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Palladium-Catalyzed Alkenylation and Alkynylation of *ortho*-C(sp^2)–H Bonds of Benzylamine Picolinamides

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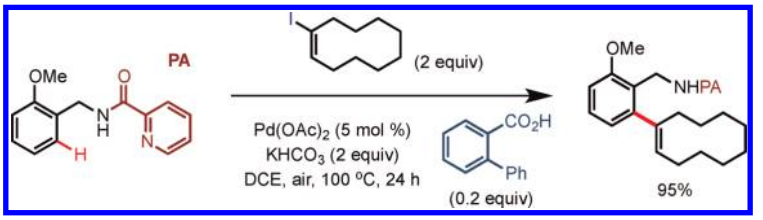
ABSTRACT



An efficient functionalization of *ortho*-C(sp^2)–H bonds of picolinamide (PA)-protected benzylamine substrates with a range of vinyl iodides as well as acetylenic bromide is reported. *ortho*-Phenyl benzoic acid (*o*PBA) acts as an effective promoter in this reaction system. This method provides a practical strategy to access highly functionalized benzylamine compounds for organic synthesis.

Aryl-substituted olefins are frequently utilized as intermediates in organic synthesis and constitute a prominent structural motif. Foremost among the modern methods for their synthesis are metal-catalyzed cross-coupling reactions, such as the Mizoroki–Heck, Suzuki, Negishi, and Stille reactions; these reactions couple functionalized arene and olefin partners to reliably form densely substituted products.[1] In contrast to this reactivity is the palladium-catalyzed arene C–H olefination reaction (so-called Fujiwara–Moritani reaction), which couples unfunctionalized starting materials and thus has a significant advantage in atom and step economy.[2−4] However, despite extensive development, Fujiwara–Moritani reactions still have relatively limited applicability; for instance, olefin substrates in these systems have been largely restricted to the more "activated" terminal olgefins such as acrylates and styrenes.[5] Complementary to these approaches is the "inverse Heck" reaction which couples unfunctionalized arenes and functionalized olefins (e.g., vinyl halides).[6] This reactivity could potentially provide valuable alternative synthetic pathways to aryl olefins, with an overall expanded substrate scope. Over the past few years, several protocols based on this strategy have been reported for heteroarene substrates bearing relatively acidic C–H bonds. However, corresponding reactions with unactivated arene substrates are scarce.[7,8]

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Herein, we report an efficient palladium-catalyzed method for the selective functionalization of *ortho*-C−H bonds of benzylamine picolinamides with vinyl iodides and acetylenic bromide. Benzylamines are versatile synthetic precursors which are easily accessible through various preparative methods. Stereochemistry at the benzylic position of α-substituted benzylamines can also be readily introduced using well-estabilised asymmetric synthesis technology. We envision that direct or directed functionalization of the C(sp^2)−H bonds of the benzylamine precursors will enable rapid access to a range of highly elaborate N-containing aromatic compounds. In a recent study, we reported that the *ortho*-C−H bonds of picolinamide (PA) protected benzylamines can be efficiently alkylated with β-H containing alkyl halides under Pd catalysis.[9] The PA group, first introduced by the Daugulis laboratory in 2005,[10] has demonstrated excellent directing abilities for a number of Pd-catalyzed C−H functionalization reactions in recent investigations.[11] Encouraged by these successes, we have proceeded to investigate whether *ortho*-C−H bonds of benzylamine picolinamides can be alkenylated with vinyl halides in a similar fashion.

