Palladium-Catalyzed Hydrobenzylation of ortho-Tolyl Alkynyl Ethers by Benzylic C–H Activation: Remarkable Alkynoxy-Directing Effect**

Yasunori Minami,* Kotomi Yamada, and Tamejiro Hiyama*

Straightforward C(sp³)-H bond functionalization by transition-metal complexes allows novel synthetic manipulations of substrates without the requirement for prefunctionalization and thus contributes to environmentally benign transformations through efficient use of natural resources and energy.^[1] Notably, a process that involves $C(sp^3)$ -H bond activation by oxidative insertion and subsequent carbometalation of unsaturated substrates represents an ideal new carbon-carbon bond formation with 100% atom economy.^[2]

As we have reported recently, alkynyl aryl ethers react with internal alkynes through selective palladium(0)-catalyzed ortho C-H activation, thus providing efficient access to 2-methylidene-2H-chromene derivatives.^[3] The facile and straightforward transformation can be attributed to the coordination of the alkynoxy directing group with palladium to effect the ortho C-H activation.[4] On the basis of this preliminary observation, we were intrigued by the possibility of benzylic C-H activation. Although cross-coupling reactions involving benzylic C-H bond cleavage have been briefly explored to some extent,^[5-7] insertion of unsaturated partners is less studied. In this respect, the work by Yamamoto and coworkers^[8] and Chatani and co-workers^[9] are remarkable examples of M^{II}-catalyzed (M=Pt, Ru) benzylic C-H cleavage of 1-alkyl-2-ethynylbenzenes by vinylidene complexes. Herein, we report that a hydrobenzylation of orthotolyl alkynyl ethers takes place through palladium-catalyzed benzylic $C(sp^3)$ -H bond insertion and subsequent syn-1,2addition across the alkyne. The adducts, 2-methylidene-2,3dihydrobenzofurans, easily react with acetic acid, azo and carbonyl compounds, and molecular oxygen to give variously functionalized benzofurans.[10,11]

The reaction of triisopropylsilylethynyl-2,6-xylyl ether (1a) was conducted in the presence of $Pd(OAc)_2$ (1 mol%), tricyclohexylphosphine (2 mol%), and Zn metal (1 mol%, in situ Pd^{II} reduction) in toluene at 90°C for 30 minutes to

[*]	Y. Minami, T. Hiyama
	Research and Development Initiative, Chuo University, JST, ACT-C
	Kasuga, Bunkyo-ku, Tokyo 112-8551 (Japan)
	E-mail: yminami@kc.chuo-u.ac.jp
	thiyama@kc.chuo-u.ac.jp
	K. Yamada
	Graduate School of Science and Engineering, Chuo University
	Kasuga, Bunkyo-ku, Tokyo 112-8551 (Japan)
[**]	This work has been supported financially by a Grant-in-Aid for
	Scientific Research (S) (21225005 to T.H.) and Young Scientists (B)
	(25870747 to Y.M.) from JSPS.
	Supporting information for this article is available on the WWW

under http://dx.doi.org/10.1002/anie.201304893.

provide 97% of the Z-exocyclic alkylidene product 2a along with 3% of the benzofuran 3a as determined by NMR spectroscopy [Eq. (1); TIPS = triisopropylsilyl]. The stereochemistry of 2a was unambiguously determined by NOE and



NOESY experiments. Attempted isolation of 2a by silica gel or alumina column chromatography resulted in its isomerization into 3a, to some extent. Thus, treatment of the crude reaction mixture with acetic acid prior to work-up gave 3a in 98% yield upon isolation.^[12] Since Pd(OAc)₂, PdCl₂, and PtCl₂ failed to effect the desired reaction, it is apparent that the cyclization is not promoted by either the Lewis acid, PCy₃. or Zn(OAc)₂ alone.^[13] Of note, the reaction took place in the absence of zinc, albeit at a slower rate, thus indicating that the combination of Pd(OAc)₂, PCy₃, and zinc promotes the cyclization. As the carbon analogue, 4-MeOC₆H₄CH- $(OMe)C \equiv CTIPS$, was inert to the standard reaction conditions, the alkynoxy moiety is definitely essential for the intramolecular hydrobenzylation reaction.

