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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Efficient Alkyl Ether Synthesis via Palladium-Catalyzed, Picolinamide-Directed Alkoxylation of Unactivated C(sp^3)−H and C(sp^2)−H Bonds at Remote Positions

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

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

Supporting Information

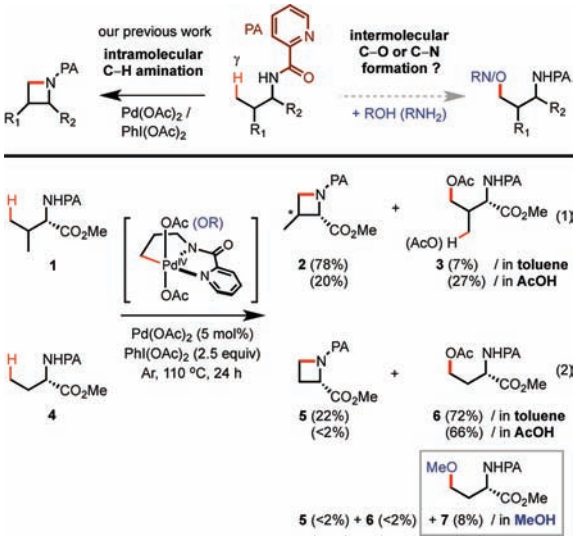
ABSTRACT: We report the efficient synthesis of alkyl ethers by the functionalization of unactivated sp^3- and sp^2-hybridized C−H bonds. In the Pd(OAc)$_2$-catalyzed, PhI(OAc)$_2$-mediated reaction system, picolinamide-protected amine substrates undergo facile alkoxylation at the γ or δ positions with a range of alcohols, including *t*-BuOH, to give alkoxylated products. This method features a relatively broad substrate scope for amines and alcohols, inexpensive reagents, and convenient operating conditions. This method highlights the emerging value of unactivated C−H bonds, particularly the C(sp^3)−H bond of methyl groups, as functional groups in organic synthesis.

A fundamental challenge in organometallic and synthetic chemistry is the development of broadly applicable methods for the catalytic functionalization of C−H bonds, particularly unactivated sp^3-hybridized C−H bonds.[1−3] Over the last two decades, C−H functionalization methods have been considerably advanced in the area of C−C bond formation. In parallel, the development of C−O bond formation reactions has greatly accelerated in recent years following landmark reports on Pd-catalyzed C(sp^3)−H acetoxylation reactions by the Sanford[4] and Yu[5] laboratories using different organic oxidants.[6−9] Despite the success of C−H oxygenation methods, C−H alkoxylation reactions remain scarce; existing reports have been limited to the directed ortho alkoxylation of the C(sp^2)−H bonds of arenes.[10] Organometallic research has yet to yield a viable method for alkyl ether formation via the alkoxylation of truly unactivated C(sp^3)−H bonds.[11]

Ether moieties are ubiquitous in natural products and pharmaceuticals.[12] Although powerful, the conventional ether syntheses (e.g., the Williamson and Mitsunobu reactions) have innate shortcomings, particularly in the preparation of complex alkyl alkyl ethers.[13] Thus, a number of other creative ether synthesis methods have emerged in the past decade, and new methods are still in great demand.[14−16] Herein we describe a highly efficient method for the synthesis of alkyl ethers via Pd-catalyzed, picolinamide (PA)-directed alkoxylation of unactivated C(sp^3)−H and C(sp^2)−H bonds at remote positions using alcohols.

Over the past three years, our laboratory has been engaged in developing synthetically useful methods based on Pd-catalyzed C−H functionalization reactions.[17] The PA group, first introduced by the Daugulis laboratory in 2005,[18] has demonstrated excellent directing abilities that enable a range of transformations, including arylation, alkenylation, and alkylation of γ-C(sp^3)−H bonds. More recently, we demonstrated the efficient synthesis of azetidine, pyrrolidine, and indoline by intramolecular amination of remote C−H bonds (Scheme 1).[19] An illustrative example is valine substrate **1**, which is readily cyclized at the γ position to form the four-membered azetidine product **2** (eq 1 in Scheme 1).

