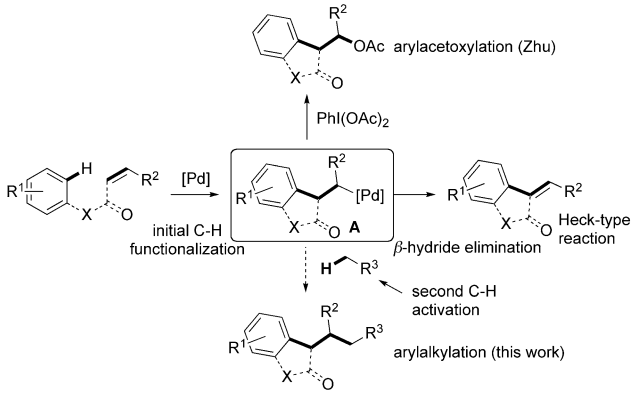
Synthetic Methods

DOI: 10.1002/anie.201104575

Palladium-Catalyzed Oxidative Arylalkylation of Activated Alkenes: Dual C–H Bond Cleavage of an Arene and Acetonitrile**

*Tao Wu, Xin Mu, and Guosheng Liu**

The oxidative difunctionalization of alkenes is a powerful strategy for the synthesis of various organic compounds.[1] Recent studies have demonstrated that palladium-catalyzed oxidative transformations, such as aminooxygenation,[2] diamination,[3] and dioxygenation[4] of alkenes, can be used efficiently to achieve bond formations at vicinal positions. However, palladium-catalyzed oxidative dicarbonation of alkenes is quite challenging.[5,6] Oxidative cross-coupling of arenes and alkenes using palladium catalysts have been extensively explored.[7] These reactions involve C–H bond functionalizations to yield the intermediate **A**, which usually undergoes β-hydride elimination to afford Heck-type products (Scheme 1). Recently, Zhu and co-workers have reported



Scheme 1. Palladium-catalyzed functionalization of alkenes initiated by C–H bond cleavage.

an oxidative intramolecular arylacetoxylation of alkenes in which the C–Pd^{II} bond of intermediate **A** can be oxidized by $PhI(OAc)_2$ to form a C–O bond.[8a] This discovery presents an intriguing strategy for the carbonation of alkenes. We postulated that if an additional C–H bond activation can take place at the palladium center of intermediate **A**,[9] the highly desired dicarbonation of alkenes could be accomplished, and would therefore offer a valuable method for constructing two C–C bonds simultaneously (Scheme 1).

The activation of the C–H bond of acetonitrile has been well-documented by using stoichiometric amounts of a transition metal,[10] such as Rh,[9a–d] Ni,[9e] Ru,[9f,g,i] and Fe,[9j] etc., to yield $L_nM–CH_2CN$ complexes under various reaction conditions. However, in general the catalytic C–H functionalization of acetonitrile by a transition metal is quite rare,[11] and a strong base is generally required.[12] Herein, we report a novel palladium-catalyzed oxidative arylalkylation of alkenes, which involves dual C–H bond cleavage to form two C–C bonds in the presence of AgF and $PhI(OPiv)_2$. It is worth noting that the rate-determining C_{sp^3}–H bond activation of CH_3CN proceeded in the absence of a strong base, and in the presence of acidic additives.

As part of our efforts to develop catalytic fluorination of alkenes, our initial investigation focused on the arylfluorination of **1a**. With the previously reported fluorination conditions involving $AgF/PhI(OPiv)_2$,[13] the reaction of **1a** only afforded a small amount of the expected arylfluorination product **2a** (Table 1). Surprisingly, the major product **3a**, having the solvent acetonitrile incorporated, was observed (Table 1, entry 1). Further optimization of the reaction conditions exhibited that a bidentate nitrogen-containing ligand is beneficial to the reaction, and the ligand **L4** was shown to give the best yield (entries 2–6). Notably, no reaction occurred in the absence of either the palladium catalyst, AgF, or $PhI(OPiv)_2$ (entries 7, 8, and 10). The reaction with $PhI(OAc)_2$ also afforded **3a** but in low yield (entry 9). Other oxidants, such as *tert*-butyl peroxide, oxone, and benzoquinone, were ineffective (see the Supporting Information). Additional screening of bases showed that AgF was unique for this reaction. No desired product **3a** was observed in the presence of other fluoride and nonfluoride bases, or in the presence of strong bases such as KO*t*Bu and $NaN(SiMe_3)_2$ (entries 11–13). The addition of $MgSO_4$ is helpful for increasing the yield of **3a** (entry 14). It is remarkable that the reaction is not influenced by acidic additives such as CH_3CO_2H or CF_3CO_2H (entries 15–16). Furthermore, there was no effect on this transformation when 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) was employed as a radical scavenger (entry 17).

