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Palladium-Catalyzed Picolinamide-Directed Alkylation of Unactivated C(sp^3)−H Bonds with Alkyl Iodides

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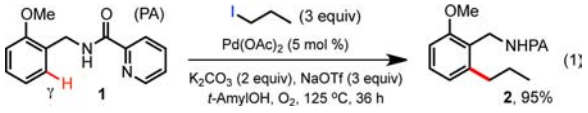
Supporting Information

ABSTRACT: We report an efficient method for the alkylation of γ-C(sp^3)−H bonds of picolinamide-protected aliphatic amine substrates with primary alkyl iodides via palladium catalysis. Ag_2CO_3 and dibenzyl phosphate, $(BnO)_2PO_2H$, are critical promoters of this reaction. These reactions provide a convenient and straightforward method for the preparation of high-value N-containing products from readily available amine and alkyl iodide precursors.

The metal-catalyzed coupling of unactivated sp^3-hybridized C−H bonds with alkyl halides remains one of the most difficult challenges in the C−H functionalization field.[1,2] Advances in this area could offer greatly simplified methods for the construction of C(sp^3)−C(sp^3) bonds from a large pool of readily accessible and economical starting materials.[3] Uniquely, palladium complexes have demonstrated the versatility both to facilitate the selective cleavage of C(sp^3)−H bonds and to effect cross-coupling with alkyl halides.[1] However, despite the progress made on Pd-catalyzed C(sp^2)−H alkylation reactions over the past decade,[4,5] alkylation of unactivated C(sp^3)−H bonds with alkyl halides has been much less advanced, and protocols with synthetic relevance are even rarer.[6,7] Herein we report our latest developments on Pd-catalyzed, picolinamide (PA)-directed alkylation of unactivated γ-C(sp^3)−H bonds of aliphatic amine substrates with primary alkyl iodides.

Over the past three years, our laboratory has pursued Pd-catalyzed C−H functionalization reactions directed by the PA group,[8] first introduced by the Daugulis laboratory in 2005.[9] Last year, we reported that the ortho γ-C(sp^2)−H bonds of PA-protected benzylamine substrates (e.g., **1**) can be alkylated with alkyl halides (e.g., *n*-PrI) under the catalysis of $Pd(OAc)_2$ (eq 1).[8b] In the course of our investigation, we found that

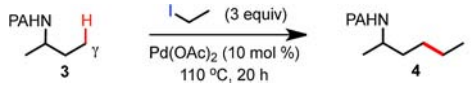


(1)

nucleophilic carboxylate ligands (e.g., OAc) quickly react with alkyl halide electrophiles to form ester side products, causing the premature termination of catalytic C−H alkylation.[4e] Gratifyingly, the desired alkylation reactions could be restored effectively with the application of K_2CO_3 as a base and NaOTf as an additive.[10] Encouraged by these results on ortho C(sp^2)−H alkylation, we proceeded to investigate whether the more inert γ-C(sp^3)−H bonds of PA-protected aliphatic amine substrates could be alkylated in a similar fashion.

Our initial attempt with aliphatic picolinamide substrate **3** and EtI failed to generate any desired product **4** under the original C(sp^2)−H alkylation conditions (Table 1, entry 1).

Table 1. Alkylation of γ-C(sp^3)−H Bonds with EtI



(2)

