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

Shu-Yu Zhang, Gang He, William A. Nack, Yingsheng Zhao, Qiong Li, and Gong Chen*

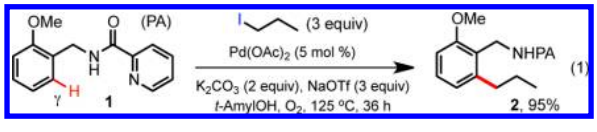
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, United States

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.

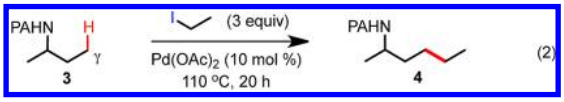
Over the past three years, our laboratory has pursued Pd-catalyzed C−H functionalization reactions directed by the PA group,[8] first introduced by the Daugulis laboratory in 2005.[9] Last year, we reported that the ortho γ-C(sp^2)−H bonds of PA-protected benzylamine substrates (e.g., **1**) can be alkylated 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



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



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.

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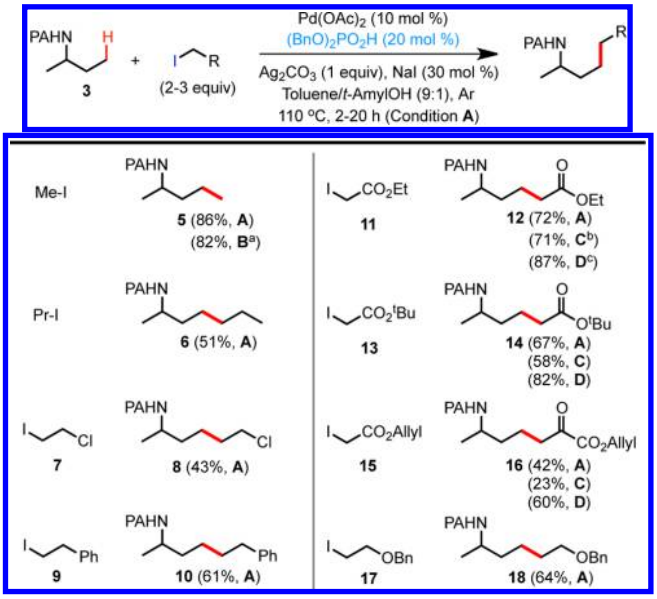
Interestingly, using simply 2 equiv of K_2CO_3 in toluene provided us with a promising starting point (entry 2). Despite the low yield, this result clearly demonstrated the feasibility of the desired C(sp^3)−H alkylation transformation. We next included Ag^+ salts, hoping that their I^- scavenging ability 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**

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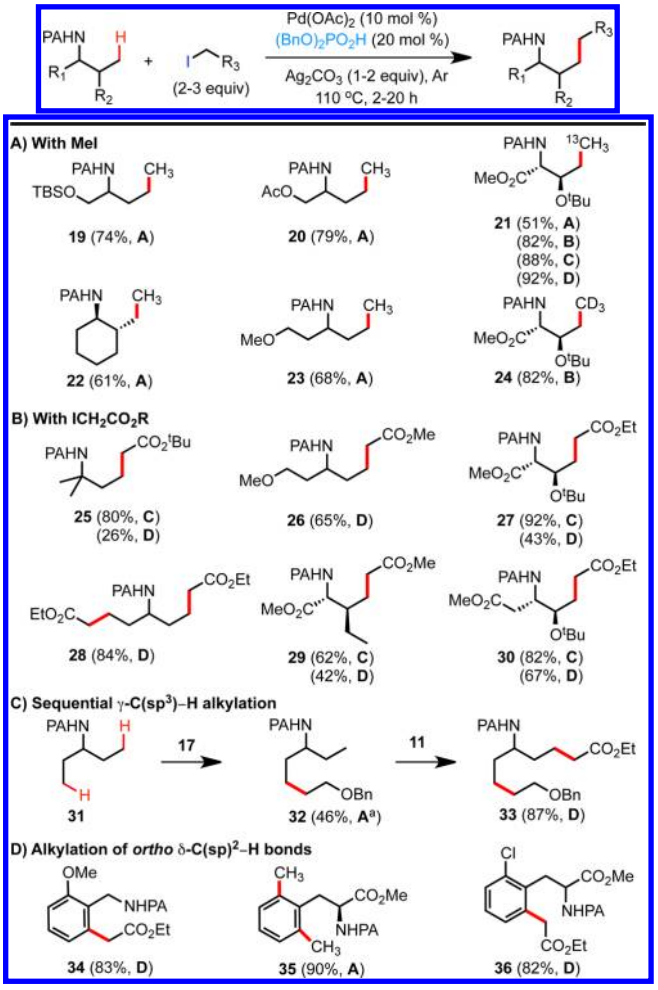
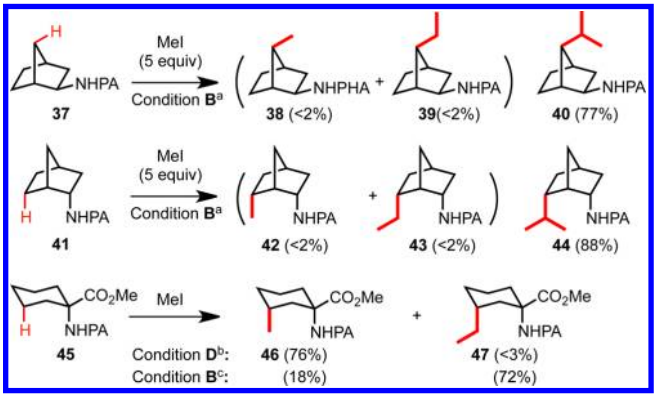
Table 3. Substrate Scope of the C−H Alkylation Reaction



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

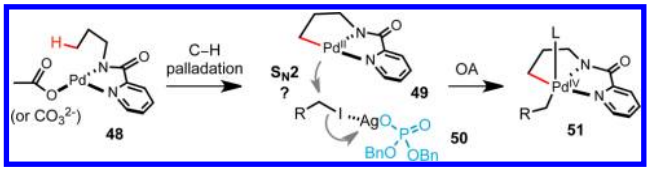


Reactions were run on a 0.2 mmol scale. Isolated yields are shown. [a]5 equiv of MeI and 2 equiv of Ag_2CO_3 were used. [b]3 equiv of MeI was used. [c]5 equiv of MeI was used.

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

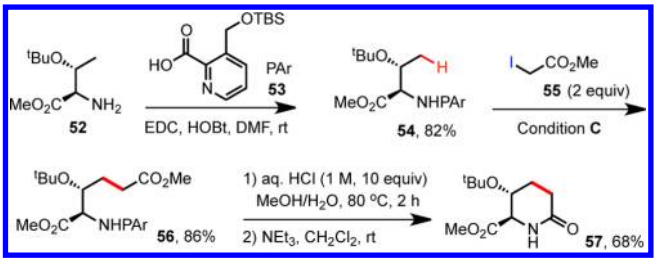
Scheme 1. Mechanistic Hypothesis



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.

■ AUTHOR INFORMATION

Corresponding Author

guc11@psu.edu

Notes

The authors declare no competing financial interest.

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(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**).

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(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).

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