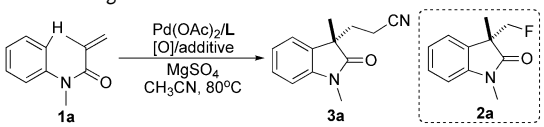
The scope of substrates was investigated as shown in Schemes 2 and 3. The effect of the protecting group on the nitrogen atom was firstly probed. For the substrates bearing an alkyl or aryl group on N, the reactions proceeded smoothly to provide products **3a** and **3b** in excellent yields. In contrast, the substrates with an electron-withdrawing group on N did not yield the desired products **3c** and **3d**. The position of the substituents on the aryl ring has no significant influence on

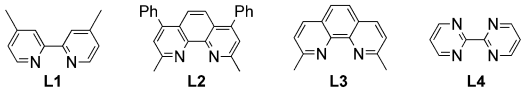
[*] T. Wu, X. Mu, Prof. Dr. G. Liu
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Road, Shanghai, 200032 (China)
E-mail: gliu@mail.sioc.ac.cn

[**] We are grateful for the financial support from the National Natural Science Foundation of China (20821002, 20872155, 20972175, and 20923005), the National Basic Research Program of China (973-2009CB825300), and the "Hundred Talent Project" of Chinese Academy of Science.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104575.

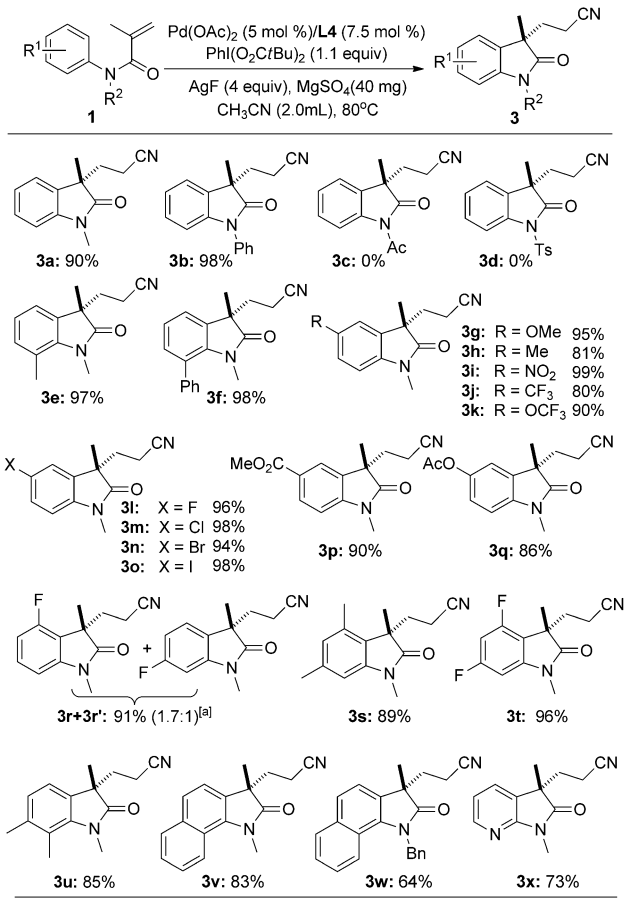
Table 1: Screening of reaction conditions.[a]