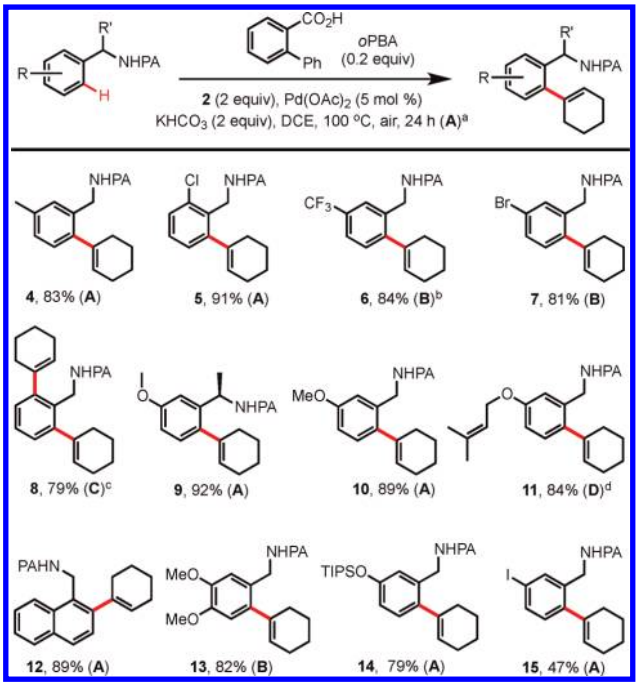
Table 1. Pd-Catalyzed *ortho*-C(sp^2)−H Alkenylation Reactions[a]

entry	catalysis (mol %)	additive (equiv)	atmosphere[b]	yield[c] (%)
1	$Pd(OAc)_2$ (10)	AgOAc (1)	Air	60
2	$Pd(OAc)_2$ (10)	AgOAc (2)	Air	71
3	$Pd(OAc)_2$ (10)	AcOH (2)	Air	10
4	$Pd(OAc)_2$ (10)	PivOH (2)	Air	14
5	$Pd(OAc)_2$ (10)	NaOAc (2)	Air	13
6	$Pd(OAc)_2$ (10)	NaOTf (2)	Air	17
7	$Pd(OAc)_2$ (10)	Cs_2CO_3 (2)	Air	trace
8	$Pd(OAc)_2$ (10)	K_2CO_3 (2)	Air	trace
9	$Pd(OAc)_2$ (10)	$KHCO_3$ (2)	Air	24
10	$Pd(OAc)_2$ (10)	$KHCO_3$ (2), NaOAc (2)	Air	66
11	$Pd(OAc)_2$ (10)	$KHCO_3$ (2), AcOH (2)	Air	32
12	$Pd(OAc)_2$ (10)	$KHCO_3$ (2), TFA (2)	Air	trace
13	$Pd(OAc)_2$ (10)	$KHCO_3$ (2), PivOH (2)	Air	78
14	$Pd(OAc)_2$ (5)	$KHCO_3$ (2), AcOH (0.2)	Air	82
15	$Pd(OAc)_2$ (5)	$KHCO_3$ (2), AdOH (0.2)	Air	89
16	$Pd(OAc)_2$ (5)	$KHCO_3$ (2), PivOH (0.2)	Air	90
17	$Pd(OAc)_2$ (5)	$KHCO_3$ (2), oPBA (0.2)	Air	92 (89[d])
18	$Pd(OAc)_2$ (5)	$NaHCO_3$ (2), oPBA (0.2)	Air	15
19	$Pd(OAc)_2$ (5)	K_2CO_3 (2), oPBA (0.2)	Air	5
20	$Pd(OAc)_2$ (5)	$KHCO_3$ (2), oPBA (0.2)	O_2	90
21	$Pd(OAc)_2$ (5)	$KHCO_3$ (2), oPBA (0.2)	Ar	91
22	$Pd(OAc)_2$ (2.5)	$KHCO_3$ (2), oPBA (0.2)	Air	66

[a] All screening reactions were carried out in a 10 mL glass vial with a PTFE-lined cap on a 0.2 mmol scale, [**1**]~ 0.2 M. [b] The reaction vial was flushed with O_2 or Ar (1 atm) and then sealed with a PTFE-lined cap. [c] Yields are based on ^{1}H-NMR analysis of the reaction mixture. [d] Isolated yield on a 1.0 mmol scale.