Other silvl groups instead of TIPS were used in the cyclization as depicted in Equation (2). Substrates containing



tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBDMS), and triethylsilyl (TES) groups on the terminal ethynyl carbon atom underwent the hydrobenzylation to produce 2b, 2c, and 2d, respectively, in quantitative yields as estimated by NMR assays. Isomerization by acetic acid led to the isolation of the corresponding 3b, 3c, and 3d in essentially quantitative yields. In contrast, the dimethylphenylsilyl-substituted ethynyl ether 1e was gave 2e in 60% yield only by

Angew. Chem. Int. Ed. 2013, 52, 1-6

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



🕏 WILEY 🛍



using a higher catalyst loading and a higher reaction temperature.

A variety of aryl triisopropylsilylethynyl ethers (1) were applied to the hydrobenzylation (Table 1). All the products were isolated after treatment of 2 with acetic acid before workup. The *ortho*-tolyl ethers ($R^2 = H$) containing ethyl,

Table 1: Palladium-catalyzed intramolecular hydrobenzylation and subsequent migration in one pot.^[a]



[a] Unless otherwise noted, a mixture of 1, $Pd(OAc)_2$ (1 mol% for entries 1–3 and 7, 5 mol% for entries 4–6, 10 mol% for entry 8), PCy_3 (2 mol% for 1–3 and 7, 10 mol% for entries 4–6, 20 mol% for entry 8), Zn (1 mol% for entries 1–3 and 7, 5 mol% for entries 4–6, 10 mol% for entry 8) and toluene (1.0 μ for entries 1–3 and 0.1 μ for entries 4–6 and 8) was heated at 90°C. Then, AcOH (3.0–10 equiv) was added, and the whole mixture was heated at 90°C for 1–10 h. [b] Yield of isolated **3** (two steps) is given.

methoxy, and trifluoromethyl groups at the other ortho position to the ethereal oxygen atom reacted selectively at the ortho-methyl C-H in excellent yields to give adducts (Table 1, entries 1-3). It is noteworthy that the terminal methyl and methylene C-H bonds in the ethyl group at the other ortho position did not participate in the reaction (Table 1, entry 1). The methoxy group also remained intact (Table 1, entry 2). The highly electron-withdrawing trifluoromethyl group in 1h did not interfere with the reaction (Table 1, entry 3). When the ortho-tolyl ether 1i was subjected to the reaction conditions in a low concentration (0.1M), the corresponding benzofuran 3i was obtained in a high yield (Table 1, entry 4).^[14] Notably, selective benzylic C(sp³)-H activation was observed in preference to the aryl $C(sp^2)$ -H activation. This observation stimulated us to apply the methodology to other ortho-tolyl alkynyl ethers. The one bearing a methyl group at the *meta* position (1j) smoothly reacted to give the 6-methylbenzofuran 3j in 92% yield (Table 1, entry 5). The fluorinated 1k was efficiently converted into 3k in 86% yield (Table 1, entry 6), and selective benzylic $C(sp^3)$ –H activation of the 2,6-diethylphenyl ether 11 provided 3l in 92% yield in the presence of 5 mol% catalyst (Table 1, entry 7) with the terminal methyl group remaining unaffected. However, 2,6-diisopropylphenyl triisopropylsilyl ethynyl ether was inert under the present reaction conditions and most likely because of the increased steric bulk of the isopropyl moiety, thus indicating that the mechanism of this reaction contrasts sharply to those of precedented work.^[8,9] 1-Methyl 2-alkynoxynapthalene (1m) was transformed into the naphthofuran 3m in 67% yield (Table 1, entry 8).

