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Palladium-Catalyzed Alkylation of *ortho*-C(sp^2)–H Bonds of Benzylamide Substrates with Alkyl Halides

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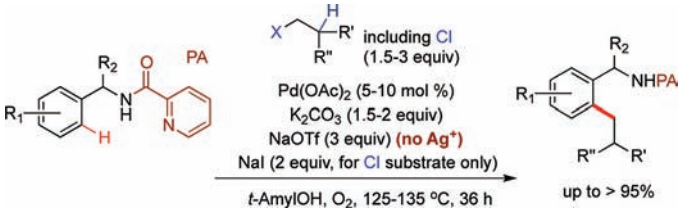
ABSTRACT



A highly efficient and generally applicable method has been developed to functionalize the *ortho*-C(sp^2)–H bonds of picolinamide (PA)-protected benzylamine substrates with a broad range of β-H-containing alkyl halides. Sodium triflate has been identified as a critical promoter for this reaction system. The PA group can be easily installed and removed under mild conditions. This method provides a new strategy to prepare highly functionalized benzylamines for the synthesis of complex molecules.

Synthetic methods based on the catalytic arylation of C–H bonds of arenes and heteroarenes have become readily available in the past decade.[1] The development of C–H alkenylation of arenes is also rapidly advancing.[2] In keeping with this trend, C–H alkylation reactions, especially using easily accessible alkyl halides, represents the next significant challenge in the C–H activation field.[3] Despite difficulties associated with the inherent resistance of alkyl halides toward oxidative addition and the tendency toward β-H elimination,[4] several metal-catalyzed C–H alkylation reactions have emerged during the past few years.[5–9] However, in order to move this C–H alkylation conceppt into the mainstream of organic synthesis, many features of these reaction systems need to be significantly improved, including broader arene and alkyl

(1) For selected reviews on C–H arylation reactions of arene and heteroarenes, see: (a) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253–1264. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (d) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169.

(2) For selected examples of C–H alkenylation reactions, see: (a) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587. (b) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156–4157. (c) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666–7673. (d) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972–1975. (e) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315–319.

(3) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877.

(4) (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (b) Rudolph, A; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670.

(5) For selected examples of Pd-catalyzed C–H alkylation reactons, see: (a) Tremont, S. J.; Rahmen, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759–5760. (b) Hennessy, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084–12085. (c) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78–79. (d) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485–1488. (e) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158–16159. (f) Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097–6100. (g) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160–4263. (h) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972. (i) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360–1363.

(6) For selected examples of Ru-catalyzed C–H alkylation reactons, see: (a) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048. (b) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1977.

(7) For a selected example of the Ni-catalyzed C–H alkylation reacton, see: Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061–3064.

(8) For a selected example of the Cu-catalyzed C–H alkylation reacton, see: Dieu, L.; Daugulis, O. *Org. Lett.* **2010**, *12*, 4277–4279.

(9) For a selected example of the Co-catalyzed C–H alkylation reacton, see: Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428–429.

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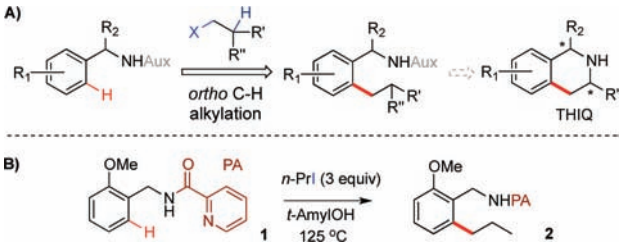
halide substrate scope, use of low-cost catalysts and reagents, and convenient and mild operating conditions (e.g., no strong bases or acids).[10] Herein, we report a highly efficient and generally applicable method to selectively functionalize the *ortho*-C−H bonds of benzyl picolinamide substrates with a broad range of β-H-containing alkyl halides under palladium-catalyzed conditions.