Alkenylation of benzylamine substrate **1** with iodocyclohexene **2** was examined under various reaction conditions (Table 1). Initial trials were conducted under the previously developed conditions for PA-directed C(sp^3)−H arylation (10 mol % $Pd(OAc)_2$ and 1 equiv of AgOAc at 100 °C). The desired alkenylated product **3** was obtained in good yield (entry 1).[10,11a] We then directed our efforts toward replacing the AgOAc additive with a cheaper alternative.[12] An experimental survey of reaction conditions revealed that the desired alkenylation could proceed in the presence of both carboxylate ligands and weak bases like $KHCO_3$.[13] Use of strong bases such as Cs_2CO_3 and K_2CO_3 (entries 7 and 8) or strong carboxylic acids such as TFA (entry 12) resulted in only trace amounts of product. Carboxylic acid additives alone were insufficient to promote alkenylation (entries 3 and 4). Use of 2 equiv of $KHCO_3$ and 0.2 equiv of carboxylic acids provided consistently improved results (entries 13−17). Interestingly, *ortho*-phenyl benzoic acid (*o*PBA), originally applied in our previously reported Pd-catalyzed amidate-directed intramolecular C(sp^3)−H arylation reactions, proved to be the most effective carboxylate promoter.[14] Finally, this alkenylation can be conveniently carried out under an air atmosphere; neither an O_2 nor Ar atmosphere has a notable effect on reaction outcome (entries 20−21).[15]

Table 2. Substrate Scope of Benzylamine Substrates

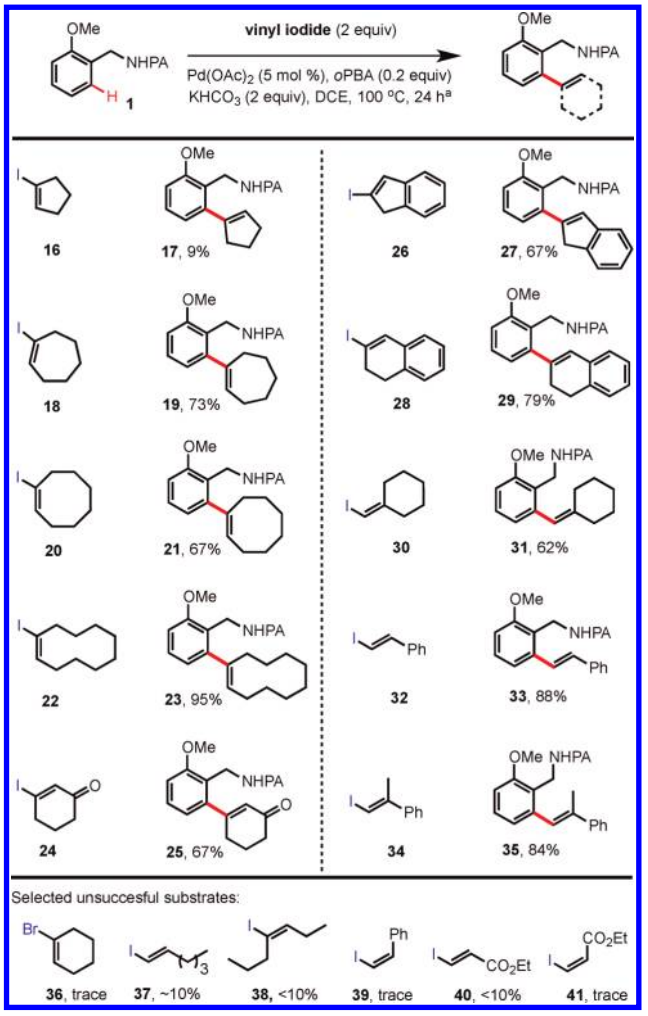


[a] General condition **A**, all yields are based on isolated product on a 0.2 mmol scale. [b] Condition **B** uses 10 mol % $Pd(OAc)_2$, 110 °C, 24 h. [c] Condition **C** uses 5 equiv of **2**, 36 h. [d] Condition **D** uses 10 mol % $Pd(OAc)_2$, 130 °C, 36 h.