Scheme 1. Pd-Catalyzed, PA-Directed Functionalization of γ-C(sp^3)−H Bonds



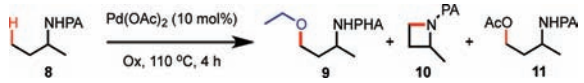
In the course of investigating this C−H amination reaction system, we made the intriguing observation of acetoxylated side products. Substrate **1** provides a small amount of acetoxylated product **3** under standard amination conditions in toluene; substrate **4** yields more acetoxylated product **6** than azetidine **5** (eq 2 in Scheme 1). When AcOH is used as the solvent, acetoxylation becomes the major reaction pathway, with substrate **1** yielding acetoxylated **3** as the major product and substrate **4** yielding acetoxylated **6** as the sole product. The mechanistic rationale for the effect of the substrate β-substituent on product distribution is currently being investigated.[20] We also observed that the concentration of

Received: March 11, 2012
Published: April 9, 2012

   dx.doi.org/10.1021/ja3023972 | *J. Am. Chem. Soc.* 2012, 134, 7313−7316

OAc ligands in solution affects the reaction pathway and thus the product distribution. When considered with our working mechanistic model,[19] this suggests that the OAc ligand can dissociate from the speculated Pd^{IV} intermediate following the $PhI(OAc)_2$ oxidation of the Pd^{II} palladacycle.[21−23] This speculation led us to investigate whether other nucleophilic reagents such as alcohols or amine compounds could be used to replace the coordinated OAc ligand; presumably, the subsequent reductive elimination (RE) of C−OR and C−NR could afford intermolecularly alkoxylated or aminated products. To evaluate the viability of this approach, we carried out the C−H functionalization reaction of **4** in MeOH solvent but under otherwise standard conditions (5 mol % $Pd(OAc)_2$, 2.5 equiv of $PhI(OAc)_2$, 110 °C, Ar atmosphere). We were delighted to observe the formation of the desired methoxylated product **7** as the major product, albeit in low yield. Encouraged by this initial finding, we commenced a systematic screening of alkoxylation conditions for substrate **8** and ethanol (Table 1).[23]

Table 1. Pd-Catalyzed, PA-Directed Ethoxylations of γ-C(sp^3)−H Bonds[a]



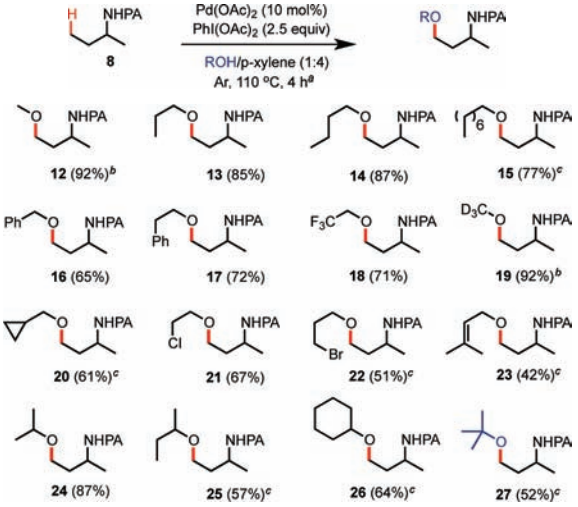
Entry	Additive (equiv)	Solvent /atmosphere	Yield (%)[b] 9	10	11
1	AgOAc (2)	EtOH, air	<2	<2	<2
2	Oxone (2)	EtOH, air	<2	<2	<2
3	$Ce(SO_4)_2$ (2)	EtOH, air	<2	<2	<2
4	$K_2S_2O_8$ (2)	EtOH, air	<2	<2	<2
5	F(+) (2)[c]	EtOH, air	<2	<2	<2
6	$PhI(OAc)_2$ (2)	EtOH, air	6	<2	<2
7	$PhI(OAc)_2$ (5)	EtOH, air	8	<2	<2
8	$PhI(OAc)_2$ (2.5)	EtOH/toluene (1:1), air	18	<2	<2
9	$PhI(OAc)_2$ (2.5)	EtOH/THF (1:1), air	<2	<2	<2
10	$PhI(OAc)_2$ (2.5)	EtOH/DCE (1:1), air	<2	<2	<2
11	$PhI(OAc)_2$ (2.5)	EtOH/AcOH (1:1), air	8	<2	<2
12	$PhI(OAc)_2$ (2.5)	EtOH/cyclohexane (1:1), air	16	<2	<2
13	$PhI(OAc)_2$ (2.5)	EtOH/DMF (1:1), air	<2	<2	<2
14	$PhI(OAc)_2$ (2.5)	EtOH/CH_3CN (1:1), air	<2	<2	<2
15	$PhI(OAc)_2$ (2.5)	EtOH/p-xylene (1:1), air	26	<2	<2
16	$PhI(OAc)_2$ (2.5)	EtOH/o-xylene (1:1), air	24	<2	<2
17	$PhI(OAc)_2$ (2.5)	EtOH/mesitylene (1:1), air	12	<2	<2
18	$PhI(OAc)_2$ (2.5)	EtOH/p-xylene (1:10), air	52	<2	<2
19	$PhI(OAc)_2$ (2.5)	EtOH/p-xylene (1:4), air	63	<2	<2
20	$PhI(OAc)_2$ (2.5)	EtOH/p-xylene (1:4), O_2	34	<2	<2
21	$PhI(OAc)_2$ (2.5)	EtOH/p-xylene (1:4), Ar	92[d]	<2	<2
22	$PhI(OPiv)_2$ (2.5)	EtOH/p-xylene (1:4), Ar	82	<2	<2
23	$PhI(OTFA)_2$ (2.5)	EtOH/p-xylene (1:4), Ar	<2	<2	<2
24	$PhI(OAc)_2$ (1.5)	EtOH/p-xylene (1:4), Ar	49	<2	<2
25[e]	$PhI(OAc)_2$ (2.5)	EtOH/p-xylene (1:4), Ar	76	<2	<2