Entry	[O]	Additive	L	Yield (**3a** [%])
1[c]	$PhI(OPiv)_2$	AgF	–	56
2	$PhI(OPiv)_2$	AgF	bpy	61
3	$PhI(OPiv)_2$	AgF	**L1**	65
4	$PhI(OPiv)_2$	AgF	**L2**	76
5	$PhI(OPiv)_2$	AgF	**L3**	79
6	$PhI(OPiv)_2$	AgF	**L4**	92
7[d]	$PhI(OPiv)_2$	AgF	**L4**	0
8	–	AgF	**L4**	0
9	$PhI(OAc)_2$	AgF	**L4**	38
10	$PhI(OPiv)_2$	–	**L4**	0
11	$PhI(OPiv)_2$	KF or CsF	**L4**	0
12	$PhI(OPiv)_2$	KO*t*Bu or $NaN(SiMe_3)_2$	**L4**	0
13	$PhI(OPiv)_2$	$CsCO_3$ or Ag_2CO_3	**L4**	0
14[e]	$PhI(OPiv)_2$	AgF	**L4**	71
15	$PhI(OPiv)_2$	AgF/AcOH[f]	**L4**	89
16	$PhI(OPiv)_2$	AgF/TFAOH[f]	**L4**	84
17	$PhI(OPiv)_2$	AgF/TEMPO[g]	**L4**	88

[a] Reaction conditions: **1a** (0.1 mmol), [Pd] (5 mol%), Ligand (7.5 mol%), AgF (0.4 mmol), $PhI(OPiv)_2$ (0.11 mmol), $MgSO_4$ (20 mg, 0.17 mmol) in 1.0 mL of CH_3CN at 80°C for 12 h. [b] Yield as determined by GC using tetradecane as an internal standard. [c] Product **2a** (8% yield). [d] Without palladium catalyst. [e] Without $MgSO_4$. [f] 2 equiv HOAc or TFAOH were used as additive. [g] TEMPO (1 equiv) was used as additive. bpy = bipyridine, **L** = ligand, Piv = pivaoyl, TFA = trifluoroacetic acid.

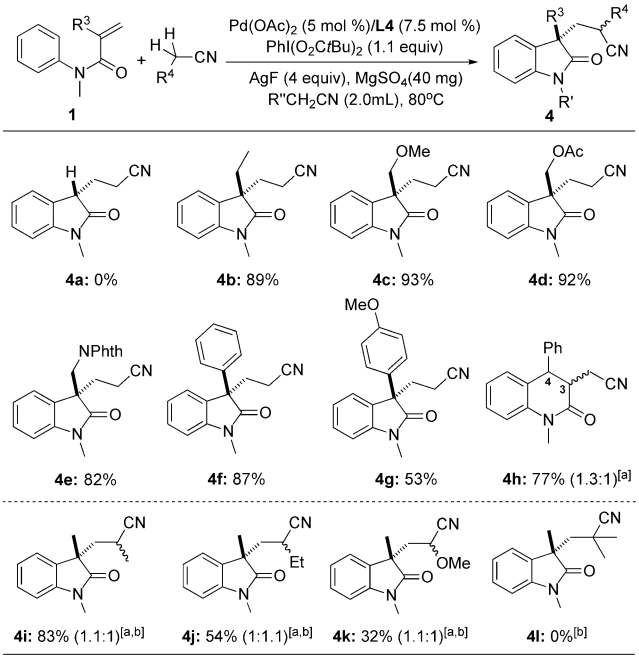


Scheme 2. Palladium-catalyzed oxidative arylalkylation of alkenes. Reactions were conducted at 0.2 mmol scale. Yields are those of the isolated product. [a] The ratio of **3r** and **3r′** was determined by ^1H NMR spectroscopy. Bn = benzyl, Ts = 4-toluenesulfonyl.