We then examined the substrate scope of the reaction for benzylamines (Table 2). Overall, electron-rich substrates were alkenylated in excellent yield under the optimized

reaction conditions (e.g., **4**, **10**; standard condition **A**: 2 equiv of **2**, 5 mol % of $Pd(OAc)_2$, 2 equiv of $KHCO_3$, 0.2 equiv of *o*PBA, 1,2-dichloroethane, air, 100 °C). Alkenylation reactions of electron-poor substrates could proceed well under slightly more demanding conditions (e.g., **6**, **7**; condition **B**: 10 mol % of $Pd(OAc)_2$, 125 °C). Bis-alkenylated products were obtained in good yields from substrates bearing two identical *ortho*-C−H bonds with 5 equiv of **2** (e.g., **8**; condition **C**). In comparison, highly regioselective monoalkenylation was achieved at the less sterically hindered position of substrates bearing two inequivalent *ortho*-C−H bonds (e.g., **4**, **6**, **7**). An elevation of reaction temperature to 130 °C was necessary for substrates bearing a prenylether group (e.g., **11**; condition **D**). Finally, α-substituted benzylamine substrates were also alkenylated in excellent yield (e.g., **9**; condition **A**).

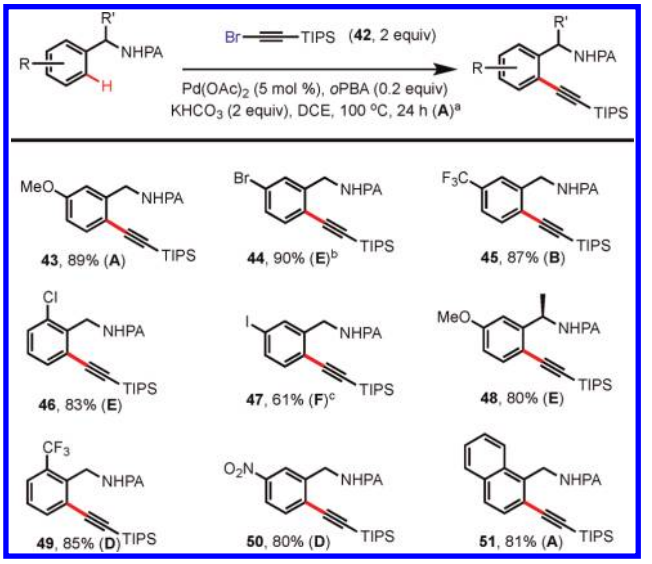
Table 3. Substrate Scope of Vinyl Halides



[a] Yields are based on isolated product on a 0.2 mmol scale.

Complementary to the collection of olefin substrates used in typical Fujiwara−Moritani reactions, a unique set of alkene coupling partners has been introduced with this PA-directed C−H alkenylation reaction (Table 3). We found that cyclic vinyl iodides of various ring sizes (e.g., **18**, **20**, **22**, **26**, and **28**),[16] with the exception of five-membered **16**, were coupled in good to excellent yields. Even electron-deficient substrate **24** provided an acceptable yield of product **25**. In contrast, acyclic vinyl iodides including **37**, **38**, **40**, and **41** failed to give a useful level of C−H alkenylation products (<10%). Interestingly, trisubstituted terminal vinyl iodide **30** gave a moderate yield of product. *trans*-2-Iodostyrenes such as **32** and **34** could undergo the desired C−H alkenylation reaction to generate the trans-substituted products in high yield and stereoselectivity, while *cis*-2-iodostyrene **39** only gave a trace amount of coupled product.[8d] The bromo, triflate, and

Table 4. Pd-Catalyzed C−H Alkynylation Reactions



[a] Yields are based on isolated products on a 0.2 mmol scale using standard conditions. Reactions of compound **43**, **45**, **46**, **51** were repeated on a 1.0 mmol scale, and consistent yields were obtained compared with the 0.2 mmol scale; see Supporting Information. [b] Condition **E** is similar to **A** except the reaction temperature is 110 °C. [c] Condition **F** is similar to **A** except 10 mol % of $Pd(OAc)_2$ was applied.