The chemistry of Pd-catalyzed picolinamide (PA)-directed arylation of C(sp^3)−H bonds with aryl halides was first introduced in a seminal paper by Daugulis in 2005.[11] Our recent reinvestigation of this system has significantly expanded the substrate scope and improved the synthetic utility of this chemistry.[12] Prompted by this success, we wanted to explore whether the PA directing group could also facilitate the C−H alkylation reactions with alkyl halides.[13] Because of the γ-regioselectivity controlled by the five-membered palladacycle intermediate, we expected that *ortho*-C−H bonds of benzylamides could be selectively functionalized to provide the corresponding *ortho*-alkylated benzylamides, which could then be readily transformed to privileged structures such as the tetrahydroisoquinoline (THIQ) scaffolds (Table 1A).[14]

Table 1. Pd-Catalyzed C(sp^2)−H Alkylation Reactions[a]



entry	catalysis (mol%)	additive (equiv)	atmosphere	time (h)	yield[b] (%)
1	$Pd(OAc)_2$ (10)	AgOAc (1)	Air	24	7
2	$Pd(OAc)_2$ (10)	AcOH (0.3)	Air	24	4
3	$Pd(OAc)_2$ (10)	NaOAc (2)	Air	24	9
4	$Pd(OAc)_2$ (10)	K_2CO_3 (2)	Air	24	43
5	$Pd(OAc)_2$ (0)	K_2CO_3 (2)	Air	24	0
6	$PdCl_2$ (10)	K_2CO_3 (2)	Air	24	38
7	$Pd(TFA)_2$ (10)	K_2CO_3 (2)	Air	24	11
8	$Pd(OAc)_2$ (10)	K_2CO_3 (2), AgOAc (1)	Air	24	10
9	$Pd(OAc)_2$ (10)	K_2CO_3 (2), PivOH (0.3)	Air	24	50
10	$Pd(OAc)_2$ (10)	K_2CO_3 (2), KOAc (3)	Air	24	22
11	$Pd(OAc)_2$ (10)	**K_2CO_3 (2), NaOAc (3)**	**Air**	**24**	**70**
12	$Pd(OAc)_2$ (10)	K_2CO_3 (2), NaOAc (3), BQ (1.5)	Air	24	10
13	$Pd(OAc)_2$ (10)	K_2CO_3 (2), NaOAc (3)	O_2[c]	24	78
14	$Pd(OAc)_2$ (5)	K_2CO_3 (2), NaOAc (3)	O_2[c]	24	36
15	$Pd(OAc)_2$ (5)	**K_2CO_3 (2),** NaOTf (3)	**O_2[c]**	**24**	**83**
				36	**> 95[d]**
16	$Pd(OAc)_2$ (5)	K_2CO_3 (2), NaOTf (3)	Ar	24	37
17	$Pd(OAc)_2$ (5)	K_2CO_3 (2), LiOTf (3)	O_2[c]	24	28
18	$Pd(OAc)_2$ (5)	K_2CO_3 (2), KOTf (3)	O_2[c]	24	26
19	$Pd(OTf)_2{\cdot}2H_2O$ (5)	K_2CO_3 (2), NaOTf (3)	O_2[c]	24	70

[a] All screening reactions were carried out in a 10 mL glass vial with a PETF-lined cap on a 0.2 mmol scale without strict exclusion of moisture. [b] Yields are based on ^{1}H NMR analysis of the reaction mixture. [c] The reaction vial was flushed with O_2 (1 atm) and then sealed with a PETF-lined cap. [d] Isolated yield.

Accordingly, the alkylation of PA-protected benzylamine substrate **1** with 1-iodopropane (3 equiv) was examined under various palladium-catalyzed conditions (Table 1B). The initial trials under the original $Pd(OAc)_2$/AgOAc conditions provided only trace amounts of product **2** even with a large excess of iodopropane (entry 1).[15] Replacing AgOAc with a carboxylic acid additive gave no improvement. Addition of 2 equiv of K_2CO_3 increased the yield of **2** to 43% (entry 4). Interestingly, a much-improved reaction was achieved with 2 equiv of K_2CO_3 and 3 equiv of NaOAc in *t*-amylalcohol at 125 °C for 24 h (entry 11). These conditions were further improved by carrying out the reaction under an O_2 atmosphere (entry 13).[16] Although efficient alkylation of **1** was observed under this set of conditions, undesired alkylation of the OAc anion with iodopropane was a side reaction, which not only consumed a significant amount of the halide substrate but also caused the incomplete alkylation of the benzylamide substrate. In the presence of AgOAc, this esterification reaction significantly competed with the desired C−H alkylation process (entry 8). To overcome this problem, a non-nucleophilic ligand for palladium was needed. To our surprise, though the OAc ligand is known to facilitate both C−H activation and catalyst regeneration, the C−H alkylation takes place in the absence of OAc (entry 6).[17] Further screening revealed that sodium triflate (NaOTf, 3 equiv) worked as a superior surrogate for NaOAc to completely avoid the side esterification reaction and promote a highly efficient C−H alkylation reaction even with reduced loading of $Pd(OAc)_2$ under an O_2 atmosphere (entry 15). Product **2** was obtained in nearly quantitative yield after simple filtration through a short silica gel plug (entry 15, 36 h). LiOTf and KOTf gave considerably lower yields than NaOTf (entries 17 and 18). $Pd(OTf)_2{\cdot}2H_2O$