[a]The screening reactions were carried out in a 10 mL glass vial with a PTFE-lined cap on a 0.2 mmol scale ([**8**] ≈ 0.1 M). The reaction vial was purged with gas (1 atm) and then sealed. [b]^{1}H NMR yields (see the Supporting Information). [c]1-Fluoro-2,4,6-trimethylpyridinium triflate. [d]Isolated yield. [e]5 mol % $Pd(OAc)_2$ was used.

In EtOH solvent, $PhI(OAc)_2$ proved to be the only effective oxidant, yielding the alkoxylated product **9** in 6% yield along with >80% unreacted **8** (entry 6). Use of a larger excess (5 equiv) of $PhI(OAc)_2$ resulted in little improvement (entry 7). Our previous observation of pronounced solvent effects in the C−H amination reaction system motivated us to examine the solvent dependence of the reaction using various solvents mixed 1:1 with EtOH. Strongly coordinating solvents such as DMF, dioxane, and CH_3CN did not promote the desired alkoxylation reaction, while noncoordinating solvents provided markedly higher yields. Xylene/EtOH mixtures stood out as the best-performing solvents (entries 15 and 16). Increasing the proportion of xylene in the mixture to 4:1 improved the yield of **9** to 63% (entry 19). Finally, we were pleased to obtain **9** in excellent yield (92%) by conducting the reaction under an Ar atmosphere (entry 21). Interestingly, O_2 seemed to inhibit the desired C−H alkoxylation reaction, resulting in a significantly diminished yield (entry 20); this contrasts with our C−H alkylation reaction, in which O_2 has a promoting effect.[17c] We suspect that O_2 binds to the palladacycle intermediate, hampering the subsequent $Pd^{II/IV}$ oxidation by $PhI(OAc)_2$.[24]

Using the optimized reaction conditions (Table 1, entry 21), we then explored the alcohol substrate scope of this C−H alkoxylation reaction (Table 2). Subject to variance in molecular weight, 20−50 equiv of alcohol was typically applied. Unsubstituted 1° alcohols, including MeOH, *n*-PrOH, and even the alcohol precursor to **15** bearing a long alkyl chain, provided good to excellent yields. BnOH and CF_3CH_2OH also gave the corresponding BnO and CF_3CH_2O ethers **16** and **18** in good yields. The reaction tolerates a range of functional groups, including halogens, cyclopropanes, esters, and alkenes (**20**−**23**). Alkoxylation using 2° alcohols proceeds well with additional reaction time (12 h) (**24**−**26**). Even *t*-BuOH provided a moderate yield of *tert*-butyl ether product **27**. Interestingly, no cyclization or alkoxylation reaction occurred when *t*-BuOH alone was used as the solvent.[25]

Table 2. Substrate Scope of Alcohols



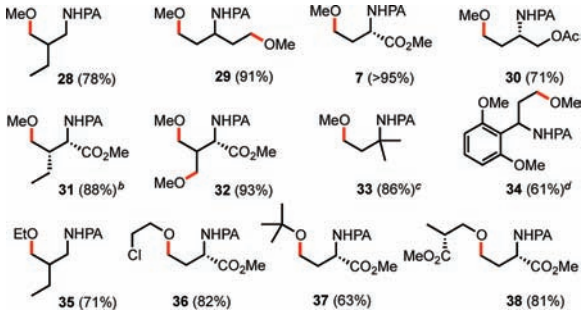
[a]Standard reaction conditions for C−H alkoxylation (4 h). Isolated yields are shown. [b]2 h. [c]12 h.