The initial hydrobenzylation product 2 probably has a zwitterionic resonance structure (2') showing a nucleophilic carbanionic character stabilized by silyl groups. From this viewpoint, the ene reaction of the in situ generated 2 was examined (Scheme 1). The compound 2d was reacted with



Scheme 1. One-pot hydrobenzylation/ene reaction. TES = triethylsilyl, TIPS = triisopropylsilyl.

diethyl azodicarboxylate (DEAD) and HC(O)CO₂Et to give the ene products 4 and 5 (1.6:1 d.r.), respectively. The major isomer of 5 was transformed into the ethyl (E)-2-benzofurylacrylate 5' in 62% yield by a Peterson olefination upon treatment with BuLi, thus showing that the major adduct is $(\alpha S,\beta R)$ -5, as described in Scheme 1. Paraformaldehyde could be used in the ene reaction at 100°C, thus giving the silylalcohol 6 in 36% yield. In stark contrast, the bulky TIPS-substituted 2a reacted with ethyl trifluoropyruvate at the 3-position, thus forming the C3-substituted benzofuran 7 in 66% yield, possibly as a result of steric repulsion. On the contrary, 2d gave a complex mixture of C2- and C3-bound products. The TIPS group in 2a was oxidized by H₂O₂ and air to give 2-benzofurylaldehyde (8) in 61% and 42% yields, respectively. Of note, the reactions of 3d with DEAD and ethyl trifluoropyruvate were futile, thus clearly demonstrating that the hydrobenzylation products 2 are ene-active olefins. The silvl groups in 3 work as an additional reactive

www.angewandte.org

2

C 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

K These are not the final page numbers!

functionality. Protodesilylation of **3a** with TBAF gave 2,7dimethyl benzofuran in a quantitative yield, and thus the silyl moiety behaves as a latent nucleophile as is shown by the TBAF-mediated 1,2-addition of **3e** to benzaldehyde, thereby leading to the corresponding alcohol **9** being isolated in 62 % yield [Eq. (3); TBAF = tetra-*n*-butylammonium fluoride].



The Pd/Zn-catalyzed intramolecular hydrobenzylation reaction is applicable to the aryl ethynyl ethers **10** bearing a carbonaceous substituent instead of a silyl group [Eq. (4)]. The cyclization smoothly took place to give the corresponding



products **11**, which upon treatment with acetic acid gave the 2alkenyl-substituted benzofurans **12** by elimination of methanol.^[15] For example, cyclization of the 2,6-xylyl 2-(1-methoxycyclohexyl)ethynyl ethers **10a** ($\mathbf{R} = \mathbf{R}' = -(\mathbf{CH}_2)_5$), **10b** ($\mathbf{R} =$ $\mathbf{R}' = \mathbf{Ph}$), and **10c** ($\mathbf{R} = \mathbf{Ph}$, $\mathbf{R}' = \mathbf{H}$) took place in the presence of 5 mol% of palladium catalyst to form the corresponding products (**11**), which readily converted into the 2-alkenyl benzofurans **12** in moderate yields over two steps. In the case of **10c**, the β -styryl-substituted benzofuran **12c** was obtained as a single isomer. However, the reaction of a less bulky substrate, the 3-methoxypropynyl ether **10d**, turned out futile. These results clearly demonstrate that the presence of a bulky substituent on the propargylic position is essential for the success of the hydrobenzylation reaction.

To gain insight into the mechanism of the present hydrobenzylation, we conducted deuterium-labeling experiments. The reaction of $[D_6]$ -**1a** in toluene resulted in the formation of $[D_6]$ -**2a** with 97% deuterium incorporation at the vinyl carbon atom as was evaluated by ¹H NMR analysis [Eq. (5)]. This result demonstrates that the deuterium located originally on the benzylic carbon atom is transposed cleanly to the 2-methylidene carbon atom.

The kinetic isotope effect (KIE) was subsequently investigated (Scheme 2). The relative rate, $k_{\rm H}/k_{\rm D}$, of the reaction of



Angew. Chem. Int. Ed. 2013, 52, 1-6

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

www.angewandte.org

These are not the final page numbers!