(10) For selected examples of C−H activation in natural product synthesis, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72. (b) Davies, H. M.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (c) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991. (d) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511. (e) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496–13497. (f) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004–3007. (g) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179–182. (h) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566–571. (i) Feng, Y. Q.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958–961. (j) Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767–5769.

(11) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.

(12) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192–5196.

(13) (a) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83–90. (b) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047–14049. (c) Xu, L.; Li, B.; Yang, Z.; Shi, Z. *Chem. Soc. Rev.* **2010**, *39*, 712–733.

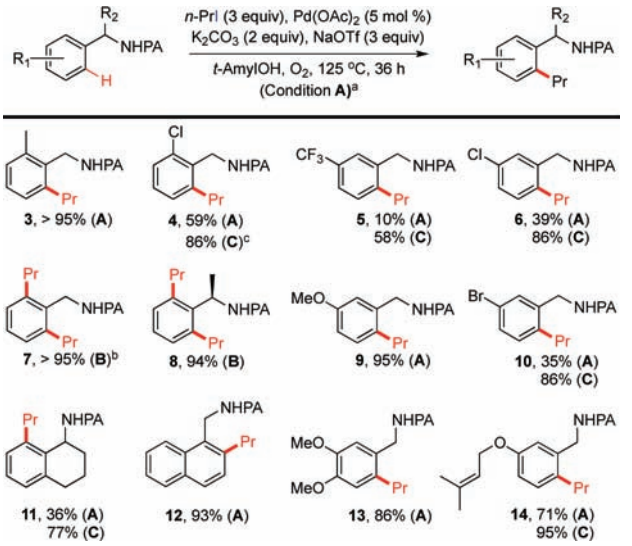
(14) Bentley, K. *Nat. Prod. Rep.* **2006**, *23*, 444–463.

(15) (a) See ref 11. (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *127*, 9879–9884.

(16) O_2 is crititial to the high yield of these alkylation reactions when low loading of $Pd(OAc)_2$ (< 10%) and/or β-H-containing alkyl halides are employed. It presumably reoxidizes Pd^0 generated from the undesired side reactions to Pd^{II} and increases the catalytic turnover number of $Pd(OAc)_2$. O_2 has no effect on the Pd-catalyzed methylation reaction with MeI.

(17) For discussions of the role of the carboxylate ligands in C−H activation, see: (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497. (c) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414–3417.

Scheme 1. Substrate Scope of Benzylamides



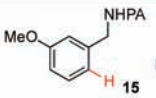
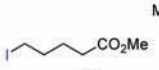
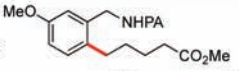
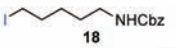
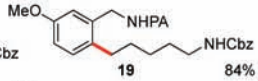
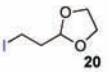
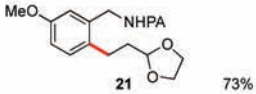
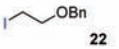
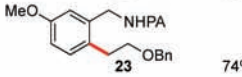
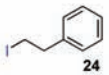
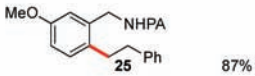
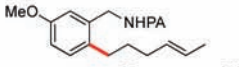
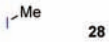
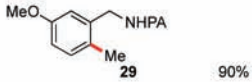
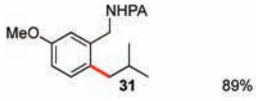
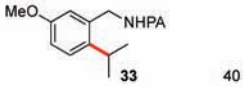
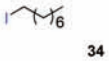
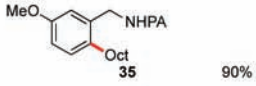
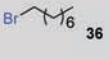
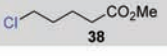
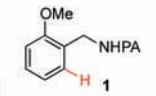
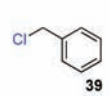
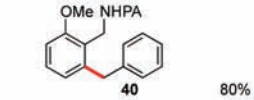
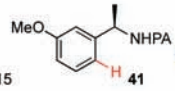
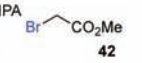
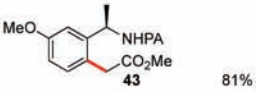
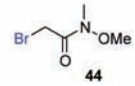
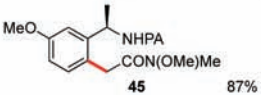
[a] All yields are based on isolated products on a 0.2 mmol scale without strict exclusion of moisture or air. [b] Condition **B** is similar to condition **A** except using 5 equiv of *n*-PrI. [c] Condition **C** is similar to condition **A** except using 10 mol % of $Pd(OAc)_2$, 3-methyl-3-pentanol as solvent, 135 °C.

