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Palladium-Catalyzed C−H Activation/Cross-Coupling of Pyridine *N*-Oxides with Nonactivated Secondary Alkyl Bromides

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Supporting Information

ABSTRACT: An unexpected C−H activation/C−C cross-coupling reaction has been found to occur between pyridine *N*-oxides and general nonactivated secondary and even tertiary alkyl bromides. It provides a practically useful approach for the synthesis of alkylated pyridine derivatives. Experimental observations indicated that the C−Br cleavage step involves a radical-type process. Thus, the title reaction provides a rather extraordinary example of Pd-catalyzed cross-coupling of secondary and tertiary aliphatic electrophiles.

Transition-metal-catalyzed intermolecular cross-coupling of inert C−H bonds has recently emerged as a powerful method for C−C bond formation.[1] This approach compares favorably with conventional cross-coupling reactions using organometallic reagents in terms of substrate availability[2] and enables the direct functionalization of rather complex molecules at their otherwise inactive C−H bonds.[3] To date, Pd catalysts have been extensively used in this field because of their advantages in reaction scope and functional group tolerance.[4] Indeed, the past decade has witnessed the development of many Pd-catalyzed C−H arylation reactions employing various sp^2-carbon electrophiles (e.g., aryl halides).[5] These reactions not only expand the concept and scope of Pd catalysis but also provide novel tools for the synthesis of pharmaceutically relevant molecules.[6] However, only a few examples of Pd-catalyzed intermolecular C−H alkylation reactions with nonactivated sp^3-carbon electrophiles have been reported.[7] In 2009, Yu and co-workers reported Pd-catalyzed ortho alkylation/lactonization of benzoic acids with 1,2-dichloroethane and related halohydrocarbons.[8] In 2010, Shabashov and Daugulis described Pd-catalyzed C−H activation/alkylation of acylaminoquinolines with primary (1°) alkyl iodides.[9,10] More recently, Bach and co-workers reported Pd-catalyzed norbornene-mediated alkylation of indole C−H bonds with 1° alkyl bromides.[11] Notably, the above studies have mainly shown C−H activation/C−C cross-coupling with 1° alkyl electrophiles,[12] whereas very little is known about alkylation of inert C−H bonds with *nonactivated secondary alkyl halides or pseudohalides* (Scheme 1).

A method for C−H alkylation with nonactivated secondary (2°) alkyl electrophiles would improve the utility of transition-metal-catalyzed C−H activation/C−C cross-coupling reactions for the synthesis of compounds with nonplanar structures.[13] In this context, we herein report a Pd-catalyzed intermolecular cross-coupling of pyridine *N*-oxides[14] with various nonactivated 2° alkyl bromides. This reaction provides a new approach for the synthesis of diverse 2-alkylpyridine derivatives that may be useful building blocks in the design of bioactive compounds.[15] More significantly, it adds to the fairly limited number of intermolecular C−H alkylation reactions with a broad spectrum of 2° alkyl electrophiles catalyzed by Pd-[16,17] or other transition metals[18] In a more general sense, the present work also offers novel insights into Pd-catalyzed C−C cross-coupling reactions, as previous studies have established the feasibility of using primary[19] *but not yet common secondary*[20,21] alkyl halides. One reason for the difficulty of cross-coupling with 2° alkyl halides is that the Pd-catalyzed S_N2 process is sensitive to the steric bulk of the substrate.[22−24] In this regard, it is extraordinary to find that the new Pd-catalyzed C−H activation/C−C cross-coupling reaction proceeds through a radical-type process with non-activated 2° or even tertiary (3°) alkyl bromides.

