ChemPubSoc Europe

DOI: 10.1002/chem.201303879

CHEMISTRY
A European Journal
Communication

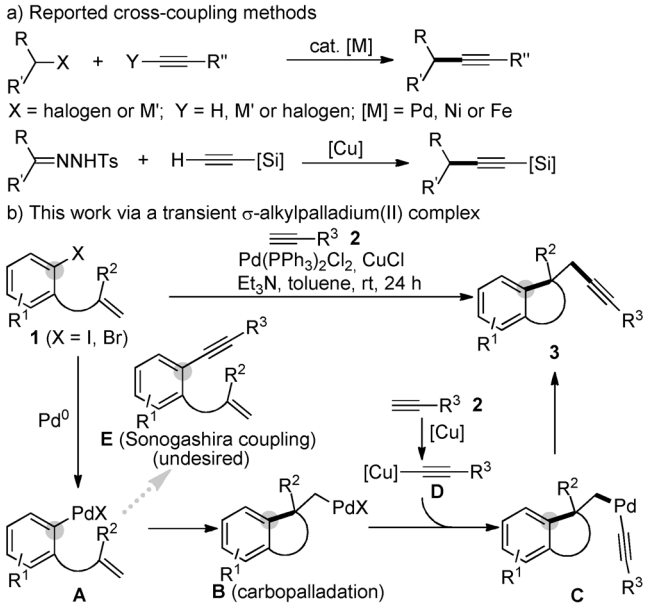
Triple Bond Chemistry

Alkylation of Terminal Alkynes with Transient σ-Alkylpalladium(II) Complexes: A Carboalkynylation Route to Alkyl-Substituted Alkynes

Ming-Bo Zhou, Xiao-Cheng Huang, Yan-Yun Liu, Ren-Jie Song, and Jin-Heng Li*[a]

Abstract: A mild and general alkylation of terminal alkynes with transient σ-alkylpalladium(II) complexes for assembling alkyl-substituted alkynes is described. This method represents a new way to the use of transient σ-alkylpalladium(II) complexes in organic synthesis through 1,2-carboalkynylation of alkenes.

Alkynes are important structural motifs in a broad range of natural products, bioactive compounds and materials, that display valuable utility as building blocks in organic synthesis.[1] The development of new methods for the synthesis of alkynes is therefore an important subject of current research.[2–5] Despite significant advances in the field, direct introduction of an alkyl group into a carbon-carbon triple bond for the assembly of alkyl-substituted alkynes remains a challenge.[3–5] Traditionally, uncatalyzed nucleophilic alkylation of alkali metal acetylides with alkyl halides is employed for the synthesis of alkyl-substituted alkynes.[1] However, the procedure is carried out in liquid ammonia and/or hexamethylphosphoramide at rather low temperatures (often −78 °C); moreover, its substrate scope is unsatisfactory due to both the strongly basic conditions and the limited solubility of acetylides in liquid ammonia. The applications of this method in organic synthesis are, therefore, limited. Alternatively, transition metal-catalyzed cross-coupling reactions afford an efficient and direct synthetic approach to diversified alkyl-substituted alkynes. To date, three elegant types of transformation have been reported (Scheme 1 a),[3–5] including the Sonogashira-type cross-coupling of alkyl halides and their derivatives with terminal alkynes,[3] cross-coupling with organometallic reagents,[4] and cross-coupling of terminal alkynes with *N*-tosylhydrazones by a migratory alkynyl insertion of copper into a carbene.[5] However, the transition metal-catalyzed synthesis of alkyl-substituted alkynes has not received much attention and remains challenging because of the potential for an undesired β-hydride elimination from the metal alkyl intermediates and oxidative dimerization of the metal alkynyl moieties during the cross-coupling process. Thus, the development of conceptually novel cross-coupling routes to alkyl-substituted internal alkynes is thus particularly important and urgent.



Scheme 1. Synthesis of alkyl-substituted alkynes.