entry	additives (equiv)	solvent	yield of **4** (%)[a]
1	K_2CO_3 (2), NaOTf (3), O_2	*t*-AmylOH	<2
2	K_2CO_3 (2), air	toluene	7
3	AgOAc (2), air	toluene	<2
4	Ag_2CO_3 (1), air	toluene	16
5	Ag_2CO_3 (1), $PdCl_2$ (0.1)[b], air	toluene	12
6	Ag_2CO_3 (1), PivOH (0.2), air	*t*-AmylOH	6
7	Ag_2CO_3 (1), BINA-PO_2H[c] (0.2), air	*t*-AmylOH	18
8	Ag_2CO_3 (1), $(PhO)_2PO_2H$ (0.2), air	*t*-AmylOH	19
9	Ag_2CO_3 (1), $(BnO)_2PO_2H$ (0.2), air	*t*-AmylOH	23
10	Ag_2CO_3 (1), $(BnO)_2PO_2H$ (0.2), air	9:1 toluene/ *t*-AmylOH	26
11	Ag_2CO_3 (1), $(BnO)_2PO_2H$ (0.2), O_2	9:1 toluene/ *t*-AmylOH	23
12	Ag_2CO_3 (1), $(BnO)_2PO_2H$ (0.2), Ar	9:1 toluene/ *t*-AmylOH	40
13	Ag_2CO_3 (1), $(BnO)_2PO_2H$ (1), Ar	9:1 toluene/ *t*-AmylOH	41
14	Ag_2CO_3 (1), $(BnO)_2PO_2H$ (0.2), NaOTf (0.3), Ar	9:1 toluene/ *t*-AmylOH	<2
15	Ag_2CO_3 (1), $(BnO)_2PO_2H$ (0.2), NaI (0.3), Ar	9:1 toluene/ *t*-AmylOH	65 (60[d])
16	Ag_2CO_3 (1), $(BnO)_2PO_2H$ (0.2), LiCl (0.3), Ar	9:1 toluene/ *t*-AmylOH	48
17	Ag_2CO_3 (1), $(BnO)_2PO_2H$ (0.2), KI (1), Ar	9:1 toluene/ *t*-AmylOH	61
18	Ag_2CO_3 (1), NaI (0.3), Ar	9:1 toluene/ *t*-AmylOH	29
19	Ag_2CO_3 (2), $(BnO)_2PO_2H$ (0.2), Ar	*t*-AmylOH	12
20	Ag_2CO_3 (2), $(BnO)_2PO_2H$ (0.2), $CuCl_2$ (0.3), Ar	*t*-AmylOH	38

All of the screening reactions were carried out in a 10 mL glass vial on a 0.2 mmol scale. See the SI for more extensive screening results. [a]Based on GC−MS analysis of the reaction mixtures. [b]$Pd(OAc)_2$ was replaced with $PdCl_2$. [c](*S*)-(+)-1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate. [d]Isolated yield; ∼25% of **3** was recovered.

Received: December 19, 2012
Published: January 27, 2013

   dx.doi.org/10.1021/ja312277g | *J. Am. Chem. Soc.* 2013, 135, 2124−2127

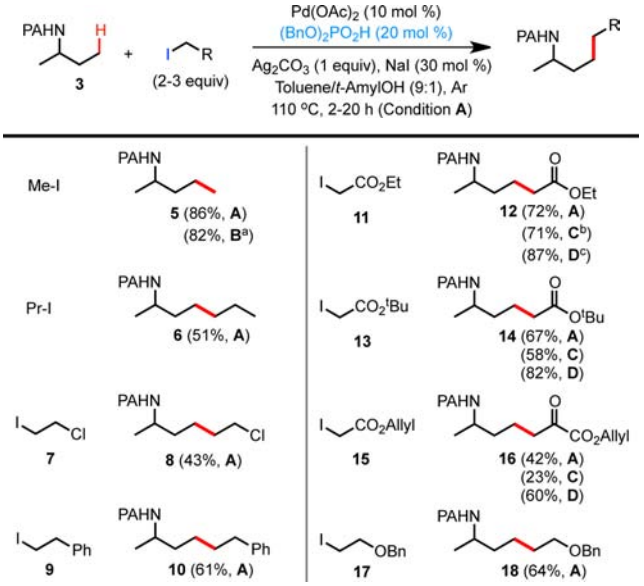
Interestingly, using simply 2 equiv of K_2CO_3 in toluene provided us with a promising starting point (entry 2). Despite the low yield, this result clearly demonstrated the feasibility of the desired C(sp^3)−H alkylation transformation. We next included Ag^+ salts, hoping that their I^- scavenging ability could improve the catalytic turnover and thus increase the conversion of **3**. Ag^+ ions might also facilitate the oxidative addition (OA) of alkyl iodides if an S_N2-type OA mechanism is operative.[11] Our subsequent survey revealed that Ag^+ salts do influence the reaction, and Ag_2CO_3 provided the best yield (16%; entry 4) [see the Supporting Information (SI) for more extensive screening results]. Interestingly, we found that the alkylation reaction could proceed, albeit to a smaller extent, when the $Pd(OAc)_2$ catalyst was replaced with $PdCl_2$, indicating that the carbonate ion from Ag_2CO_3 could also facilitate the PA-directed palladation of γ-C(sp^3)−H bonds (entry 8).[12] While Ag^+ ions could enhance the alkylation reaction, high concentrations of free Ag^+ ion might cause significant decomposition of the electrophile, presumably through an E2 elimination pathway.