The reaction system tolerates a variety of picolinamide substrates (Table 3). In general, substrates bearing 1° γ-C(sp^3)−H groups (with or without α-substitutents) were readily methoxylated (**28**−**30**). A bismethoxylated product was obtained in excellent yield when two γ-methyl groups were present (**32**). Products **28**, **31**, and **35** demonstrate a high regiopreference for 1° over 2° γ-C(sp^3)−H bonds. No δ-alkoxylated products were observed. Notably, under our optimized C−H alkoxylation conditions, the C−H amination reaction pathway is greatly suppressed and little amination product is generated. Excellent yields of **31** and **32** were obtained despite the particularly facile cyclization of the corresponding picolinamides under amination conditions.

Encouraged by the successful alkoxylation of γ-C(sp^3)−H bonds, we then investigated whether this C−H alkoxylation reaction can be used to functionalize C(sp^2)−H bonds of

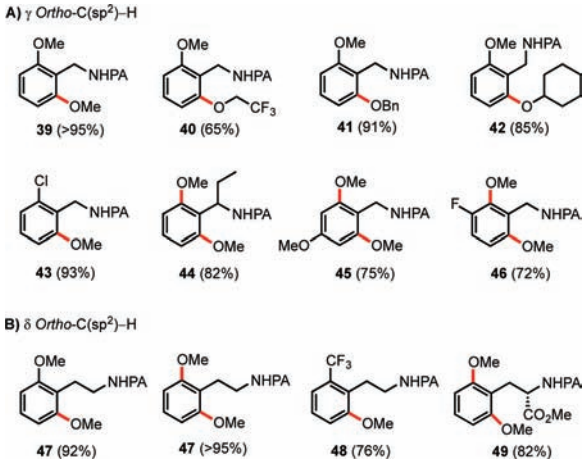
dx.doi.org/10.1021/ja3023972 | J. Am. Chem. Soc. 2012, 134, 7313−7316

Table 3. Substrate Scope of Picolinamides and Alcohols[a]



[a]The standard reaction conditions were used. Isolated yields are shown. [b]MeOH/toluene (1:1) was used as the solvent. [c]MeOH/AcOH (1:1) was used as the solvent. [d]4 equiv of $PhI(OAc)_2$ was used.

Scheme 2. Alkoxylation of *o*-C(sp²)−H Bonds of Arenes[a]

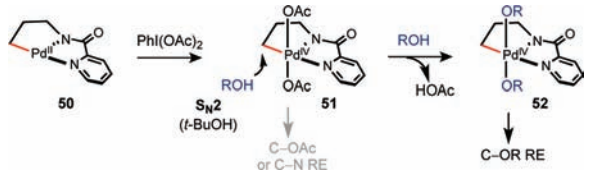


[a]The standard reaction conditions with 2.5 equiv of $PhI(OAc)_2$ were used for all of the bisalkoxylation reactions, and 1.5 equiv of $PhI(OAc)_2$ was used for all of the monoalkoxylation reactions.

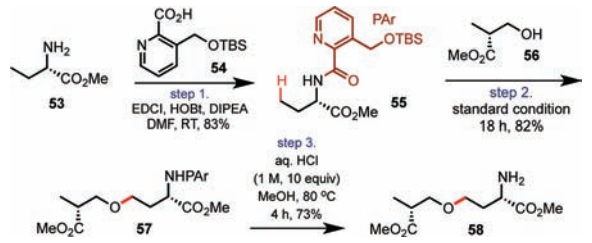
arenes. As shown in Scheme 2A, the γ-*o*-C−H bonds of benzylpicolinamides can be readily replaced with a variety of alkoxyl groups. Both electron-rich and electron-deficient substrates provide good to excellent yields of aryl ether products. Only 1.5 equiv of $PhI(OAc)_2$ is required for monoalkoxylation, compared with 2.5 equiv under the standard C(sp³)−H alkoxylation conditions. Substrates with two *o*-C−H bonds yield bismethoxy products with 2.5 equiv of $PhI(OAc)_2$ (e.g., **45** and **46**). This reactivity is also observed in benzylamine substrates bearing α-benzylic substituents, demonstrating a regiopreference for C(sp²)−H over C(sp³)−H (**44**). Additionally, β-arylethylamine substrates can be alkoxylated at the δ-*o*-C−H position under the standard reaction conditions (Scheme 2B). For instance, a protected phenylalanine substrate was bismethoxylated in high yield (**49**). Cyclization products were not observed, again indicating that the previously dominant intramolecular C−H amination pathway in toluene solvent is completely diverted toward alkoxylation under the new reaction conditions.