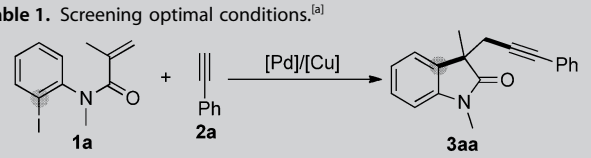
Among these examples of transition metal-catalyzed cross-coupling, in situ generation of the metal alkyl intermediates is the key driving force.[3–5] Inspired by these, we reason that the metal alkyl intermediates from other transition metal-catalyzed processes, such as carbopalladation of alkenes (intermediate **B**; Scheme 1 b),[6] may be enough stable to be trapped by terminal alkynes leading to alkyl-substituted alkynes. Herein, we report a new, highly selective palladium-catalyzed cross-coupling of a transient σ-alkylpalladium(II) complex **B**, generated in situ from 4-(*o*-haloaryl)alkenes and a Pd^0 precursor[7] with a terminal alkyne as a concise and convenient means of accessing diverse alkyl-substituted alkynes (Scheme 1 b). Importantly, these alkyl-substituted alkyne derivatives containing heterocyclic rings make this methodology more useful in organic synthesis because heterocyclic rings, such as oxindoles and indolines, are important skeletal units that found in numerous natural products and pharmaceutical compounds.[8]

Our work began with extensive screening of Pd catalysts, Cu catalysts, bases and solvents, and the optimization data are

[a] M.-B. Zhou, X.-C. Huang, Y.-Y. Liu, Dr. R.-J. Song, Prof. Dr. J.-H. Li
State Key Laboratory of Chemo/Biosensing and Chemometrics
College of Chemistry and Chemical Engineering
Hunan University, Changsha 410082 (China)
Fax: (+86) 731-8871-3642
E-mail: jhli@hnu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303879.

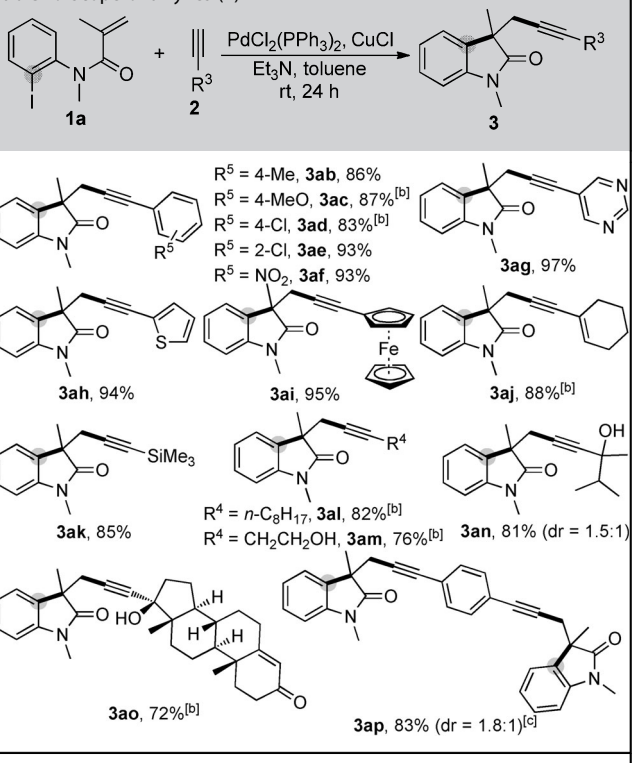
Table 1. Screening optimal conditions.[a]



Entry	[Pd] ([mol%])	[Cu]	Base ([equiv])	*t* [h]	Isolated yield [%]
1	$PdCl_2(PPh_3)_2$ (5)	CuI	Et_3N (24)	THF	85
2	$PdCl_2(PPh_3)_2$ (5)	CuI	Et_3N (48)	–	93
3	$PdCl_2(PPh_3)_2$ (5)	–	Et_3N (48)	–	0
4	–	CuI	Et_3N (48)	–	0
5	$Pd(OAc)_2$ (5)	CuI	Et_3N (48)	–	74
6	$Pd(PPh_3)_4$ (5)	CuI	Et_3N (48)	–	83
7	$PdCl_2(PPh_3)_2$ (5)	CuI	Et_3N (6)	toluene	88
8	$PdCl_2(PPh_3)_2$ (5)	CuI	Et_3N (4)	toluene	82
9	$PdCl_2(PPh_3)_2$ (5)	CuBr	Et_3N (6)	toluene	64
10	$PdCl_2(PPh_3)_2$ (5)	CuCl	Et_3N (6)	toluene	98
11	$PdCl_2(PPh_3)_2$ (1)	CuCl	Et_3N (6)	toluene	99
12	$PdCl_2(PPh_3)_2$ (1)	CuCl	pyridine (6)	toluene	trace
13	$PdCl_2(PPh_3)_2$ (1)	CuCl	K_2CO_3 (6)	toluene	95
14[b]	$PdCl_2(PPh_3)_2$ (1)	CuCl	Et_3N (6)	toluene	47
15[c]	$PdCl_2(PPh_3)_2$ (1)	CuCl	Et_3N (6)	toluene	97

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), [Pd], [Cu] (4 mol%), base, and solvent (1 mL) at room temperature under argon atmosphere for 24 h. [b] Under air atmosphere. [c] **1a** (4 mmol, 1.204 g) and **2a** (4.8 mmol).