Scheme 2. Kinetic isotope effect experiments.

1a versus $[D_6]$ -**1a** was observed under the catalysis with 5 mol% of Pd(OAc)₂/2PCy₃/Zn in C₆D₆ for 2 hours at 50°C, and the ratio was determined to be 12.7 (Scheme 2a), thus indicating that the C–H bond is probably cleaved by a concerted metalation/deprotonation (CMD) transition state (TS).^[16] The substrate $[D_3]$ -**1a**, containing both CH₃ and CD₃ groups, was exposed to the hydrobenzylation conditions (50°C, 14 h in C₆D₆) and the resultant KIE value was found to be 6.9, although an H/D exchange occurred to some extent at the vinyl carbon atom α to the silyl group (Scheme 2b). Accordingly, the most probable rate-determining step may be attributed to the C–H bond cleavage.

The effect of Zn(OAc)₂, generated in situ from the reaction of Pd(OAc)₂ with Zn, is obvious. The [Pd(dba)₂]/ PCy₃-catalyzed reaction of **1a** in the presence or absence of Zn(OAc)₂ was monitored at 60°C. The hydrobenzylation took place in the presence of $Zn(OAc)_2$; without $Zn(OAc)_2$ 1a was recovered almost unchanged. To clarify the role of $Zn(OAc)_2$, we examined other additives such as $ZnCl_2$ (20 mol%), Zn(OTf)₂ (20 mol%), NBu₄OAc (2 mol%), or AcOH (2 mol%) for the cyclization of 1a in the presence of $[Pd(dba)_2]$ (1 mol%) and PCy₃ (2 mol%), and found that only AcOH only promoted the reaction and gave 2a quantitatively. In contrast, the less bulky TES-substituted 1d cyclized to form the isomerized product 3d in 45% in the presence of NBu₄OAc (2 mol%), thus indicating that the generated $Zn(OAc)_2$ is not merely for the acetate ion donor.^[17] These observations combined with the previous results indicate that in situ generated $Zn(OAc)_2$ acts as a Lewis acid and acetate ion donor to promote the cleavage of benzylic C-H bond.

Although more information is necessary to discuss the reaction mechanism in detail, we propose a mechanism for the Pd(OAc)₂/PCy₃/Zn-catalyzed hydrobenzylation as summarized in Scheme 3 with **1i** as a representative substrate. First, the alkyne-coordinated palladium(0) complex **13** is formed, wherein the intramolecular nucleophilic attack of electron-rich palladium(0) on the α -carbon atom of the alkynoxy group presumably occurs to give the complex **14**. The alkynoxy group is reasonably assumed to have a ketene-like polarized resonance structure, thus indicating that the α -carbon atom bound to the oxygen center is electrophilic and the β -carbon atom nucleophilic.^[18] Thus, the β -carbanionic center in **14** is neutralized by Zn(OAc)₂ to give the vinyl



Scheme 3. Proposed reaction mechanism.

palladium acetate 15 by the migration of the generated acetate ion to the palladium center. An alternative pathway from 13 to 15 may be also possible: ligation of the β -carbon atom of 13 to $Zn(OAc)_2$ could give 16, whose palladium ligated by acetoxy group on Zn attacks the α -carbon atom to give 15. The benzylic C-H bond is cleaved by CMD to give the acetic-acid-coordinated palladacycle intermediate 17,^[19,20] with subsequent rapid protonation of the vinyl zinc moiety by acetic acid and reductive elimination to the cis-adduct 2i and regeneration of the palladium(0) complex and Zn(OAc)₂.^[21] It is evident that the substituents on the ethynyl carbon atom are crucial for the success of the cyclization. Bulky substituents on the terminal ethyne carbon atom apparently push the η^2 -palladium(0) complex to the α -carbon atom owing to steric repulsion. Moreover, the silyl group (e.g., TIPS) stabilizes the negative charge at the silicon-bearing carbon atom (α effect) to promote the cyclization.