Our study was instigated by an unexpected observation during efforts to extend the scope of the Pd-catalyzed C−H functionalization reaction of pyridine *N*-oxides pioneered by Fagnou and co-workers.[14] During tests with different cross-coupling partners, we were surprised to find that cyclohexyl bromide (**1a**) reacts with 2-methylpyridine *N*-oxide (**2a**), albeit in a modest yield of 54% (Table 1, entry 1). Other cyclohexyl halides and pseudohalides gave inferior results (entries 2−4). Since 2° alkyl bromides are readily accessible substrates in organic synthesis, we decided to focus on their cross-coupling reactions with pyridine *N*-oxides. The yield increased to 82%

Scheme 1. Transition-Metal-Catalyzed Cross-Coupling of Carbon Electrophiles with Inert C−H Bonds

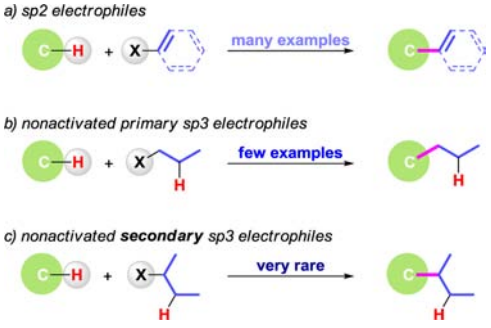

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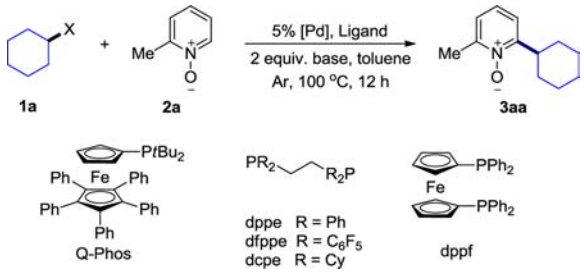
Table 1. Optimization of the Reaction Conditions[a]



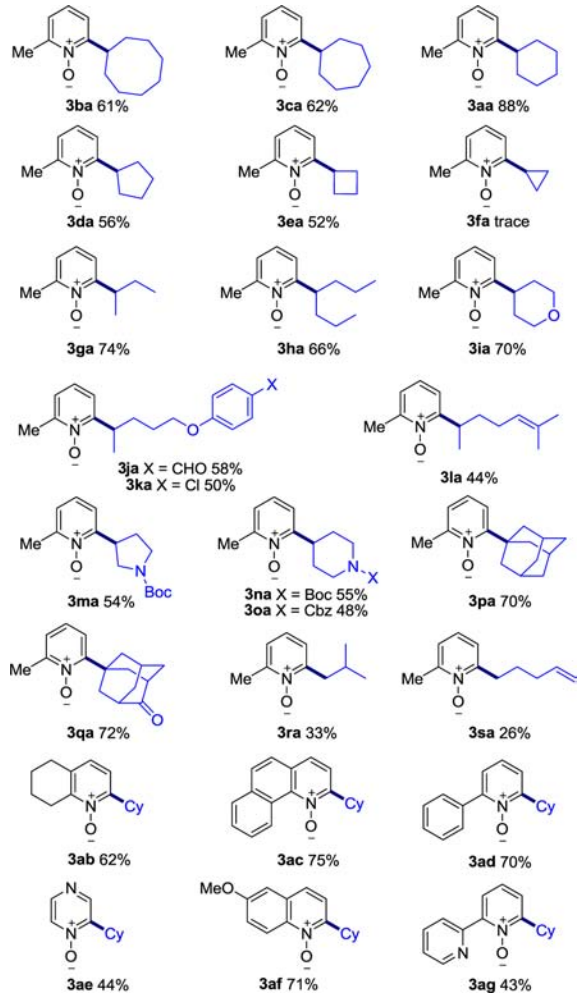
entry	X	[Pd]	Ligand	Base	GC[b] Yield (%)
1	Br	$Pd(OAc)_2$	PCy_3 (10 %)	K_2CO_3	54
2	OTs	$Pd(OAc)_2$	PCy_3 (10 %)	K_2CO_3	0
3	Cl	$Pd(OAc)_2$	PCy_3 (10 %)	K_2CO_3	5
4	I	$Pd(OAc)_2$	PCy_3 (10 %)	K_2CO_3	22
5	Br	$Pd(OAc)_2$	PCy_3 (10 %)	Cs_2CO_3	82
6	Br	$Pd(OAc)_2$	$PMetBu_2$ (10 %)	Cs_2CO_3	82
7	Br	$Pd(OAc)_2$	$PtBu_3$ (10 %)	Cs_2CO_3	38
8	Br	$Pd(OAc)_2$	Q-phos (10 %)	Cs_2CO_3	19
9	Br	$Pd(OAc)_2$	dppe (5 %)	Cs_2CO_3	78
10	Br	$Pd(OAc)_2$	dcpe (5 %)	Cs_2CO_3	77
11	Br	$Pd(OAc)_2$	dfppe (5 %)	Cs_2CO_3	27
12	Br	$Pd(OAc)_2$	dppf (5 %)	Cs_2CO_3	84
13	Br	$Pd(OAc)_2$	dppf (7.5 %)	Cs_2CO_3	55
14	Br	$Pd(OAc)_2$	dppf (10 %)	Cs_2CO_3	29
15	**Br**	**5 % $Pd(OAc)_2$dppf**		**Cs_2CO_3**	**90**
16	Br	$Pd(OAc)_2$	-	Cs_2CO_3	0
17	Br	-	dppf (5 %)	Cs_2CO_3	0
18	Br	$Pd_2(dba)_3$	dppf (5 %)	Cs_2CO_3	trace