Table 2. Scope of alkynes (**2**)[a]

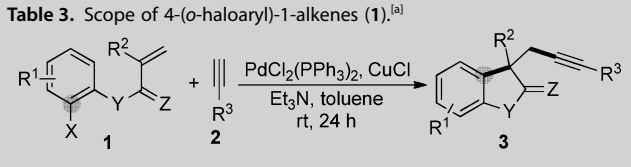


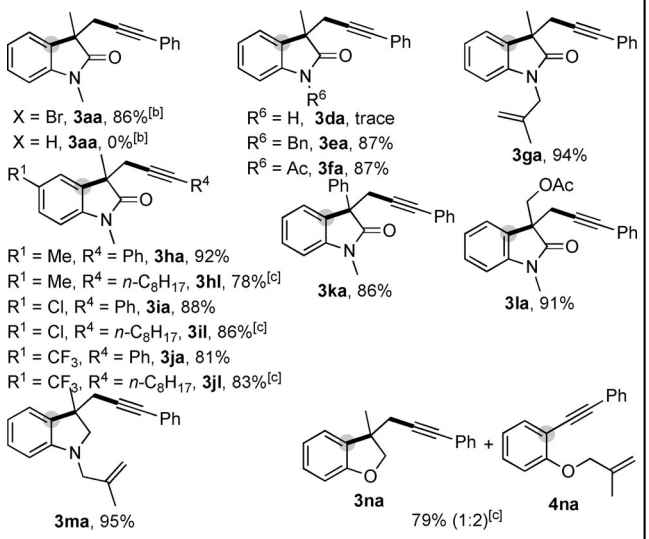
[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.36 mmol), $PdCl_2(PPh_3)_2$ (1 mol%), CuCl (4 mol%), Et_3N (6 equiv), and toluene (1 mL) at room temperature under argon atmosphere for 24 h. [b] At 50 °C. [c] **1a** (0.5 mmol) and **2p** (0.2 mmol).

summarized in Table 1. Interestingly, treatment of *N*-(2-iodophenyl)-*N*-methylmethacrylamide (**1a**) with phenylacetylene (**2a**) $Pd(PPh_3)_2Cl_2$, CuI and Et_3N in THF at room temperature under argon atmosphere furnished the desired product, 1,3-dimethyl-3-(3-phenylprop-2-ynyl)indolin-2-one (**3aa**), in 85% yield (Table 1, entry 1). With Et_3N as the base and medium, the yield of **3aa** was increased to 93% (Table 1, entry 2). However, substrate **1a** is sluggish without either Pd or Cu catalysts (Table 1, entries 3 and 4). Screening revealed that other Pd catalysts, $Pd(OAc)_2$ and $Pd(PPh_3)_4$, were less efficient than $Pd(PPh_3)_2Cl_2$ (Table 1, entry 2 vs. Table 1, entries 5–6). We were pleased to find that an excellent yield was still obtained when the reaction was carried out with six equivalents of Et_3N in toluene (Table 1, entry 7); however, the yield was lowered to 82% in the presence of four equivalents of Et_3N (Table 1, entry 8). Among the Cu catalysts examined, it turned out that CuCl was the most effective: CuCl (98% yield) > CuI (88% yield) > CuBr (64% yield) (Table 1, entries 7, 9 and 10). Notably, the current reaction could successfully be carried out at 1 mol% Pd, leading to product **3aa** in quantitative yield (Table 1, entry 11). In the presence of 1 mol% Pd, two bases, pyridine and K_2CO_3, were examined (Table 1, entries 12 and 13): whereas the reaction with pyridine resulted in no conversion of substrate **1a**, excellent yield was achieved in the presence of K_2CO_3. It is noteworthy that the presence of air does not favor the reaction because homocoupling of alkyne **2a** readily takes place (Table 1, entry 14). Gratifyingly, on a 4 mmol scale with substrate **1a** the reaction also takes place smoothly to furnish product **3aa** in excellent yield (Table 1, entry 15).