In conclusion, the present study demonstrates that the palladium-catalyzed hydrobenzylation of *ortho*-tolyl alkynyl ethers provides efficient access to reactive 2-methylidene-2,3-dihydrobenzofurans by selective benzylic $C(sp^3)$ -H activation. The alkynoxy moiety containing bulky substituents as a directing group plays a key role in the present transformation. It is worthy of note that $Zn(OAc)_2$ promotes the cyclization. The proper choice of the substituents bound to the terminal ethynyl carbon atom allows additional transformations. Efforts are currently directed toward further understanding of the reaction mechanism and synthesis of various heterocycles useful for organic light-emitting materials.

Received: June 7, 2013 Revised: July 5, 2013 Published online:

Keywords: alkynes · arenes · heterocycles · palladium · synthetic methods

 For recent reviews, see: a) F. Kakiuchi, T. Kochi, Synthesis 2008, 3013; b) O. Daugulis, H. Q. Do, D. Shabashov, Acc. Chem. Res. 2009, 42, 1074; c) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, Angew. Chem. 2009, 121, 5196; Angew. Chem. Int. Ed. 2009, 48, 5094; d) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, Chem. Soc. Rev. 2009, 38, 3242; e) T. W. Lyons, M. S. Sanford, Chem. Rev. 2009, 109, 1147; f) G. P. Chiusoli, M. Catellani, M. Costa, E. Motti, N. Della Ca', G. Maestri, *Coord. Chem. Rev.* **2010**, 254, 456; g) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, 110, 1147; h) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, 16, 2654; i) J.-Q. Yu, M. Shi, *C-H Activation*, Springer, Heidelberg, **2010**; j) O. Baudoin, *Chem. Soc. Rev.* **2011**, 40, 4902; k) C. L. Sun, B. J. Li, Z. J. Shi, *Chem. Rev.* **2011**, 111, 1293.