[a]Conditions: 0.5 mmol of **1a** and 1.0 mmol of **2a** in 1 mL of toluene. [b]Benzophenone was used as an internal standard.

when the base K_2CO_3 was replaced with Cs_2CO_3 (entry 5). Changing the rather simple ligand PCy_3 to $PMetBu_2$ did not improve the yield (entry 6), and bulkier monophosphine ligands such as $PtBu_3$ and Q-Phos were less efficient (entries 7 and 8). These observations are consistent with Fu's previous finding that monodentate (rather than bidentate) phosphine ligands with appropriate cone angles are beneficial for Pd-catalyzed cross-coupling reactions of 1° alkyl halides.[19] At this point, it was very surprising to discover that the bidentate phosphine ligand dppe also can promote the reaction, affording the desired product in 78% yield (entry 9). A more electron-rich ligand, dcpe, gave a comparable yield (77%; entry 10), whereas the electron-deficient ligand dfppe was less effective (27%; entry 11). The optimal result was obtained when a fairly inexpensive ligand, dppf, was used (entry 12). We found that the use of a premade $Pd(OAc)_2$dppf complex gave the highest yield (90%; entry 15). No reaction occurred in the absence of $Pd(OAc)_2$ or dppf (entries 16 and 17) or when $Pd(OAc)_2$ was replaced with $Pd_2(dba)_3$ (entry 18).

With the optimized conditions in hand, we next examined the reaction scope (Table 2). Various cyclic and acyclic alkyl bromides (**1b**−**o**), except for cyclopropyl bromide (**1f**), underwent this transformation with **2a** to generate the desired products (**3ba**−**ea**, **3ga**−**oa**) in modest to good yields (44−88%). Importantly, NMR analysis of **3ga**−**oa**, **3ra**, and **3sa** showed that no rearrangement of the carbon skeleton took place when nonsymmetric substrates **1** were used. Also, many synthetically relevant functional groups, including ether (**3ia**, **3ja**), aldehyde (**3ja**), chloride (**3ka**), alkene (**3la**), and protected amines (**3ma**−**oa**) tolerated the reaction conditions. Interestingly, 3° alkyl bromides were smoothly converted in good yields (**3pa**, **3qa**), whereas 1° alkyl bromides exhibited relatively lower activity (**3ra**, **3sa**). Furthermore, the reactions of several pyridine

Table 2. Substrate Scope[a]



[a]Isolated yields. See the Supporting Information for details.

