product **3ak** in 75 % yield (Table 1, entry 11).

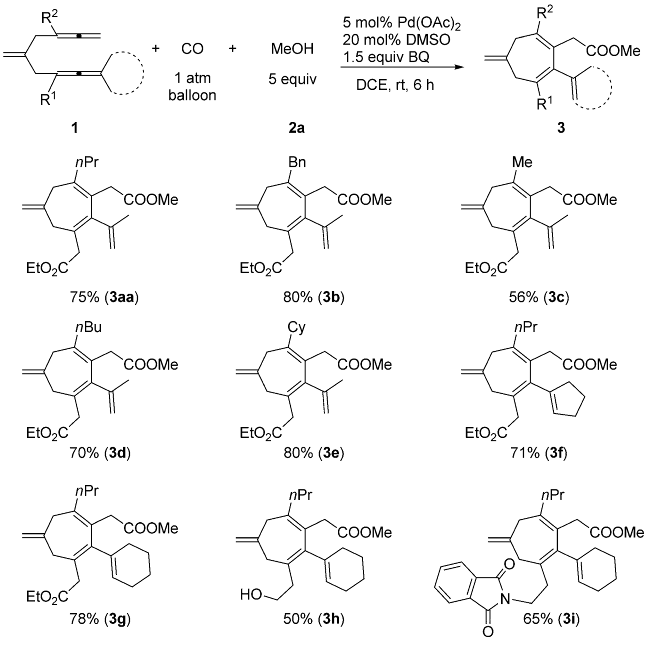
Table 1: Scope of alcohols.[a]



Entry	R (**2**)	Yield of **3** [%][b]
1	Me	75 (**3 aa**)
2	Bn	80 (**3 ab**)
3	p-$BrC_6H_4CH_2$	70 (**3 ac**)
4	*i*Pr	68 (**3 ad**)
5	*c*-butyl	65 (**3 ae**)
6	*c*-pentyl	75 (**3 af**)
7	Cy	68 (**3 ag**)
8	allyl	74 (**3 ah**)
9	$CH_2CH_2CH{=}CH_2$	71 (**3 ai**)
10	$CH_2C{\equiv}CCH_3$	71 (**3 aj**)
11	$CH_2C{\equiv}CSiMe_3$	75 (**3 ak**)

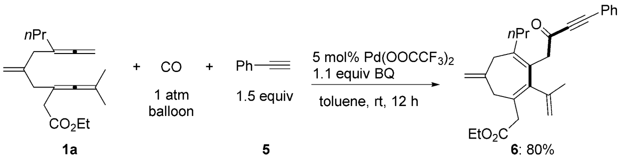
[a] The reaction was conducted at rt in DCE (1 mL) with **1a** (0.2 mmol), alcohol **2** (5 equiv), and BQ (1.5 equiv) in the presence of $Pd(OAc)_2$ (5 mol%) and DMSO (20 mol%). [b] Yield of isolated product after column chromatography.

The reactivity of substrates with different substituents on the bisallene moiety was next investigated (Scheme 3). When R^1 is Bn, Me, or *n*Bu, the reaction gave moderate to good yields. Cy-substituted bisallene could also be employed to afford product **3e** in 80 % yield. Under the optimal reaction conditions, cyclopentylidene bisallene afforded **3f** in 71 % yield, while cyclohexylidene bisallene gave the corresponding product **3g** in 78 % yield. To investigate the scope of bisallenes in this carbocyclization reaction, we chose bisallenes with different functional groups: To our delight, the reaction of bisallene **1h** ($R^1 = CH_2CH_2OH$), containing a free OH group, produced seven-membered carbocycle **3h** instead of proceeding via oxypalladation as observed in many other cases.[14,15] Moreover, a functional group such as the imide group also worked as shown by the formation of **3i** in 65 % yield. Finally, it is worth noting that phenyl acetylene (1.5 equiv) could also be employed instead of alcohol to quench the reaction, thus producing ynone **6** in 80 % yield [Eq. (1)].[8] Three new C−C bonds were formed during the latter cascade reaction.

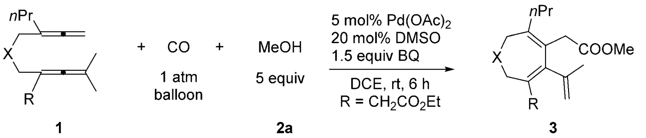


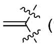
Scheme 3. Scope of bisallenes for the olefin-assisted palladium-catalyzed oxidative carbonylative carbocyclization.