To suppress such decomposition, we sought better control of the concentration of Ag^+ species in solution. In a recent report from the Toste laboratory,[13] organic phosphoric acids were applied as solid-to-solution phase-transfer catalysts (PTCs) for Ag_2CO_3.[14] Inspired by this study, we surveyed organic phosphate additives and found that use of a catalytic amount of organic phosphate (~20 mol %) did promote the C−H alkylation reaction. Simple dibenzyl phosphate $(BnO)_2PO_2H$, commercially available at low cost, was most effective (entry 9). In contrast with our previous C(sp^2)−H alkylation system, we found that O_2 has an inhibitory effect on the reaction and that an atmosphere of Ar provides better results (entries 10−12). The addition of NaOTf, which promotes C(sp^2)−H alkylation, instead shut down the reaction, whereas the addition of 30 mol % NaI or 1 equiv of KI improved the yield of the reaction by ~20% (entries 14−20; see the SI for more conditions).[15] Finally, a 60% isolated yield of **4** was obtained under the following conditions: 10 mol % $Pd(OAc)_2$, 20 mol % $(BnO)_2PO_2H$, and 30 mol % NaI in 9:1 toluene/*t*-AmylOH at 110 °C for 20 h (entry 15).

With the optimized conditions in hand, we then probed the scope of alkyl halides with substrate **3** (Table 2). A number of linear primary alkyl iodides, such as 2-chloroethyl iodide (**7**) and OBn-substituted ethyl iodide **17**, provided alkylated products in moderate to good yields under the standard conditions (**A**). Moreover, MeI and α-iodoacetic ester **11** were identified as two superior alkylating reagents that afforded the corresponding products in high yield. Methylation of **3** with MeI in the absence of the NaI additive (condition **B**; see **5**) gave a comparable yield. Efficient alkylation with **11** could also be achieved in the absence of NaI in *t*-AmylOH solvent (condition **C**; see **12**). Interestingly, the alkylation of **3** with other less effective α-iodoacetic esters (e.g., *tert*-butyl ester **13** and allyl ester **15**) could be notably improved with the application of 30 mol % $CuCl_2$ additive (condition **D**).[16] In general, we found that NaI is beneficial to alkylations with simple alkyl iodides in toluene/*t*-AmylOH, while $CuCl_2$ improves alkylations with α-iodoacetic esters in *t*-AmylOH.[17] The clean transformation of PA starting materials was observed in all of the above reactions; no N-alkylation product was formed, and unreacted PAs could be largely recovered.

The scope of PA substrates was examined next (Table 3). The primary γ-C(sp^3)−H bonds of a variety of PA-protected