N-oxide derivatives **2b**−**g** with **1a** showed very high regioselectivity, as the alkylation occurred only at the position ortho to the *N*-oxide moiety (**3ab**−**ag**). Even in the case of substrate **2g** containing a pyridyl group, we did not observe the alkylation byproduct due to the directing effect of the pyridyl group.

To explore further the utility of the newly developed reaction for the synthesis of complex molecules, we tested the C−H alkylation of quinine *N*-oxide **2h** with **1a** (Scheme 2). The use of 1 equiv of **1a** was sufficient to generate the desired alkylation product in 82% yield. Neither the 3° amino nor terminal alkene group was affected by the alkylation reaction. Furthermore, we examined the cross-coupling of cinchonine *N*-oxide **2i** with 1-bromoadamantane (**1p**), which gave the desired product **3pi** in 74% yield. X-ray analysis of **3pi** confirmed that the structure of the cinchonine skeleton was fully maintained under the alkylation reaction conditions.

To study the stereochemistry of the C−H alkylation process, we took advantage of the fact that chiral 2° alkyl bromides can readily be prepared from the corresponding alcohols via S_N2 bromination.[25] Thus, 2° alkyl bromides **1t** and **1t′** were successfully synthesized from epiandrosterone and androsterone, respectively. When **1t** and **1t′** were reacted with **2a**, mixtures of two diastereomers in ratios of 1.0:2.6 and 1.0:1.9, respectively, were obtained (Scheme 3). Fortunately, the two isomers could

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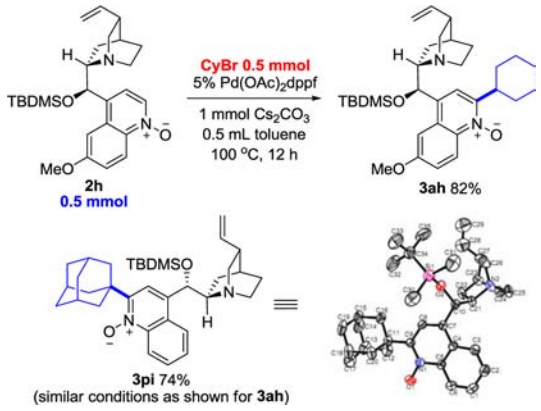
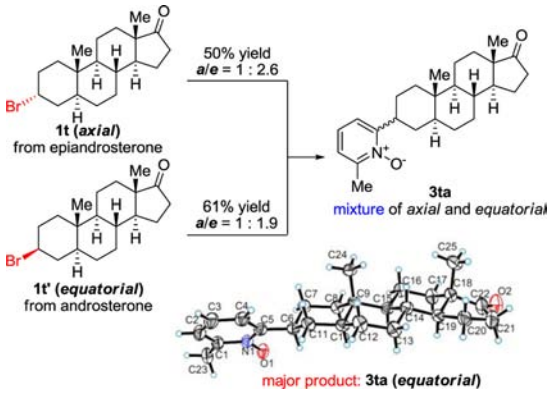
Scheme 2. Alkylation of Quinine/Cinchonine *N*-Oxides