To demonstrate the necessity of the olefin unit in this chemistry, we examined the reactivity of bisallenes with different linkers: bisallenes **1a′**, **1a″**, and **1a‴**, in which



(1)

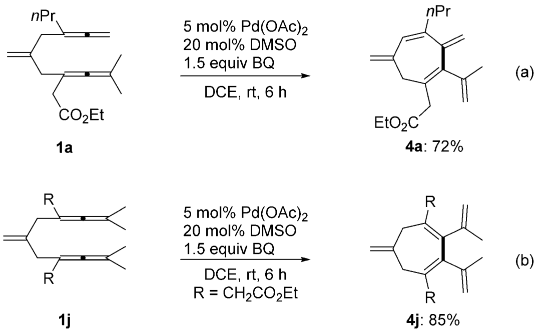


X	Yield of **3** [%]	Recovery of **1**[a]
 (**1a**)	75% (**3aa**)	-
O (**1a'**)	-	89%
NTs (**1a''**)	-	92%
CH_2 (**1a'''**)	-	90%

Scheme 4. Investigation of different linkers in bisallenes for the Pd-catalyzed cross-dehydrogenative coupling reactions. [a] Yield determined by ^1H NMR analysis using anisole as the internal standard. Ts = 4-methylbenzenesulfonyl.

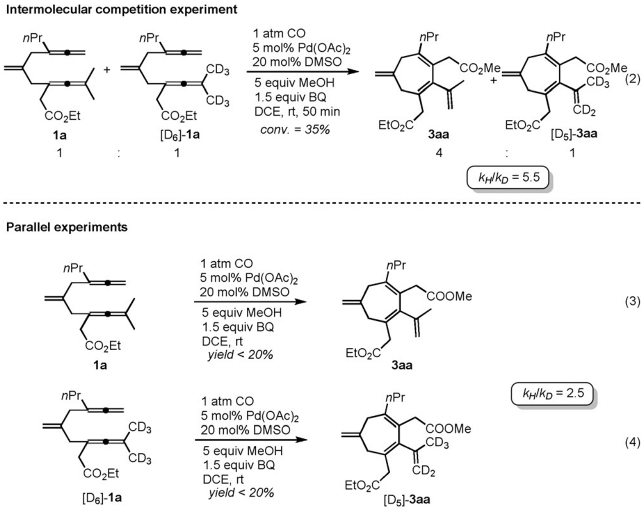
oxygen, nitrogen, or carbon was introduced in place of the olefin unit in **1a**, respectively, failed to undergo such dehydrogenative carbocyclization, indicating the indispensability of the olefin group (Scheme 4).

Further studies showed that the intramolecular dehydrogenative coupling could be realized in the absence of CO and alcohol (Scheme 5): The direct intramolecular oxidative coupling of **1a** produced seven-membered ring **4a** in 72% yield (Scheme 5a), which we observed as the side product in initial attempt (see Scheme 2). When two methyl groups were introduced as substituents on the terminal position, the symmetric carbocycle **4j** was obtained in 85% yield from **1j** (Scheme 5b).

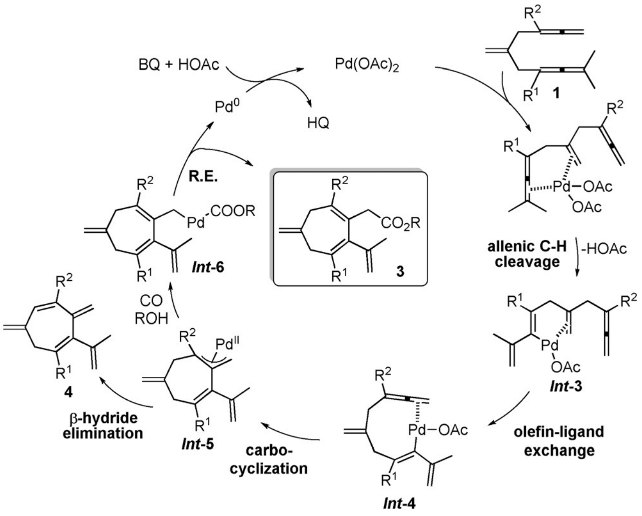


Scheme 5. Intramolecular dehydrogenative coupling using **1a** and **1j**.