The detailed mechanism for this Pd-catalyzed, $PhI(OAc)_2$-mediated C−H alkoxylation reaction has not been firmly established. We speculate that palladacycle **50** is first generated and then oxidized to form Pd^{IV} intermediate **51**, which can undergo RE to form either C−N or C−OAc products (Scheme 3). In the presence of alcohol cosolvent, the OAc ligands of **51**

Scheme 3. Plausible Mechanism



Scheme 4. Facile Removal of the PA Auxiliary



could be displaced to form Pd^{IV} intermediate **52**, which could undergo C−OR RE to give alkoxylated products.[26,27] Formation of alkoxylated products could also be explained by an alternative S_N2 pathway, but this is likely inoperative since the use of non-nucleophilic *t*-BuOH also affords the alkoxylated product.[28] The role of xylene solvent in promoting the alkoxylation reaction pathway is still under investigation.[29]

To enhance the synthetic utility of Pd-catalyzed, PA-directed C−H functionalization chemistry, we previously introduced a modified PA auxiliary **54**, which can be cleaved under relatively mild conditions (Scheme 4).[17b,c] This auxiliary can be readily employed in the C−H alkoxylation reaction system. For example, amino acid substrate **53** was equipped with the auxiliary using a standard amide coupling. The resulting substrate **55** was then alkoxylated by our method with (−)-Roche ester **56** (~18 equiv). The PAr group of **57** was then cleanly removed in aqueous HCl/MeOH solution to give the complex amine product **58** in good yield.

In summary, we have developed a highly efficient method for the synthesis of alkyl ethers via Pd-catalyzed intermolecular alkoxylation of truly unactivated γ-C(sp³)−H and *o*-C(sp²)−H bonds at the γ and δ positions of picolinamide substrates using a wide range of alcohols. With a simple change of reaction solvent, the previously established intramolecular C−H amination reaction pathway is cleanly diverted to intermolecular C−H alkoxylation, forming alkyl ether products. This reaction features a broad substrate scope, inexpensive reagents, and convenient operating conditions. We are currently engaged in more detailed mechanistic studies, the application of this methodology to the synthesis of complex molecules, and the pursuit of intermolecular C−H amination reactions.

■ 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.

dx.doi.org/10.1021/ja3023972 | J. Am. Chem. Soc. 2012, 134, 7313−7316

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support by The Pennsylvania State University and NSF (CAREER CHE-1055795).

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(23) EtOH is a more challenging coupling partner than MeOH, presumably because of available β-elimination pathways that generate undesired side products.

(24) Similar inhibition by O_2 was observed in Pd-catalyzed intramolecular C−H amination of β-arylethylamine picolinamide substrates. More detailed studies will be published elsewhere.

(25) Arylation of **8** with ArI (1.5 equiv) under our previously reported γ-C−H arylation conditions [10 mol % $Pd(OAc)_2$, Ag_2CO_3 (1 equiv), *t*-BuOH, 80 °C, 12 h] proceeds smoothly to give the arylated product in good yield.[17b] This suggests that C−H palladation of **8** can readily occur in *t*-BuOH at 80 °C (see the SI).

(26) Studies of related C−OR REs from other hypervalent metal complexes: (a) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576. (b) Han, R. Y.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135. (c) Vedernikov, A. N. *Acc. Chem. Res.* **2012**, DOI: 10.1021/ar200191k.

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(28) For discussion of the S_N2 pathway, see refs 4a and 10b.

(29) Our data suggest that xylene promotes the $PhI(OAc)_2$-mediated oxidation step to form Pd^{IV} intermediate **51**. Detailed studies of the solvent effect will be published elsewhere.