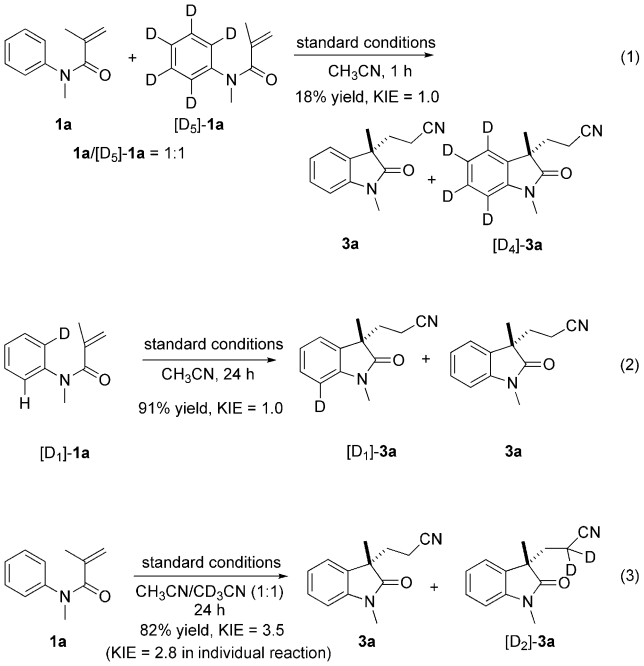
the efficiency. The substrates bearing electron-withdrawing or electron-donating group always afforded the desired products **3e**–**3t** in good to excellent yields. Notably, both halides and ester groups, which are sensitive to strong base, were tolerated and furnished the corresponding products **3l**–**3o**, **3p**, and **3q** with excellent yields. The substrates bearing *meta* substitents exhibited very good reactivity but poor regioselectivity (**3r**). The substrates having two substituents on the aryl ring are still good for this transformation (**3s**–**3u**). Finally, when the benzene ring of the substrates was changed to naphthalene, the reactions successfully provided the arylalkylation products **3v**–**3w**. Importantly, the pyridine group was also compatible with these oxidative reaction conditions (**3x**).

Substrates with various olefins were additionally examined. For substrates without a substituent at the α position ($R^3 = H$) of the olefin, the reaction did not afford the desired product **4a** (Scheme 3). Analogous to substrate **1a**, substrates with ethyl, methoxymethyl, acetoxymethyl, and imide groups at the α position generated the corresponding products **4b**–**4e** in excellent yields. Substrates with an aryl group at the α position also afforded products **4f** and **4g** in moderate to good yields. In contrast, substrates with a phenyl group at the β position undergoes arylation with opposite regioselectivity to afford the six-membered product **5h** in 77% yield, but with low diastereoselectivity. Finally, a series of nitriles were also tested. As shown in Scheme 3, a significant steric effect was observed, and the reactivity of the nitrile decreased as follows: $CH_3CN > EtCN > nPrCN > iPrCN$. The reactions of propionitrile and *n*-butyronitrile furnished the products **4i** and **4j** in 83% and 54% respectively; the lower yield of **4k** was delivered with methoxyacetonitrile, and no reaction occurred in the solvent of isobutyronitrile (**4l**). Except for acetonitrile, these reactions were carried out at 110°C.

The formation of **3** and **4** indicates that a dual C–H bond functionalization of both aniline and acetonitrile was involved in this reaction. To probe the mechanism of the C–H bond cleavage, a mixture of the substrates **1a** and [D_5]-**1a** (1:1) was subjected to the standard reaction conditions to determine the intermolecular isotope effect, and substrate [D_1]-**1a** was used to probe the intramolecular isotope effect. Neither intra- nor intermolecular kinetic isotopic effects were observed [$k_H/k_D = 1.0$, Eqs. (1) and (2)].[14] The absence of an intramolecular isotope effect suggests that the reaction involves an electrophilic aromatic substitution process.[15] Interestingly, when the reaction of **1a** was conducted in a 1:1 mixture of CH_3CN/CD_3CN as the solvent, a large primary isotope effect ($k_H/k_D = 3.5$) was obtained [Eq. (3)]. A similar KIE value (2.8) was also observed in the individual reaction in CH_3CN

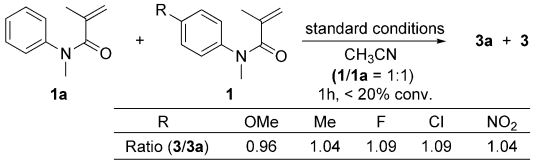


Scheme 3. Palladium-catalyzed oxidative arylalkylation of alkenes. Reactions were conducted at 0.2 mmol scale. Yields are those of the isolated products. [a] The ratio in parentheses is the diasteroselectivity of the reaction as determined by ^{1}H NMR spectroscopy. [b] The reaction was conducted at 110 °C. PhthNH = Phthalimide.



and CD_3CN. Furthermore, no significant substituent effect on the reaction rate was observed in the competition experiments [Eq. (4)]. These results suggest that a C_{sp^3}–H bond activation of acetonitrile contributed to the rate-determining step.