To gain a deeper insight into this dehydrogenative coupling reaction, the deuterium kinetic isotope effects (KIE) were studied. An intermolecular competition experiment was conducted using a 1:1 mixture of bisallene **1a** and [D_6]-**1a** at room temperature for 50 min [Eq. (2)]. The product ratio **3aa**/[D_5]-**3aa** (ca. 35% conv.) was measured as 4:1. From this ratio, the competitive KIE was determined to $k_H/k_D = 5.5$.[16] Moreover, two parallel experiments gave a KIE (k_H/k_D from initial rate) value of 2.5 [Eqs. (3) and (4)].[16] These observed kinetic isotope effects indicate that the allenic C–H bond cleavage is the first irreversible step and occurs during the rate-limiting step. However, the difference observed from these two KIE experiments suggests that this step is not fully, but only partially rate-limiting during the overall steps. The large competitive isotope effect in the allenic C–H bond cleavage ($k_H/k_D = 5.5$) requires that this step has to occur before any irreversible steps.[17]



Based on the observations of KIE studies and the reaction outcome, a possible mechanism for this dehydrogenative coupling reaction is proposed in Scheme 6. Simultaneous coordination of the allene and olefin units to the Pd^{II} center would give a chelate palladium complex.[18] The additional coordination of the olefin to Pd^{II} is essential for the allene attack involving allenic C–H bond cleavage to occur, which also was previously demonstrated.[10] Instead of a sequential insertion of CO into the C–Pd bond of ***Int*-3** (see Scheme 1b),[8] the ligand exchange of olefin with the second allene moiety would promote the formation of ***Int*-4**. Carbocyclization of ***Int*-4** would close the ring to give cyclic π-allyl palladium intermediate ***Int*-5**.[19] Finally, in the presence of CO and ROH, ***Int*-6** would be generated from ***Int*-5**, which on a selective reductive elimination would lead to ester **3** as the single regioisomer.[20] The transformation from ***Int*-5** to **4**



Scheme 6. Proposed mechanism.

could also be realized in the absence of CO and ROH, which provides supporting evidence for η^3-allyl complex ***Int*-5**. The released Pd^0 is reoxidized to Pd^{II} by *p*-benzoquinone closing the catalytic cycle.

In conclusion, we have developed a one-pot olefin-assisted palladium-catalyzed oxidative carbocyclization–alkoxycarbonylation reaction of bisallenes to afford seven-membered carbocycles. This cascade reaction showed high efficiency and selectivity, and ester **3** was the only regioisomer obtained. The olefin group has been demonstrated to be indispensable to promote this transformation. The ligand exchange of olefin with the second allene moiety was proposed as the key for the formation of the 7-membered ring. The η^3-allyl coordination to palladium in ***Int*-5** could be deduced from the formation of **4a** and **4j** (see Scheme 5). The transformation towards ester **3** exhibited high chemo- and regioselectivity in the presence of CO and alcohol. Furthermore, mechanistic studies have shown that the allenic C–H bond cleavage occurred during a rate-limiting step. Finally, because of the highly efficient and selective construction of medium-sized carbocycle skeletons, this method will be useful in synthetic chemistry. Further mechanistic studies and synthetic application are currently under way in our laboratory.

Acknowledgements

Financial support from the European Research Council (ERC AdG 247014), The Swedish Research Council (621-2013-4653), The Berzelii Center EXSELENT, and the Knut and Alice Wallenberg Foundation is gratefully acknowledged.

Keywords: bisallene · carbocyclization · olefins · palladium · seven-membered carbocycles

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 14405–14408
Angew. Chem. **2016**, *128*, 14617–14620

---

[1] For reviews on seven-membered carbocycles, see: a) T. V. Nguyen, J. M. Hartmann, D. Enders, *Synthesis* **2013**, 845; b) E. J. Kantorowski, M. J. Kurth, *Tetrahedron* **2000**, *56*, 4317.

[2] For selected recent examples on transition metal-catalyzed construction of seven-membered carbocycles, see: a) S. Ydhyam, J. K. Cha, *Org. Lett.* **2015**, *17*, 5820; b) I. D. G. Watson, S. Ritter, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2056; c) H. Xu, J.-L. Hu, L. Wang, S. Liao, Y. Tang, *J. Am. Chem. Soc.* **2015**, *137*, 8006; d) N. S. Dange, B.-C. Hong, C.-C. Lee, G.-H. Lee, *Org. Lett.* **2013**, *15*, 3914; e) O. L. Epstein, S. Lee, J. K. Cha, *Angew. Chem. Int. Ed.* **2006**, *45*, 4988; *Angew. Chem.* **2006**, *118*, 5110; f) J. Fu, Y. Gu, H. Yuan, T. Luo, S. Liu, Y. Lan, J. Gong, Z. Yang, *Nat. Commun.* **2015**, *6*, 8617 DOI: 10.1038/ncomms9617.

[3] For reviews, see: a) C. H. Heathcock, S. L. Grahams, M. C. Pirrung, F. Plavac, C. T. White in *The Total Synthesis of Natural Products, Vol. 5* (Ed.: J. ApSimon), Wiley, New York, **1983**, pp. 333–390; b) M. Vandewalle, P. De Clercq, *Tetrahedron* **1985**, *41*, 1765; c) L. Yet, *Chem. Rev.* **2000**, *100*, 2963; d) N. Blanchard, J. Eustache in *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts* (Eds.: J. Cossy, S. Arseniyadis, C. Meyer), Wiley-VCH, Weinheim, **2010**, pp. 1–43.

