Heterocycles

DOI: 10.1002/anie.201304893

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

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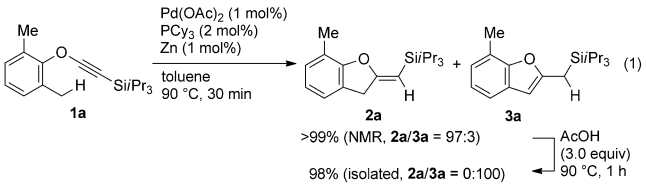
Straightforward C(sp^3)–H bond functionalization by transition-metal complexes allows novel synthetic manipulations of substrates without the requirement for prefunctionalization and thus contributes to environmentally benign transformations through efficient use of natural resources and energy.[1] Notably, 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]

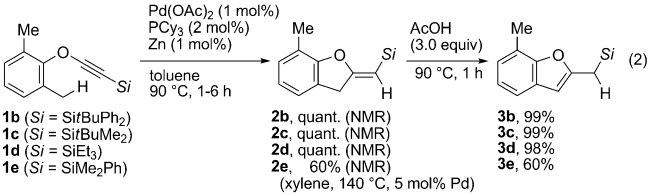
As we have reported recently, alkynyl aryl ethers react with internal alkynes through selective palladium(0)-catalyzed *ortho* C–H activation, thus providing efficient access to 2-methylidene-2*H*-chromene derivatives.[3] The facile and straightforward transformation can be attributed to the coordination 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 co-workers[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 *ortho*-tolyl alkynyl ethers takes place through palladium-catalyzed benzylic C(sp^3)–H bond insertion and subsequent *syn*-1,2-addition across the alkyne. The adducts, 2-methylidene-2,3-dihydrobenzofurans, 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 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 $Pd(OAc)_2$, $PdCl_2$, and $PtCl_2$ failed to effect the desired reaction, it is apparent that the cyclization is not promoted by either the Lewis acid, PCy_3, 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 $Pd(OAc)_2$, PCy_3, and zinc promotes the cyclization. As the carbon analogue, 4-$MeOC_6H_4$CH(OMe)C≡CTIPS, was inert to the standard reaction conditions, the alkynoxy moiety is definitely essential for the intramolecular hydrobenzylation reaction.

Other silyl 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

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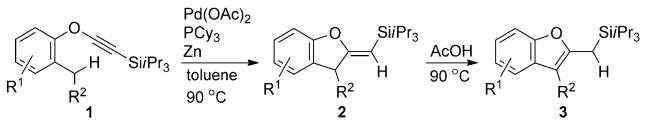
[**] This work has been supported financially by a Grant-in-Aid for Scientific Research (S) (21225005 to T.H.) and Young Scientists (B) (25870747 to Y.M.) from JSPS.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304893.

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, 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 $C(sp^3)$–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 **1l** 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).

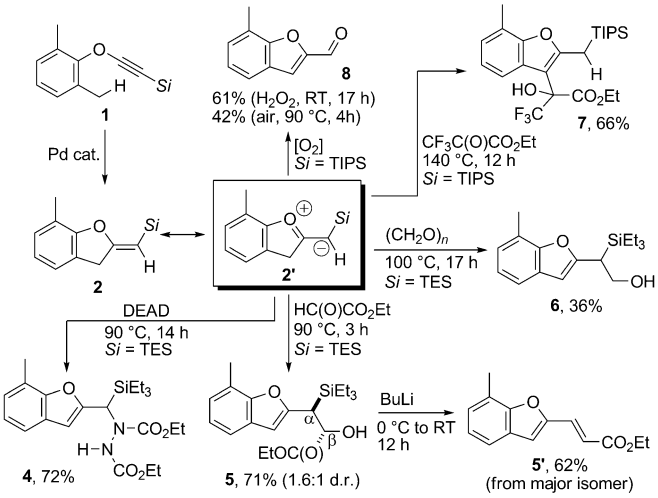
Table 1: Palladium-catalyzed intramolecular hydrobenzylation and subsequent migration in one pot.[a]



Entry	1	t [h]	Product	Yield [%][b]
1	**1f** (R^1 = 6-Et)	2	**3f** (R^1 = 7-Et)	98
2	**1g** (R^1 = 6-MeO)	5	**3g** (R^1 = 7-MeO)	89
3	**1h** (R^1 = 6-CF_3)	1	**3h** (R^1 = 7-CF_3)	88
4	**1i** (R^1 = H)	18	**3i** (R^1 = H)	85
5	**1j** (R^1 = 5-Me)	38	**3j** (R^1 = 6-Me)	92
6	**1k** (R^1 = 4-F)	38	**3k** (R^1 = 5-F)	86
7	**1l**	19	**3l**	92
8	**1m**	13	**3m**	67