The detailed mechanism of the oxidative arylalkylation of alkenes is not clear to us at the moment. Preliminary studies



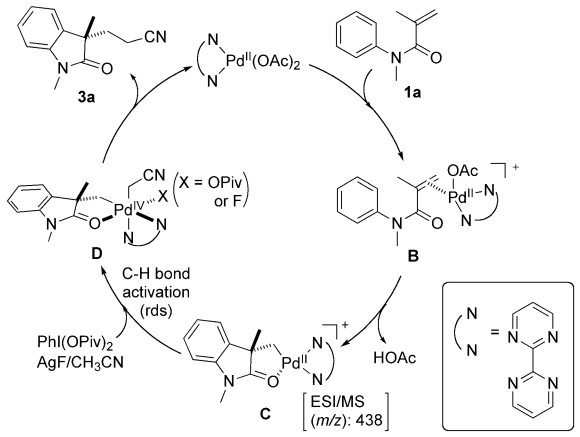
R	OMe	Me	F	Cl	NO_2
Ratio (**3**/**3a**)	0.96	1.04	1.09	1.09	1.04

indicate that the C–C bond formation might be derived from a Pd^{IV} intermediate: 1) the reaction occurred in the presence of $PhI(OPiv)_2$, but no reaction occurs with other oxidants, such as BQ or O_2. 2) The desired product **3a** was not obtained and starting material **1a** was recovered from the stoichiometric reaction in the absence of an oxidant. 3) The good compatibility of halide (Br for **3n**, I for **3o**) also suggests that the $Pd^{0/II}$ cycle is less likely.

Compared to acetonitrile, no reaction takes place in noncoodinating protonic solvents, such as EtOAc and $MeNO_2$.[16] This observation indicates that the coordination of acetonitrile with AgF or the palladium complex may be crucial for the C–H bond activation of acetonitrile.[10] Additionally, the reaction occurs in the presence of AgF, and is quite sensitive to the amount of AgF.[17] Such observations suggest that AgF plays a key role in activating C_{sp^3}–H bond of acetonitrile.[18]

On the basis of the above analysis, a possible catalytic cycle is shown in Scheme 4. The reaction is initiated by coordination of the olefin to Pd^{II}, with subsequent nucleophilic attack of the tethered arene to give the palladium complex **C**.[19] Then the C_{sp^3}–H bond activation of CH_3CN takes place in the presence of $PhI(OPiv)_2$ and AgF, thus generating the Pd^{IV} complex **D** that undergoes reductive elimination to afford the product **3a**.[20,21]

In conclusion, we have discovered a novel palladium-catalyzed oxidative arylalkylation of alkenes, in which dual C–H bond activation of both aniline and acetonitrile are involved. The addition of $PhI(OPiv)_2$ and AgF are the key for this transformation, and AgF plays a roles to promote the C_{sp^3}–H bond cleavage in acetonitrile. The reactions afford a variety of nitrile-bearing indolinones in excellent yields. Additional studies on the mechanism and synthetic application are in progress.



Scheme 4. The proposed mechanism for this oxidative arylalkylation of alkenes.

Experimental Section

General procedure: In a TFE sealed dry glass tube, $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), AgF (102 mg, 0.8 mmol), $PhI(O_2CtBu)_2$ (90 mg, 0.22 mmol), 2,2′-bipyrimidine (2.4 mg, 0.015 mmol), $MgSO_4$ (40 mg, 0.34 mmol), and alkene **1a** (0.2 mmol) were dissolved in dry CH_3CN (2.0 mL). The mixture was stirred at 80 °C for 24 h. Then ethyl acetate was added and the mixture was filtered through a plug of celite. After removal of the solvent under vacuum, the residue was purified by column chromatography on silica gel with a gradient eluant of petroleum ether and ethyl acetate to afford the product **3a** (39 mg, 90 % yield).