Table 2. Evaluation of Alkyl Halides



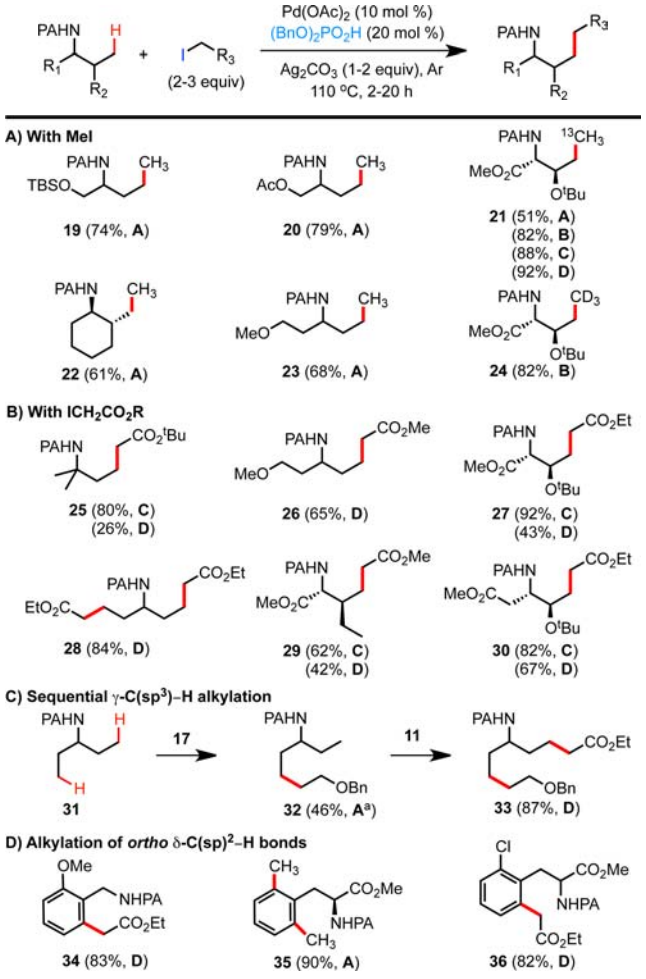
Reactions were run on a 0.2 mmol scale. Isolated yields are shown. [a]Condition **B** is similar to condition **A** except for the omission of 0.3 equiv of NaI (see Table 1, entry 12). [b]Condition **C** is similar to condition **B** except that 2 equiv of Ag_2CO_3 and *t*-AmylOH solvent are used (see Table 1, entry 19). [c]Condition **D** is similar to condition **C** except for the addition of 0.3 equiv of $CuCl_2$ (see Table 1, entry 20).

amine substrates, including protected threonine, alloisoleucine, and β-homothreonine, can be alkylated with MeI and α-iodoacetic esters in good to excellent yields under the standard conditions (see **21**, **27**, **29**, and **30**). The alkylation of threonine substrates could provide a convenient method for the synthesis of a variety of β-hydroxylated amino acids, which are found in many complex peptide natural products.[18] Methylation using inexpensive isotope-enriched $^{13}CH_3I$ and CD_3I could also provide a simple method for site-selective isotopic labeling of various amino acids, which is challenging by other means (e.g., **21** and **24**).[19] 3-Pentylamine picolinamide **31** bearing two equivalent γ-methyl groups could be bisalkylated with α-iodoacetic ester **11** to give **28**; **31** could also be monoalkylated with **17** to form **32**, and the remaining primary γ-C(sp^3)−H bond subsequently could be alkylated with **11** to give **33**. Furthermore, we found that ortho C(sp^2)−H bonds of benzylamine (see **34**) and even β-arylethylamine substrates (see **35** and **36**) could be alkylated in good yields. Under our previously reported Ag-free conditions, alkylation of the more remote δ-C(sp^2)−H bonds of **35** and **36** was unsuccessful.[8b]

In general, methylene 2° γ-C(sp^3)−H bonds are much less reactive than the 1° γ-C(sp^3)−H bonds of methyl groups in this reaction system; most of the substrates tested above were selectively monoalkylated at the γ-methyl position. However, we were surprised to observe that a 2° γ-C(sp^3)−H bond of *exo*-norbornene substrate **37** can be cleanly substituted with an isopropyl group to form **40** in 77% yield under the typical methylation conditions **B** with 5 equiv of MeI (Table 4).[20] We postulate that a 2° γ-C(sp^3)−H bond of **37** was first methylated to form **38**, which was then methylated twice at the δ-C(sp^3)−H position, providing the isopropyl product. A similar result was obtained using *endo*-norbornene substrate **41**. Moreover, substrate **45** could be selectively alkylated at the γ-methylene position to give either methyl- or ethyl-substituted product **46**