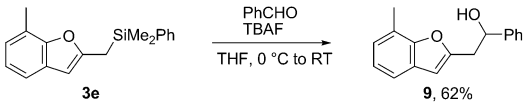
[a] Unless otherwise noted, a mixture of **1**, $Pd(OAc)_2$ (1 mol% for entries 1–3 and 7, 5 mol% for entries 4–6, 10 mol% for entry 8), PCy_3 (2 mol% for 1–3 and 7, 10 mol% for entries 4–6, 20 mol% for entry 8), Zn (1 mol% for entries 1–3 and 7, 5 mol% for entries 4–6, 10 mol% for entry 8) and toluene (1.0 M for entries 1–3 and, 0.1 M 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.

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 diethyl azodicarboxylate (DEAD) and $HC(O)CO_2Et$ 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 (α*S*,β*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 H_2O_2 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 silyl groups in **3** work as an additional reactive



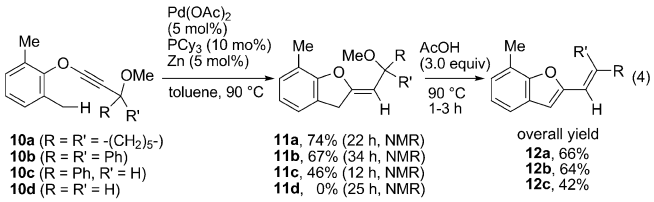
Scheme 1. One-pot hydrobenzylation/ene reaction. TES = triethylsilyl, TIPS = triisopropylsilyl.

functionality. Protodesilylation of **3a** with TBAF gave 2,7-dimethyl 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].



(3)

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

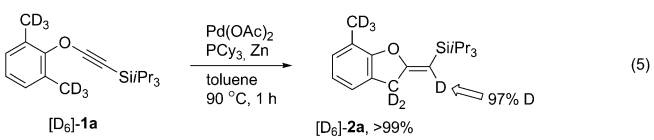


(4)

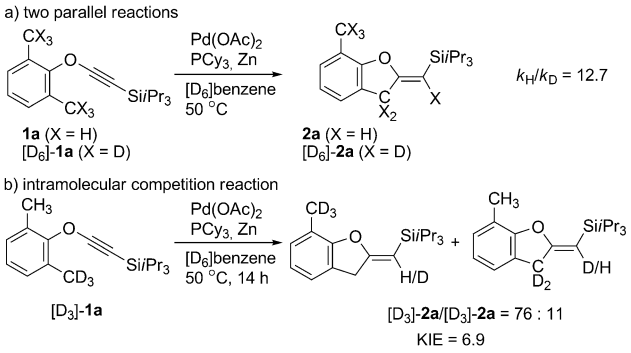
products **11**, which upon treatment with acetic acid gave the 2-alkenyl-substituted benzofurans **12** by elimination of methanol.[15] For example, cyclization of the 2,6-xylyl 2-(1-methoxycyclohexyl)ethynyl ethers **10a** (R = R′ = −$(CH_2)_5$), **10b** (R = R′ = Ph), and **10c** (R = Ph, R′ = H) 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 ^{1}H 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_H/k_D, of the reaction of



(5)

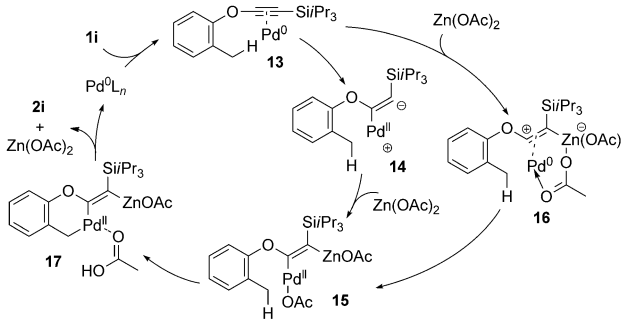


Scheme 2. Kinetic isotope effect experiments.

1a versus [D_6]-**1a** was observed under the catalysis with 5 mol% of $Pd(OAc)_2$/2PCy_3/Zn in C_6D_6 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 CH_3 and CD_3 groups, was exposed to the hydrobenzylation conditions (50 °C, 14 h in C_6D_6) 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 [$Pd(dba)_2$]/PCy_3-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%), NBu_4OAc (2 mol%), or AcOH (2 mol%) for the cyclization of **1a** in the presence of [$Pd(dba)_2$] (1 mol%) and PCy_3 (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 NBu_4OAc (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 $Pd(OAc)_2$/PCy_3/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: August 16, 2013

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

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