Received: July 2, 2011
Revised: September 9, 2011
Published online: November 11, 2011

Keywords: acetonitrile · alkenes · arylalkylation · C–H activation · palladium

[1] For some recent reviews on the oxidative difunctionalization of alkenes, see: a) K. H. Jensen, M. S. Sigman, *Org. Biomol. Chem.* **2008**, *6*, 4083 – 4088; b) V. Kotov, C. C. Scarborough, S. S. Stahl, *Inorg. Chem.* **2007**, *46*, 1910 – 1923; c) B. Jacques, K. Muinz in *Catalyzed Carbon-Heteroatom Bond Formation* (Ed.: A. K. Yudin), Wiley, VCH, **2010**, pp. 119 – 135; d) S. R. Chemler, *Org. Biomol. Chem.* **2009**, *7*, 3009 – 3019.

[2] a) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.* **2005**, *127*, 7690; b) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 7179 – 7181; c) L. V. Desai, M. S. Sanford, *Angew. Chem.* **2007**, *119*, 5839 – 5842; *Angew. Chem. Int. Ed.* **2007**, *46*, 5737 – 5740.

[3] a) J. Streuff, C. H. Hövelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586 – 14587; b) K. Muñiz, *J. Am. Chem. Soc.* **2007**, *129*, 14542 – 14543; c) P. A. Sibbald, F. E. Michael, *Org. Lett.* **2009**, *11*, 1147 – 1149; d) A. Iglesias, E. Pérez, K. Muñiz, *Angew. Chem.* **2010**, *122*, 8286 – 8288; *Angew. Chem. Int. Ed.* **2010**, *49*, 8109 – 8111.

[4] a) A. Wang, H. Jiang, H. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 3846 – 3847; b) Y. Li, D. Song, V. M. Dong, *J. Am. Chem. Soc.* **2008**, *130*, 2962 – 2964.

[5] The palladium-catalyzed oxidative enyne cyclization is the only one case involving intramolecular dicabonation of alkenes. See: a) X. Tong, M. Beller, M. K. Tse, *J. Am. Chem. Soc.* **2007**, *129*, 4906 – 4907; b) L. L. Welbes, T. W. Lyons, K. A. Cychosz, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 5836 – 5837.

[6] For the Pd^{II}-catalyzed dicarbonation of alkenes, see: K. B. Urkalan, M. S. Sigman, *Angew. Chem.* **2009**, *121*, 3192 – 3195; *Angew. Chem. Int. Ed.* **2009**, *48*, 3146 – 3149, and references therein.

[7] For recent reviews on the oxidative cross-coupling Heck-type reactions, see: a) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170 – 1214; b) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; For select recent examples, see: c) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315 – 319; d) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072 – 5074; e) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 6552 – 6555; *Angew. Chem. Int. Ed.* **2008**, *47*, 6452 – 6455; f) J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888 – 13889; g) K. M. Engle, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 14137 – 14151; h) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680 – 3681; i) K. J. Stowers, K. C. Fortner, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 6541 – 6544.

[8] a) S. Jaegli, J. Dufour, H.-L. Wei, T. Piou, X.-H. Duan, J.-P. Vors, L. Neuville, J. Zhu, *Org. Lett.* **2010**, *12*, 4498 – 4501; For the similar transformation, see: b) H.-L. Wei, T. Piou, J. Dufour, L. Neuville, J. Zhu, *Org. Lett.* **2011**, *13*, 2244 – 2247; c) A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. Eur. J.* **2007**, *13*, 961 – 967.

[9] For recent reports on palladium-catalyzed carboamination of alkenes, C–H bond activation of arenes was promoted by a C_{sp^3}–Pd complex. See: a) C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 9488 – 9489; b) K.-T. Yip, D. Yang, *Org. Lett.* **2011**, *13*, 2134 – 2137; The Au-catalyzed carboamination of alkenes, see: c) G. Zhang, Y. Luo, Y. Wang, L. Zhang, *Angew. Chem.* **2011**, *123*, 4542 – 4546; *Angew. Chem. Int. Ed.* **2011**, *50*, 4450 – 4454; For the Cu-catalyzed carboamination, see: d) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948 – 12949.