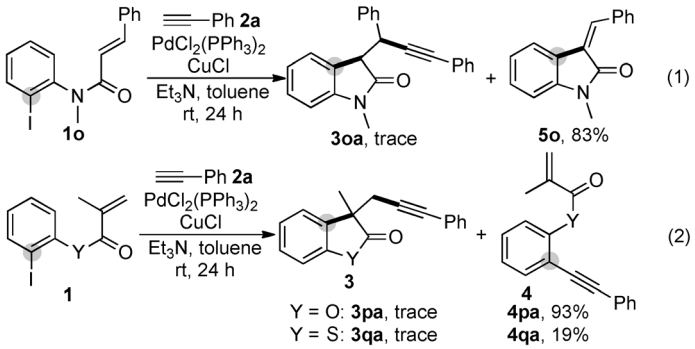
With the optimized conditions in hand, we set out to probe the scope of the reaction with both 4-arylalkenes (**1**) and alkynes (**2**; Tables 2 and 3). As shown in Table 2, the optimized conditions can be applied to a wide range of terminal alkynes, such as aryl alkynes, aliphatic alkynes and alkynes with functional groups including olefins, $SiMe_3$ and unprotected alcohols. Initially, a variety of aryl alkynes **2b**–**2i** were investigated in the presence of *N*-(2-*i*odophenyl)-*N*-methylmethacrylamide (**1a**), $Pd(PPh_3)_2Cl_2$, CuCl and Et_3N (Products **3ab**–**3ai**). Either electron-rich or electron-deficient aryl alkynes reacted, but the reactivity of the former is lower than that of the latter. For example, 4-methyl- or 4-methoxy-substituted aryl alkynes **2b** and **2c** reacted smoothly to afford 3-alkynylindolin-2-ons **3ab** and **3ac** in 86% and 87% yields, respectively. Gratifyingly, the 4-nitro-susbtitued alkyne **2f** furnished product **3af** in 93% yield. It was noted that a Cl group in the *para*- or *ortho*-position could be tolerated, thereby facilitating additional modifications at the halogenated position (Products **3ad** and **3ae**). Heteroaryl alkyes 5-ethynylpyrimidine (**2g**), 2-ethynylthiophene (**2h**), particularly ethynylferrocene (**2i**), were found to be compatible with the optimized conditions, providing the corresponding 3-alkynylindolin-2-ons **3ag**–**3ai** in excellent yields. For the aliphatic dec-1-yne (**2l**), a good yield was still achieved, although higher temperature (50 °C) was required to improve the conversion (Product **3al**). Several functional groups including olefins, $SiMe_3$ and unprotected alcohols, at the terminal alkynes were tolerated, making this method useful for the preparation of pharmaceuticals and natural products (Products **3aj**, **3ak**, **3am and 3an**). Notably, product **3ao** contains two bioactive

Table 3. Scope of 4-(*o*-haloaryl)-1-alkenes (**1**).[a]





[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.36 mmol), $PdCl_2(PPh_3)_2$ (1 mol%), CuCl (4 mol%), Et_3N (6 equiv) and toluene (1 mL) at room temperature under argon atmosphere for 24 h. Unless specified otherwise, X = I. [b] At 80 °C. [c] At 50 °C.



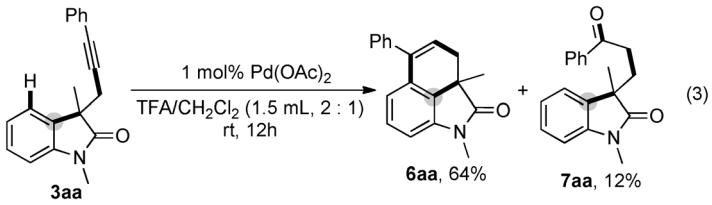
Scheme 2. Reactions of other 4-(*o*-haloaryl)-1-alkenes (**1**).

molecule frameworks, indolin-2-one and testosterone, that may elevate its pharmacokinetic properties. With 1,4-diethynylbenzene (**2p**), a symmetric bis(alkynyl)bis(indolin-2-one) **3ap** was assembled in 83% yield.