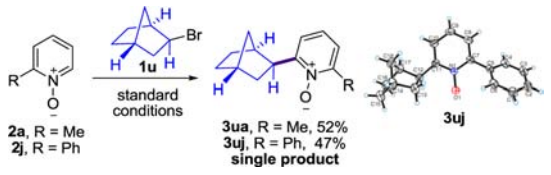


Scheme 3. Cross-Coupling with Steroid Substrates



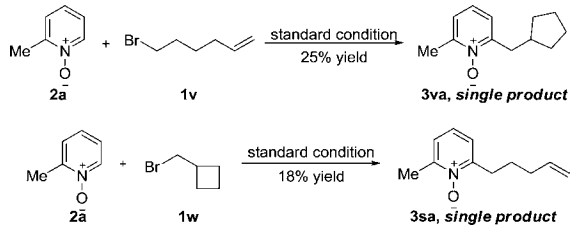
easily be separated by column chromatography. X-ray analysis of the major product revealed that the pyridyl group was placed at the equatorial position. Furthermore, in the cross-coupling of either **2a** or 2-phenylpyridine *N*-oxide (**2j**) with *exo*-2-bromonorbornane (**1u**), we obtained a single product (Scheme 4). X-ray analysis showed that these two reactions proceeded with retention of configuration.[26]

Scheme 4. Cross-Coupling with *exo*-2-Bromonorbornane



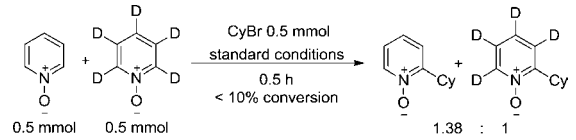
The above observations indicated that the new C−H alkylation reaction proceeds through a radical-type mechanism. This proposition distinguishes the present transformation from most of the previous Pd-catalyzed cross-coupling reactions of alkyl halides, which have been shown to proceed via an S_N2 process. The radical-type mechanism is also consistent with the observations in Table 2 that 3° alkyl halides can also undergo this reaction whereas 1° halides are less reactive. Further evidence for the radical-type mechanism was provided by the reaction of **2a** with 6-bromohex-1-ene (**1v**), where only the cyclopentylmethylated product was obtained (Scheme 5). Moreover, when (bromomethyl)cyclobutane (**1w**) was used, we obtained only the ring-opening product. These results hinted that the C−Br bond is activated (presumably with the help of Pd) through a

Scheme 5. Substrates Causing Cyclization and Ring Opening



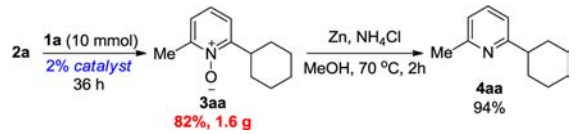
radical-type process. In an ^1H NMR experiment, we obtained a fairly low kinetic isotope effect of 1.38 (Scheme 6). More studies are needed to understand how the radical-type carbon−halide activation process is engaged in a Pd-catalyzed C−H functionalization reaction.

Scheme 6. Kinetic Isotope Effect



Finally, in a scale-up experiment, we successfully prepared **3aa** in gram quantity with a satisfactory yield of 82% (Scheme 7).

Scheme 7. Gram-Scale Synthesis and Reduction of *N*-Oxide



This gram-scale reaction could be carried out with a lower loading of Pd catalyst (2 mol %). Furthermore, **3aa** was easily reduced by Zn to produce the corresponding pyridine derivative, showing that the new C−H alkylation reaction is practically useful for the preparation of 2-alkylpyridines.

In summary, we have found an unexpected C−H activation/C−C cross-coupling reaction of pyridine *N*-oxides with non-activated secondary and even tertiary alkyl bromides. This reaction constitutes a rather rare example of Pd-catalyzed activation of ordinary 2° or 3° carbon−halide bonds. It shows good compatibility with many synthetically relevant functional groups and therefore provides a novel practical tool for the preparation of alkylpyridine derivatives. The reaction stereochemistry and the observation of cyclization or ring opening with particular substrates suggested that the C−Br bond cleavage may proceed through a hybrid organometallic-radical mechanism. The present results may indicate the existence of more opportunities for the use of Pd catalysts to handle 2° or even 3° aliphatic electrophiles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Recent reviews: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (g) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (h) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (i) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540. (j) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57. (k) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (l) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2009**, *110*, 624. (m) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.

(2) (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Bergman, R. G. *Nature* **2007**, *446*, 391. (c) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.

(3) Examples: (a) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194. (b) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (c) Chen, M. S.; White, M. C. *Science* **2007**, *327*, 566.