[10] a) A. J. Vetter, R. D. Rieth, W. D. Jones, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 6957 – 6962; b) M. E. Evans, T. Li, A. J. Vetter, R. D. Rieth, W. D. Jones, *J. Org. Chem.* **2009**, *74*, 6907 – 6914; c) M. E. Evans, T. Li, W. D. Jones, *J. Am. Chem. Soc.* **2010**, *132*, 16278 – 16284; d) T. Tanabe, M. E. Evans, W. W. Brennessel, W. D. Jones, *Organometallics* **2011**, *30*, 834 – 843; e) A. M. Oertel, V. Ritleng, M. J. Chetcuti, L. F. Veiros, *J. Am. Chem. Soc.* **2010**, *132*, 13588 – 13589; f) E. J. Derrah, K. E. Giesbrecht, R. McDonald, L. Rosenberg, *Organometallics* **2008**, *27*, 5025 – 5032; g) M. G. Crestani, A. Steffen, A. M. Kenwright, A. S. Batsanov, J. A. K. Howard, T. B. Marder, *Organometallics* **2009**, *28*, 2904 – 29142; h) N. A. Foley, T. B. Gunnoe, T. R. Cundari, P. D. Boyle, J. L. Petersen, *Angew. Chem.* **2008**, *120*, 738 – 742; *Angew. Chem. Int. Ed.* **2008**, *47*, 726 – 730; i) H. J. Heeres, A. Meetsma, J. H. Teuben, *Angew. Chem.* **1990**, *102*, 449 – 450; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 420 – 422; j) S. D. Ittel, C. A. Tolman, A. D. English, J. P. Jesson, *J. Am. Chem. Soc.* **1978**, *100*, 7577 – 7585.

[11] For an example of deprotonation of acetonitrile in the presence of a ruthenium complex by employing 1,8-diazabicyclo[5-4-0]undec-7-ene (DBU) as a base: N. Kumagai, S. Matsunage, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 13632 – 13633.

[12] For palladium-catalyzed α-arylation of acetonitriles with a stoichiometric amount of a strong base, $NaN(SiMe_3)_2$, see: a) D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 9330 – 9331; b) J. You, J. G. Verkade, *Angew. Chem.* **2003**, *115*, 5205 – 5207; *Angew. Chem. Int. Ed.* **2003**, *42*, 5051 – 5053.

[13] T. Wu, G. Yin, G. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 16354 – 16355.

[14] For the reaction in Equation (1), no H/D scrambling was observed in the recovered starting material **1a** and [D_5]-**1a**. For details, see the Supporting Information.

[15] For the corresponding KIE value of electrophilic aromatic substitution process, see: a) J. A. Tunge, L. N. Foresee, *Organometallics* **2005**, *24*, 6440 – 6444; b) R. Taylor in *Electrophilic Aromatic Substitution*, Wiley, New York, **1990**, pp. 25 – 57.

[16] The pK_a values of solvents in DMSO: CH_3CN (31.3), EtO_2CCH_3 (29.4), $MeNO_2$ (17.2).

[17] If the amount of AgF is less than 2 equivalents, only trace amounts of arylalkylation product can be detected; for details see the Supporting Information.

[18] A reasonable explanation is that the C–H bond of actonitrile might be activated by coordination to Ag, and then the weaker C–H was cleaved by a second AgF, which serves as a base at this point. For details, see the Supporting Information.

[19] The intermediate **C** does exist in the catalytic cycle as a signal for *m*/*z* 438.05 was detected by ESI/MS. For details, see the Supporting Information.

[20] For the catalytic C–C bond formation from a Pd^{IV} complex, see: a) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972 – 4973; b) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 14047 – 14049; c) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 468 – 469.

[21] For the final C–C bond formation, the alternative pathway involving a nucleophilic attack by the carbanion of acetonitrile on the carbon center of the Pd^{IV} complex cannot be excluded.