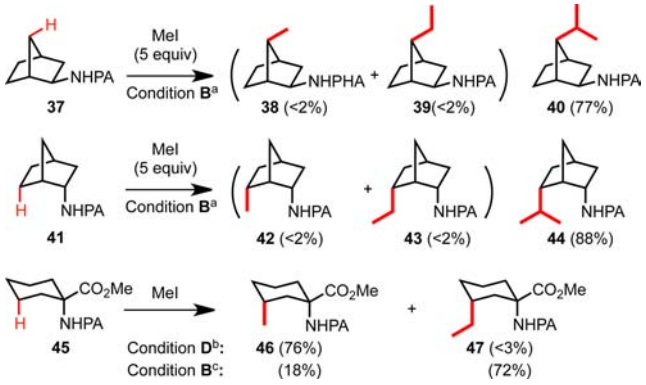
dx.doi.org/10.1021/ja312277g | J. Am. Chem. Soc. 2013, 135, 2124−2127

Table 3. Substrate Scope of the C−H Alkylation Reaction



Reactions were run on a 0.2 mmol scale. Isolated yields are shown. Conditions **A** and **B** use 9:1 toluene/*t*-AmylOH solvent (±NaI); conditions **C** and **D** use *t*-AmylOH solvent (∓$CuCl_2$). [a]~38% of the starting material **31** was recovered.

Table 4. Sequential C(sp^3)−H Methylation

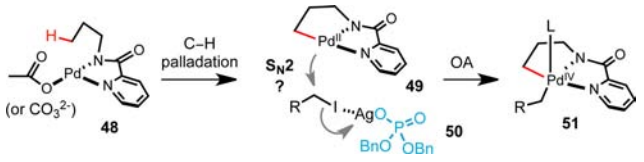


Reactions were run on a 0.2 mmol scale. Isolated yields are shown. [a]5 equiv of MeI and 2 equiv of Ag_2CO_3 were used. [b]3 equiv of MeI was used. [c]5 equiv of MeI was used.

or **47**, respectively, as the major product, depending on the reaction conditions (Table 4).

This Pd-catalyzed PA-directed C−H alkylation reaction likely proceeds through a C−H palladation/coupling sequence, and a $Pd^{II/IV}$ manifold might be operative (Scheme 1).[21] We

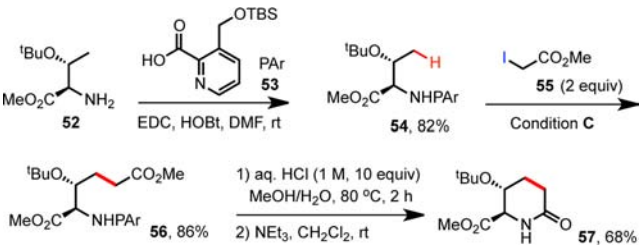
Scheme 1. Mechanistic Hypothesis



tentatively propose that palladacycle intermediate **49**, presumably generated from **48** via a concerted palladation/deprotonation mechanism,[22] undergoes OA with the alkyl iodide via an S_N2 mechanism, although a radical mechanism or Pd^{III} pathway[23] cannot be ruled out. Dibenzyl phosphate might work as a PTC, slowly bringing Ag^+ ions into the solution phase to activate the alkyl iodide.[24] The functional roles of the NaI and $CuCl_2$ additives are not known at present.[15,16]

A more easily removable PA auxiliary (**53**)[8a] can be employed in this C−H alkylation reaction system (Scheme 2). For example, threonine methyl ester **52** was equipped with

Scheme 2. Facile Synthesis of 2-Piperidinone



auxiliary **53** by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)-mediated amide coupling. The resulting substrate **54** was then alkylated with **55** under standard conditions (**C**) in excellent yield. The auxiliary group of **56** was then removed in HCl(aq)/MeOH solution to give a free amine intermediate, which cyclized in CH_2Cl_2 at room temperature to form 5,6-disubstituted piperidinone **57**.[25]

In summary, we have developed a new set of readily applicable Pd-catalyzed reactions to alkylate unactivated, remote C(sp^3)−H bonds of picolinamide-protected aliphatic amines with primary alkyl iodides. The reactions require Ag_2CO_3 and a newly identified organic phosphate promoter, $(BnO)_2PO_2H$. In particular, the use of MeI and *α*-iodoacetic esters provides an efficient and straightforward method for preparing high-value N-containing products from readily available precursors.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. 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.

■ ACKNOWLEDGMENTS

We thank The Pennsylvania State University, NSF (CAREER CHE-1055795), and ACS-PRF (51705-DNI1) for financial support of this work.