(4) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(5) Recent reviews of Pd-catalyzed C−H functionalization: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.; Lazareva, A. *Synlett* **2006**, 3382. (d) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (e) Sigman, M. S.; Werner, E. W. *Acc. Chem. Res.* **2012**, *45*, 874. (f) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (g) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (h) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987.

(6) Recent review of the use of C−H bond functionalization in natural product and drug synthesis: Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.

(7) Recent review of transition-metal-catalyzed C−H alkylation: Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866.

(8) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097.

(9) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(10) Zhao and Chen reported a related C−H alkylation reaction of 1° alkyl halides: Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850.

(11) (a) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990. (b) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563.

(12) There are also some examples of C−H alkylation of activated C−H bonds with 1° alkyl halides: (a) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647. (b) Yue, W.; Li, Y.; Jiang, W.; Zhen, Y.; Wang, Z. *Org. Lett.* **2009**, *11*, 5430.

(13) Recent reviews: (a) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.

(14) Previous examples of C−H functionalization of pyridine *N*-oxides: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (c) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (d) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (e) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (f) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (g) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888.

(15) (a) Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 4277. (b) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459.

(16) Sporadic examples of Pd-catalyzed C−H alkylation of inert C−H bonds with nonactivated 2° alkyl halides were previously reported. For example, Zhao and Chen[10] reported the C−H alkylation of a picolinamide derivative with i-PrI in 40% yield. Also, Catellani et al. reported a C−H alkylation with 2-bromopropane over 144 h: Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* **2000**, 157. These reactions have not been shown to be applicable to 2° alkyl halides with any generality.

(17) In the intramolecular Catellani reaction of 2° alkyl iodides, the domino process causes C−H bond functionalization of arenes in the final products: Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485.

(18) (a) With Ru catalyst: Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045. (b) Very recently, Hu and co-workers reported a Cu-catalyzed alkylation of benzoxazole C−H bonds with 2° alkyl halides: Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. *Org. Lett.* **2012**, *14*, 1748.

(19) Examples of Pd-catalyzed cross-coupling of nonactivated 1° alkyl electrophiles: (a) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (b) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945. (c) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910. (d) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (e) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642. (f) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527. (g) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340. (h) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718. (i) Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5079. (j) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616. (k) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056.

(20) For examples of Pd-catalyzed cross-coupling of *activated* 2° electrophiles, see ref 13a.

(21) Glorius and co-workers reported the first Pd/Cu co-catalyzed Sonogashira reaction of nonactivated 2° alkyl bromides: Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925. Whether Cu is necessary to promote the cross-coupling with nonactivated 2° alkyl bromides remains to be elucidated.

(22) Experimental evidence for the S_N2 mechanism of Pd-catalyzed cleavage of nonactivated 1° alkyl bromides and tosylates has been collected.[19c,g] A Pd-catalyzed alkyne insertion/Suzuki reaction of 1° alkyl iodides was also shown to proceed via an S_N2 mechanism: Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 15297.

(23) Very recently, Sigman and co-workers reported a Suzuki cross-coupling of homoallylic tosylates that occurred with inversion of configuration, suggesting the involvement of an S_N2 oxidative addition process: Stokes, B. J.; Opra, S. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11408.

(24) Recent studies by Alexanian and co-workers showed that nonactivated 2° alkyl iodides (but not 2° alkyl bromides) could undergo a Heck reaction through a radical-type mechanism: (a) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146. (b) Bloome, K. S.; Alexanian, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 12823.

(25) Goldenstein, K.; Fendert, T.; Proksch, P.; Winterfeldt, E. *Tetrahedron* **2000**, *56*, 4173.

(26) Similar results were observed in Ni-catalyzed cross-coupling reactions of 2° alkyl halides, where a radical-type mechanism was proposed: (a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340. (b) González-Bobes, F. *J. Am. Chem. Soc.* **2006**, *128*, 5360. (c) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788.