- [2] B. M. Trost, Science 1991, 254, 1471.
- [3] Y. Minami, Y. Shiraishi, K. Yamada, T. Hiyama, J. Am. Chem. Soc. 2012, 134, 6124.
- [4] For examples of C-C multiple bonds as a directing group, see:
 a) R. Takeuchi, H. Yasue, J. Org. Chem. 1993, 58, 5386; b) K. Tanaka, G. C. Fu, Org. Lett. 2002, 4, 933; c) M. Murakami, T. Itahashi, Y. Ito, J. Am. Chem. Soc. 2002, 124, 13976; d) K. Takeishi, K. Sugishima, K. Sasaki, K. Tanaka, Chem. Eur. J. 2004, 10, 5681; e) N. Chernyak, V. Gevorgyan, J. Am. Chem. Soc. 2008, 130, 5636; f) M. Tobisu, I. Hyodo, M. Onoe, N. Chatani, Chem. Commun. 2008, 6013; g) N. Chernyak, V. Gevorgyan, Adv. Synth. Catal. 2009, 351, 1101; h) N. Chernyak, S. I. Gorelsky, V. Gevorgyan, Angew. Chem. 2011, 123, 2390; Angew. Chem. Int. Ed. 2011, 50, 2342; i) P. Gandeepan, C.-H. Chen, J. Am. Chem. Soc. 2012, 134, 5738; j) T. Xu, G. Dong, Angew. Chem. 2012, 124, 7685; Angew. Chem. Int. Ed. 2012, 51, 7567.
- [5] For directing-group-assisted benzylic C-H activation, see: a) C.-H. Jun, D.-C. Hwang, S.-J. Na, *Chem. Commun.* **1998**, 1405; b) F. Kakiuchi, K. Tsuchiya, M. Matusmoto, E. Mezushima, N. Chatani, *J. Am. Chem. Soc.* **2004**, *126*, 12792.
- [6] For recent examples of benzyl C-H functionalization, see: a) T. Xiong, Y. Li, X. Bi, Y. Lv, Q. Zhang, Angew. Chem. 2011, 123, 7278; Angew. Chem. Int. Ed. 2011, 50, 7140; b) M. Ichinose, H. Suematsu, Y. Yasutomi, Y. Nishioka, T. Uchida, T. Katsuki, Angew. Chem. 2011, 123, 10058; Angew. Chem. Int. Ed. 2011, 50, 9884; c) H. J. Kim, J. Kim, S. H. Cho, S. Chang, J. Am. Chem. Soc. 2011, 133, 16382; d) J. Zhang, C. Stanciu, B. Wang, M. M. Hussain, C.-S. Da, P. J. Carroll, S. D. Dreher, P. J. Walsh, J. Am. Chem. Soc. 2011, 133, 20552; e) Z. Ni, Q. Zhang, T. Xiong, Y. Zheng, Y. Li, H. Zhang, J. Zhang, Q. Liu, Angew. Chem. 2012, 124, 1270; Angew. Chem. Int. Ed. 2012, 51, 1244; f) J.-J. Chen, S. Onogi, Y.-C. Hsieh, C.-C. Hsiao, S. Higashibayashi, H. Sakurai, Y.-T. Wu, Adv. Synth. Catal. 2012, 354, 1551; g) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, H. Huang, J. Am. Chem. Soc. 2012, 134, 9902; h) J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, J. Am. Chem. Soc. 2012, 134, 13765.
- [7] For recent examples of aza-aryl methyl C-H functionalization, see: a) H. Tsurugi, K. Yamamoto, K. Mashima, J. Am. Chem. Soc. 2011, 133, 732; b) P. M. Burton, J. A. Morris, Org. Lett. 2010, 12, 5359; c) H. Komai, T. Yoshino, S. Matsunaga, M. Kanai, Org. Lett. 2011, 13, 1706; d) G. Song, Y. Su, X. Gong, K. Han, X. Li, Org. Lett. 2011, 13, 1968; e) H. Komai, T. Yoshino, S. Matsunaga, M. Kanai, Synthesis 2012, 2185; f) S. Duez, A. K. Steib, S. M. Manolikakes, P. Knochel, Angew. Chem. 2011, 123, 7828; Angew. Chem. Int. Ed. 2011, 50, 7686.
- [8] G. B. Bajracharya, N. K. Pahadi, I. D. Gridnev, Y. Yamamoto, J. Org. Chem. 2006, 71, 6204.
- [9] M. Tobisu, H. Nakai, N. Chatani, J. Org. Chem. 2009, 74, 5471.
- [10] Tanaka and co-workers reported the synthesis of dibenzofurans by rhodium-catalyzed [2+2+2] cycloaddition of *ortho*-ethynyl alkynyl aryl ethers with alkynes or nitriles. Y. Komine, A. Kamisawa, K. Tanaka, *Org. Lett.* **2009**, *11*, 2361.
- [11] Benzofurans represent an important structural motif. For selected reviews on bioactive natural products and medicinal chemistry, see: a) G. W. Gribble in *Comprehensive Heterocyclic Chemistry II, Vol. 2* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, pp. 207–257; b) X.-L. Hou, Z. Yang, H. N. C. Wong in *Progress in Heterocyclic Chemistry*, *Vol. 14* (Eds.: G. W. Gribble, T. L. Gilchrist), Pergamon, Oxford, **2002**, pp. 139–179; c) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.*

www.angewandte.org

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!



2007, 24, 843. For selected examples in material chemistry, see: d) H. Tsuji, C. Mitsui, L. Ilies, Y. Sato, E. Nakamura, J. Am. Chem. Soc. 2007, 129, 11902; e) H. Tsuji, C. Mitsui, Y. Sato, E. Nakamura, Adv. Mater. 2009, 21, 3776; f) A. Muranaka, S. Yasuike, C.-Y. Liu, J. Kurita, N. Kakusawa, T. Tsuchiya, M. Okuda, N. Kobayashi, Y. Matsumoto, K. Yoshida, D. Hashizume, M. Uchiyama, J. Phys. Chem. A 2009, 113, 464; g) C. Mitsui, J. Soeda, K. Miwa, H. Tsuji, J. Takeya, E. Nakamura, J. Am. Chem. Soc. 2012, 134, 5448.