The scope of 4-arylalkenes **1** in the presence of phenylacetylene (**2a**) or dec-1-yne (**2l**), $Pd(PPh_3)_2Cl_2$, CuCl and Et_3N (Table 3) was investigated. Gratifyingly, *N*-(2-bromophenyl)-*N*-methylmethacrylamide (**1b**) was a viable substrate for the tandem reaction with alkyne **2a** leading to product **3aa** in 86% yield. Unfortunately, *N*-phenyl-*N*-methylmethacrylamide (**1c**) was inert under the optimized conditions. Use of the analogous amide with the *N*-methyl group replaced by a benzyl or an acetyl group also resulted in good yields (Products **3ea** and **3fa**), but substitution by a hydrogen atom was sluggish (Product **3da**). Substituents, such as Me, Cl or CF_3, on the aromatic ring of the *N*-aryl moiety were examined: they were well-tolerated, although slight alterations to the conditions (temperature) for reacting with aliphatic alkynes **2l** (Products **3ha**–**3ja** and **3hl**–**3jl**) are necessary. For substrates **1k** and **1l** with a functional group, Ph or CH_2OAc, at the 2-position of acrylamide, good yields were still obtained (Products **3ka** and **3la**). This process was successfully performed for the cyclization of 2-iodo-*N*-(2-methylallyl)aniline **1m**, an amine, in high yields (Product **3ma**). Interestingly, 1-iodo-2-(2-methylallyloxy)benzene (**1n**), an ether, was suitable for the tandem cyclization reaction, affording the desired product **3na** together with a Sonogashira cross-coupled product, 1-(2-methylallyloxy)-2-(phenylethynyl)benzene (**4na**), in 79% total yield with 1:2 ratio.

As shown in Scheme 2, three other 4-(*o*-iodophenyl)alkenes **1o**–**q** were tested with respect to phenylacetylene (**2a**) under the optimal conditions. The results demonstrated the chemoselectivity of the cross-coupling reaction based on the structure of the substrates of type **1**. For example, the internal alkene **1o** gave a Heck-type product **5o**, exclusively, in good yields [Eq. (1)]. However, 2-iodophenyl methacrylate (**1p**), an ester, only afforded a Sonogashira-type product **4pa** [Eq. (2)]. With *S*-2-iodophenyl 2-methylprop-2-enethioate (**1q**), only Sonogashira-type product **4qa** was observed in a low yield.

Interestingly, product **3aa** could be readily converted into 2a,3-dihydrobenzo[*cd*]indol-2(1*H*)-one **6aa** in moderate yield through the palladium-catalyzed hydroarylation process along with a hydration by-product **7aa** in low yield [Eq. (3)].[9]



In summary, we have developed a novel direct and mild protocol for the synthesis of diverse alkyl-substituted alkynes by palladium-catalyzed alkylation of terminal alkynes with transient σ-alkylpalladium(II) complexes. This cross-coupling method is achieved through a carbopalladation-alkynylation tandem process, and has a broad substrate scope with respect to both 4-(*o*-haloaryl)alkenes and alkynes. Studies of the mechanism and applications of this transient σ-alkylpalladium(II) complex in organic synthesis are currently underway in our laboratory.

Experimental Section

Typical experimental procedure for palladium-catalyzed synthesis of alkyl-substituted alkynes: To a Schlenk tube were added 4-(*o*-haloaryl)alkenes **1** (0.3 mmol), alkynes **2** (0.36 mmol), $PdCl_2(PPh_3)_2$ (1 mol%), CuCl (4 mol%), Et_3N (6 equiv) and toluene (2 mL).

Then the tube was charged with argon, and was stirred at the indicated temperature for about 24 h until complete consumption of starting material as monitored by TLC and/or GC-MS analysis. After the reaction was finished, the reaction mixture was washed with brine and the aqueous phase re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the desired alkyl-substituted alkynes **3**.

Acknowledgements

We thank the Specialized Research Fund for the Doctoral Program of Higher Education (No. 20120161110041), Hunan Provincial Natural Science Foundation of China (No. 13JJ2018), and Natural Science Foundation of China (No. 21172060) for financial support.

Keywords: 4-(*o*-haloaryl)alkenes · alkylation · alkynes · carboalkynylation · palladium

[1] a) *The Chemistry of Triple-Bonded Functional Groups* (Ed.: S. Patai), Wiley, New York, **1994**; b) *Modern Acetylene Chemistry*; (Eds. P. J. Stang, F. Diederich), VCH, Weinheim, Germany, **1995**.

[2] For special reviews, see: a) K. Sonogashira, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley, New York, **2002**, pp. 493 – 529; b) E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979; c) R. R. Tykwinski, *Angew. Chem.* **2003**, *115*, 1604; *Angew. Chem. Int. Ed.* **2003**, *42*, 1566; d) H. Plenio, *Angew. Chem.* **2008**, *120*, 7060; *Angew. Chem. Int. Ed.* **2008**, *47*, 6954; e) *Cross-coupling Reactions: A Practical Guide* (Ed.: N. Miyaura), Springer, Berlin, **2002**; f) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.*, Wiley-VCH, Weinheim, **2004**.