(commercially unavailable) was a slightly less effective catalyst for this reaction (entry 19).[18]

With an optimized set of conditions in hand (condition A), we next explored the benzylamine substrate scope (Scheme 1). The electronic property of the benzylamine substrates used has a strong effect on its reactivity toward alkylation. In general, electron-rich substrates (e.g., **3**) could be readily alkylated in excellent yield while electron-deficient substrates (e.g., **4**, **5** and **6**) gave lower yields. The alkylation reactions of the latter could be improved using slightly more forcing conditions (condition C: 10 mol % of $Pd(OAc)_2$, 3-methyl-3-pentanol solvent, 135 °C, 36 h). Bis-alkylation usually predominates in the reaction of substrates with two equivalent *ortho*-C−H bonds (e.g., **7** and **8**). However, highly regioselective monoalkylation can be achieved with substrates bearing *para*-directing substituents (e.g., **6**, **9**, **10** and **14**); steric factors may also play a role in the high regioselectivity observed in these substrates. Furthermore, both bromine and alkene substituents on the benzylamine substrates (e.g., **10** and **14**) are conserved under these conditions. Finally, α-substituted benzylamine substrates also alkylate well (e.g., **8** and **11**).

The substrate scope of the alkyl halides has also been explored (Table 2). A broad range of primary alkyl iodides were readily incorporated. Most common functional groups including CO_2Me, CbzNH, cyclic ketals, benzyl ethers, and alkenes are well-tolerated (entries 1−6). Steric hindrance usually retards the reactivity as evidenced by the low yield obtained in alkylations with secondary alkyl

Table 2. Substrate Scope of Alkyl Halides

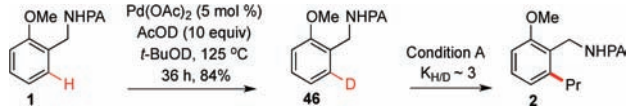
entry	substrate	alkyl halide	product	yield[a]
1	 15	 16	 17	85% (A)
2		 18	 19	84% (A)
3		 20	 21	73% (A)
4		 22	 23	74% (A)
5		 24	 25	87% (A)
6		 26	 27	84% (A)
7		 28	 29	90% (A)
8		 30	 31	89% (A)
9		 32	 33	40 %(C)[b]
10		 34	 35	90% (A)
11		 36	35	18% (A) 86% (D)[c]
12		 37	35	<5% (A) 87% (D)[c]
13		 38	17	<5% (A) 80% (D)[c]
14	 1	 39	 40	80% (A)
15	 41	 42	 43	81% (E)[d]
16		 44	 45	87% (A)

[a] Yields are based on isolated products on a 0.2 mmol scale with 3 equiv of alkyl halides. [b] Under condition **C**. [c] Condition **D** is similar to condition **A** except the addition of 2 equiv of NaI. [d] Condition **E** is similar to condition **A** except using 10 mol % of $Pd(OAc)_2$.

iodides (entry 9). Compared to alkyl iodides, primary alkyl bromides and chlorides only gave trace amount of products under the standard conditions. However, the

(18) For a selected example of OTf ligand used in Pd-catalyzed C−H activations, see: (a) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520–7521. (b) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *133*, 1466–1474.

Scheme 2. Preliminary Mechanistic Studies



reactions could be dramatically improved by the addition of 2 equiv of NaI (condition **D**, entries 11–13). More electrophilic halides such as benzyl chloride (**39**), α-bromo acetic ester (**42**), and Weinreb amide (**44**) could also be effectively employed; the NaOTf additive was critical to the success of these more reactive substrates. Finally, it is noteworthy that N-alkylated products were not observed in any of the reactions.