- [12] a) J. D. Brewer, J. A. Elix, Aust. J. Chem. 1975, 28, 1059. For 1,3migration of hydroxy group, see: b) B. Gabriele, R. Mancuso, G. Salerno, J. Org. Chem. 2008, 73, 7336.
- [13] For reactions of alkynyl ethers with Lewis acids, see: a) L. Zhang, S. A. Kozmin, J. Am. Chem. Soc. 2004, 126, 11806; b) A. S. K. Hashmi, M. Rudolph, J. W. Bats, W. Frey, F. Rominger, T. Oeser, Chem. Eur. J. 2008, 14, 6672; c) A. S. K. Hashmi, M. Rudolph, J. Huck, W. Frey, J. W. Bats, M. Hamzić, Angew. Chem. 2009, 121, 5962; Angew. Chem. Int. Ed. 2009, 48, 5848.
- [14] The reaction in 1.0 M concentration gave a mixture of 3i and a dimeric product, by *ortho* C-H activation, in 31 and 55 % yield, respectively.
- [15] L. Yu Ukhin, L. V. Belousova, Z. I. Orlova, M. S. Korobov, G. S. Borodkin, *Chem. Heterocycl. Compd.* 2002, 38, 1174.

- [16] N. Guimond, S. I. Gorelsky, K. Fagnou, J. Am. Chem. Soc. 2011, 133, 6449.
- [17] It is assumed that the steric repulsion between the TIPS group and NBu₄OAc interferes with the interaction of a palladium center with the acetate ion to prevent the cyclization.
- [18] a) R. Tanaka, S. I. Miller, *Tetrahedron Lett.* 1971, *12*, 1753;
 b) P. J. Stang, K. A. Roberts, *J. Am. Chem. Soc.* 1986, *108*, 7125;
 c) M. Shindo, *Tetrahedron* 2007, *63*, 10.
- [19] a) H.-Y. Aun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau, K. Fagnou, J. Org. Chem. 2010, 75, 8180; b) S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, J. Am. Chem. Soc. 2010, 132, 10692.
- [20] Selective benzylic C-H cleavage rather than *ortho* C-H bond by intramolecular imino-coordinated bromoplatinum(II) complex was reported. See: M. Crespo, C. M. Anderson, N. Kfoury, M. Font-Bardia, T. Calvet, *Organometallics* **2012**, *31*, 4401.
- [21] The cyclization proceeded in the absence of Zn under the standard reaction conditions. In this case, it is assumed that the $[Pd(PCy_3)(OAc)]^-$ complex is the active catalyst which attacks the α -carbon atom of the alkynoxy group to give a vinyl palladium acetate. See: a) C. Amatore, A. Jutand, M. A. M'Barkl, *Organometallics* **1992**, *11*, 3009; b) C. Amatore, E. Carré, A. Jutand, M. A. M'Barkl, *Organometallics* **1995**, *14*, 1818.



Communications





Palladium-Catalyzed Hydrobenzylation of *ortho*-Tolyl Alkynyl Ethers by Benzylic C-H Activation: Remarkable Alkynoxy-Directing Effect

- | | | |



It's selective: The title reaction involves palladium(0)-catalyzed insertion of C=C bonds into benzylic $C(sp^3)$ -H bonds, thus providing efficient access to 2-methylene-2,3-dihydrobenzofurans,

which transform into benzofurans upon treatment with a weak acid (e.g., AcOH) and electrophiles. The alkynoxy group serves as a directing group in promoting C-H bond functionalization.

6 www.angewandte.org

C 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Angew. Chem. Int. Ed. 2013, 52, 1-6

These are not the final page numbers!