[4] *Modern Physical Organic Chemistry* (Eds.: E. V. Anslyn, D. A. Dougherty), Higher Education Press, Beijing, **2009**.

[5] For a highlight review of bisallenes, see: G. Chen, X. Jiang, C. Fu, S. Ma, *Chem. Lett.* **2010**, *39*, 78.

[6] For selected examples on bisallenes, see: a) X. Jiang, X. Cheng, S. Ma, *Angew. Chem. Int. Ed.* **2006**, *45*, 8009; *Angew. Chem.* **2006**, *118*, 8177; b) X. Lian, S. Ma, *Chem. Eur. J.* **2010**, *16*, 7960; c) J. Cheng, X. Jiang, S. Ma, *Org. Lett.* **2011**, *13*, 5200; d) F. Inagaki, S. Narita, T. Hasegawa, S. Kitagaki, C. Mukai, *Angew. Chem. Int. Ed.* **2009**, *48*, 2007; *Angew. Chem.* **2009**, *121*, 2041; e) S. M. Kim, J. H. Park, Y. K. Kang, Y. K. Chung, *Angew. Chem. Int. Ed.* **2009**, *48*, 4532; *Angew. Chem.* **2009**, *121*, 4602; f) M. R. Volla, J.-E. Bäckvall, *ACS Catal.* **2016**, *6*, 6398.

[7] S. Ma, P. Lu, L. Lu, H. Hou, J. Wei, Q. He, Z. Gu, X. Jiang, X. Jin, *Angew. Chem. Int. Ed.* **2005**, *44*, 5275; *Angew. Chem.* **2005**, *117*, 5409.

[8] C. Zhu, B. Yang, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2015**, *137*, 11868.

[9] For selected examples of allene chemistry with Pd, see: a) J. Mazuela, D. Banerjee, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2015**, *137*, 9559; b) C. Zhu, X. Zhang, X. Lian, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 7817; *Angew. Chem.* **2012**, *124*, 7937; c) C. Zhu, S. Ma, *Org. Lett.* **2013**, *15*, 2782; d) C. Zhu, S. Ma, *Org. Lett.* **2014**, *16*, 1542; e) B. Yang, C. Zhu, Y. Qiu, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* **2016**, *55*, 5568; *Angew. Chem.* **2016**, *128*, 5658.

[10] C. Zhu, B. Yang, T. Jiang, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* **2015**, *54*, 9066; *Angew. Chem.* **2015**, *127*, 9194.

[11] For selected examples, see: a) K. J. Fraunhoffer, M. C. White, *J. Am. Chem. Soc.* **2007**, *129*, 7274; b) K. J. Fraunhoffer, N. Prabagaran, L. E. Sirois, M. C. White, *J. Am. Chem. Soc.* **2006**, *128*, 9032.

[12] For a review on cross-dehydrogenative coupling (CDC) reactions, see: C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335.

[13] Yield was determined by ^{1}H NMR analysis with anisole as the internal standard. Crude ^{1}H NMR spectrum is also provided to show the involved selectivity of the reaction. For details, see the Supporting Information.

[14] For selected reviews involving catalytic nucleopalladation, see: a) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; c) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285; d) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644.

[15] **1h** (one with a free hydroxy group) is unstable at room temperature when exposed to air. For details, see the Supporting Information.

[16] For details, see the Supporting Information.

[17] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066; *Angew. Chem.* **2012**, *124*, 3120.

[18] a) Y. Qiu, B. Yang, C. Zhu, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* **2016**, *55*, 6520; *Angew. Chem.* **2016**, *128*, 6630; b) C. Zhu, B. Yang, Y. Qiu, J.-E. Bäckvall, *Chem. Eur. J.* **2016**, *22*, 2939; c) Y. Qiu, B. Yang, C. Zhu, J.-E. Bäckvall, *Chem. Sci.* **2016**, DOI: 10.1039/C6SC02660E.

[19] a) B. M. Trost, T. J. Fullerton, *J. Am. Chem. Soc.* **1973**, *95*, 292; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; c) B. M. Trost, M. R. Machacek, A. Aponick, *Acc. Chem. Res.* **2006**, *39*, 747.

[20] J. Liu, Z. Han, X. Wang, Z. Wang, K. Ding, *J. Am. Chem. Soc.* **2015**, *137*, 15346.

Received: August 23, 2016