[3] a) M. Eckhardt, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 13642; b) G. Altenhoff, S. Wurtz, F. Glorius, *Tetrahedron Lett.* **2006**, *47*, 2925; c) O. Vechorkin, D. Barmaz, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 12078; d) D. Rayabarapu, J. Tunge, *J. Am. Chem. Soc.* **2005**, *127*, 13510; e) H. Bi, L. Zhao, Y. Liang, C. Li, *Angew. Chem.* **2009**, *121*, 806; *Angew. Chem. Int. Ed.* **2009**, *48*, 792; f) W.-W. Zhang, X.-G. Zhang, J.-H. Li, *J. Org. Chem.* **2010**, *75*, 5259.

[4] a) L. Yang, L. Huang, T. Luh, *Org. Lett.* **2004**, *6*, 1461; b) H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 3093; c) Y. Zhao, H. Wang, X. Hou, A. Lei, H. Zhang, L. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 15048; d) G. Cahiez, O. Gager, J. Buendia, *Angew. Chem.* **2010**, *122*, 1300; *Angew. Chem. Int. Ed.* **2010**, *49*, 1278; e) M. Chen, X. Zheng, W. Li, J. He, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 4101; f) O. Vechorkin, A. Godinat, R. Scopelliti, X. Hu, *Angew. Chem.* **2011**, *123*, 11981; *Angew. Chem. Int. Ed.* **2011**, *50*, 11777; g) T. Hatakeyama, Y. Okada, Y. Yoshimoto, M. Nakamura, *Angew. Chem.* **2011**, *123*, 11165; *Angew. Chem. Int. Ed.* **2011**, *50*, 10973.

[5] a) F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 5742; b) L. Zhou, F. Ye, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 13590.

[6] For reviews: a) R. Grigg, V. Sridharan, *J. Organomet. Chem.* **1999**, *576*, 65; b) S. I. Kozhushkov, A. Meijere, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley, New York, **2002**, pp. 1317 – 1334; For selected recent papers: c) A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. Eur. J.* **2007**, *13*, 961; d) X. Liu, X. Ma, Y. Huang, Z. Gu, *Org. Lett.* **2013**, *15*, 4814; e) Z. Liu, Y. Xia, S. Zhou, L. Wang, Y. Zhang, J. Wang, *Org. Lett.* **2013**, *15*, 5032, and references therein.

[7] See Supporting Information (Figure S1) for the in-situ ^{1}H NMR analysis results.

[8] For reviews: a) B. S. Jensen, *CNS Drug Rev.* **2002**, *8*, 353; b) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209; c) H. Lin, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 38; *Angew. Chem. Int. Ed.* **2003**, *42*, 36; d) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; e) A. Millemaggi, R. J. K. Taylor, *Eur. J. Org. Chem.* **2010**, 4527; f) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381; g) S. R. S. Rudrangi, V. K. Bontha, V. R. Manda, S. Bethi, *Asian J. Res. Chem.* **2011**, *4*, 335; For selected papers: h) G. Deak, M. Doda, L. Gyorgy, L. Hazai, L. Sterk, *J. Med. Chem.* **1977**, *20*, 1384; i) A. Numata, P. Yang, C. Takahashi, R. Fujiki, M. Nabae, E. Fujita, *Chem. Pharm. Bull.* **1989**, *37*, 648; j) S. Hibino, T. Choshi, *Nat. Prod. Rep.* **2001**, *18*, 66; k) A. S. Ratnayake, W. Y. Yoshida, S. L. Mooberry, T. K. Hemscheidt, *J. Org. Chem.* **2001**, *66*, 8717; l) M. Kuriyama, S. Tanigawa, Y. Kubo, Y. Demizu, O. Onomura, *Tetrahedron: Asymmetry* **2010**, *21*, 1370; m) B. M. Trost, J. Xie, J. D. Sieber, *J. Am. Chem. Soc.* **2011**, *133*, 20611.

[9] For reviews, see: a) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Soc.* **2001**, *34*, 633; b) C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167; c) I. J. S. Fairlamb, *Annu. Rep. Prog. Chem. Sect. B* **2006**, *102*, 50.

Received: October 3, 2013
Revised: November 1, 2013
Published online on January 21, 2014