■ REFERENCES

(1) For selected reviews of C−H alkylations, see: (a) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814.

(2) For selected reviews of C(sp^3)−H functionalizations, see: (a) Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083. (b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (c) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992.

(3) For selected reviews of cross-coupling of alkyl halides, see: (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (c) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

(4) For selected examples of Pd-catalyzed alkylation of C(sp^2)−H bonds, see: (a) Tremont, S. J.; Rahmen, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119. (c) Hennessy, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084. (d) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (e) Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097. (f) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160. (g) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360. (h) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990.

(5) For selected examples of C(sp^2)−H alkylation catalyzed by other metals, see: (a) Murai, S.; Kakiuchi, S.; Sekine, S.; Tanaka, A.; Kamatani, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045. (c) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332. (d) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061. (e) Dieu, L.; Daugulis, O. *Org. Lett.* **2010**, *12*, 4277. (f) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428.

(6) For a recent report on an elegant C(sp^3)−H alkylation reaction, see: Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(7) (a) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (b) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (d) Young, A. J.; White, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (e) Feng, Y.; Chen, G. *Org. Lett.* **2010**, *49*, 958.

(8) (a) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (b) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. (c) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (d) Zhang, S.-Y.; He, G.; Zhao, Y.-S.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (e) He, G.; Lu, C.-X.; Zhao, Y.-S.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944. (f) Zhao, Y.-S.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2948.

(9) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 7.

(10) The addition of NaOTf is necessary to obtain high yields; its functional role remains elusive. Both Na^+ and OTf^- ions could play an active role in the reaction system.

(11) (a) Reference 4a. (b) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83. (c) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434. For discussion of S_N2-type OAs of alkyl halides to other metal complexes, see: (d) Labinger, J. A.; Braus, R. J.; Dolphin, D.; Osborn, J. A. *Chem. Commun.* **1970**, 612. (e) Ellis, P. R.; Pearson, J. M.; Haynes, A.; Adams, H.; Bailey, N. A.; Maitlis, P. M. *Organometallics* **1994**, *13*, 3215.

(12) For a recent example of carbonate-promoted Pd-catalyzed C(sp^3)−H functionalization, see: Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J. L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157.

(13) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984.

(14) For two recent applications of organic phosphate ligands in Pd-catalyzed reactions, see: (a) Jiang, G.; Halder, R.; Fang, Y.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9752. (b) Chai, Z.; Rainey, T. J. *J. Am. Chem. Soc.* **2012**, *134*, 3615.

(15) Cations (e.g., Na^+, K^+, and even H^+) might play a useful role in this PA-directed C−H functionalization reaction. The relatively high solubility of NaI and KI in toluene/*t*-AmylOH could allow the metal cations to be readily introduced into the reaction system. We suspect that the cations might interact with the O atom of the PA group, which might adopt an iminol type of binding mode with Pd^{II}. Similar cation promoting effects have been observed in several Pd-catalyzed amide-directed C−H functionalization reactions. For an elegant mechanistic investigation on related reaction systems, see: (a) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948. For a strong promoting effect from LiCl, see: (b) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984.

(16) The functional role of the $CuCl_2$ additive is unclear. Besides a possible interaction with the PA directing group, its weak Lewis acidity could also activate the α-iodoester electrophile.

(17) The effect of the $CuCl_2$ additive appears to be more substrate-dependent (see **27**, **29**, and **30**).

(18) Boger, D. L. *Med. Res. Rev.* **2001**, *21*, 356.

(19) Gruhler, S.; Kratchmarova, I. *Methods Mol. Biol.* **2008**, *424*, 101.

(20) A small amount of further methylated product was observed when the NaI additive was used under condition **A**.

(21) For selected reviews of Pd^{IV} chemistry, see: (a) Sehnal, P.; Taylor, R. J.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824. (b) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177.

(22) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118.

(23) (a) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234.

(24) The phosphate ion might play an active role during the OA step; for instance, it might act as a weakly coordinating anion for Pd intermediates (e.g., **49** or **51**; see ref 14a for an isolated Pd^{II} complex containing a phosphate ligand).

(25) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.