A few preliminary mechanistic studies have been carried out to probe the details of this C–H alkylation reaction. Although the entire process likely proceeds through a palladation/cross-coupling sequence, our efforts to obtain the putative palladacycle intermediate have been unsuccessful. However, the *ortho*-C–H bond of substrate **1** could be completely deuterated under the catalysis of $Pd(OAc)_2$ and AcOD (10 equiv) to provide product **46** (Scheme 2). A primary kinetic isotope effect (~3) was observed for the alkylation of **1** and **46** with *n*-PrI. The nature of the subsequent cross-coupling remains elusive. Although a $Pd^{II/IV}$ cycle via the oxidative addition of alkyl halide might be operative, a σ metathesis mechanism cannot be ruled out.[5a,e]

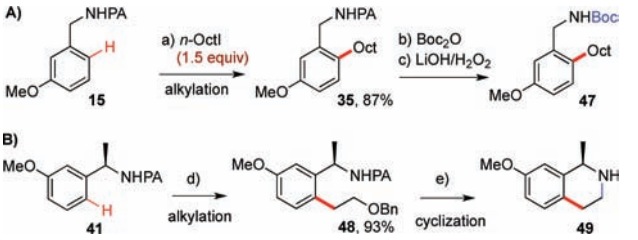
Due to their low cost[19] and high stability, PA could be employed as an amide-linked protecting group for benzylamine substrates. For example, PA could be easily introduced in **15** by reacting 3-methoxybenzylamine with 2-picolinyl chloride or by standard amide coupling with 2-picolinic acid (Scheme 3A). Regioselective alkylation of **15** could be achieved under the standard conditions with only 1.5 equiv of octyl iodide. Unlike the PA-protected aliphatic amine substrates with bulky α-substituents,[12] the PA of **35** could be activated with Boc_2O and cleaved by $LiOH/H_2O_2$ to give the Boc-protected amine product **47** in high yield.

To further demonstrate the synthetic utility of this C–H alkylation chemistry, **41**, prepared from the commercially

(19) The price for 2-picolinic acid (99%, Aldrich) is $40 for 100 g.

(20) In contrast with the Pictet–Spengler route, the key stereochemistry at the C1 position of THIQ could be readily and reliably established in the chiral benzylamine precursors in the early stage of synthesis, e.g., via asymmetric reduction of corresponding imines.

Scheme 3. Synthetic Utilities of the C–H Alkylation Method[a]



[a] Reagents and conditions: (a) octyl iodide (1.5 equiv), condition **A**, 87%; (b) Boc_2O, DMAP, CH_3CN, rt, 92%; (c) LiOH, H_2O_2, H_2O/THF, rt, 90%; (d) **22** (3 equiv), condition **E**, 93%; (e) (i) Pd/C, HCl/MeOH, rt, 76%; (ii) TsCl, pyridine, 0 °C; (iii) NaH, THF, 78% over two steps; (iv) NaOMe, MeOH, 100 °C, 84%. All yields were based on isolation.

available amine precursor, could be alkylated to provide **48** in high yield. The OBn group of **48** could be converted to OTs, followed by intramolecular N-alkylation and cleavage of the tertiary picolinamide, to give the THIQ **49** in good yield (Scheme 3B). We expect that this C–H alkylation/cyclization strategy, especially with easily accessible chiral α-substituted benzylamine substrates, provides an attractive complement to the classical Pictet–Spengler synthesis of complex THIQs.[20]

In summary, we have developed a generally applicable method to alkylate the *ortho*-C–H bonds of picolinamide-protected benzylamines with β-H-containing alkyl halides. The non-nucleophilic promoter NaOTf is critical for this reaction. Excellent product yields and selectivities were obtained with a broad range of benzylamides and primary alkyl halides, including chlorides. The alkylation reaction is silver-free and does not require expensive ligands or reagents. The PA directing group can be easily exchanged for a Boc group under mild conditions. Further mechanistic studies and applications of this C–H alkylation methodology in the synthesis of complex THIQ natural products are currently under investigation.

Acknowledgment. We would like to dedicate this paper to Professor Steven M. Weinreb on the occasion of his 70th birthday. This work was supported by a startup fund from The Pennsylvania State University and an NSF CAREER Award (CHE-1055795).

Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.