(7) For selected examples of C−H alkenylation of arenes with vinyl halides, see: (a) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113–3119. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128–1129. (c) Geary, L. M.; Hultin, P. G. *Org. Lett.* **2009**, *11*, 5478–5481.

(8) For selected examples of C−H alkenylation of heteroarenes with vinyl halides, see: (a) Koubachi, J.; El Kazzouli, S.; Berteina Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synthesis* **2008**, 2537–2542. (b) Gottumukkala, A. L.; Derridj, F.; Djebbar, S.; Doucet, H. *Tetrahedron Lett.* **2008**, *49*, 2926–2930. (c) Besselièvre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. *Org. Lett.* **2008**, *10*, 4029–4032. (d) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647–650. (e) Mousseau, J. J.; Fourtier, A.; Charette, A. B. *Org. Lett.* **2010**, *12*, 516–519.

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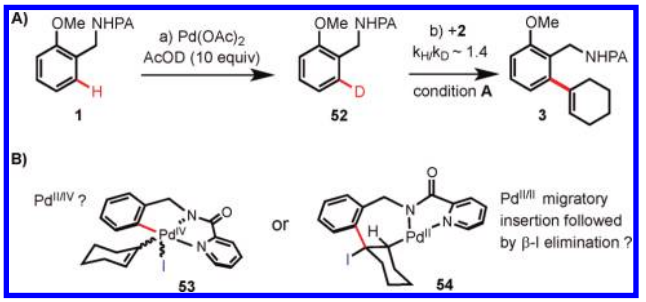
(12) Ag^+ reagents are indispensable to many of the known metal-catalyzed C−H functionalization reaction systems.

phosphate analogues of **2** are completely unreactive under the standard conditions.

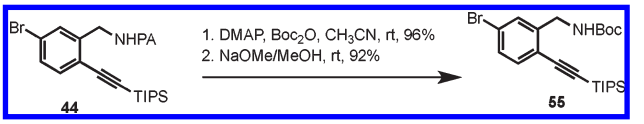
In addition to vinyl iodides evaluated above, TIPS protected acetylenic bromide **42**[17] was utilized to generate alkynylated products in excellent yield under our standard reaction conditions (Table 4). Analogous to Chatani's pinoneer studies on the Pd-catalyzed C−H alkynylation reactions, **42** performs much better than any other acetylene substrate tested in this reaction system. Alkynylation reactivity patterns, regioselectivity, and functional group tolerance are similar to those observed in the PA-directed C−H alkenylation reactions.

Scheme 1. Prelimilary Mechanistic Studies



The mechanism of these reactions has not been firmly established. Under the catalysis of $Pd(OAc)_2$ and in the presence of 10 equiv of AcOD, the *ortho*-C−H bond of substrate **1** was deuterated to provide compound **52** (Scheme 1A). A relatively small kinetic isotope effect (~1.4) was observed for the alkenylation of **1** and **52** with **2**. The C−H functionalization process likely proceeds through a C−H palladation/cross-coupling sequence. However, our efforts to obtain the speculated Pd^{II} palladacycle intermediate have been unsuccessful. The nature of the cross-coupling step remains elusive. Although a $Pd^{II/IV}$ catalytic cycle via the oxidative addition of vinyl halide or acetylene bromide to Pd^{II} appears reasonable,[18] a migratory insertion followed by a β-heteroatom elimination pathway could also be operative (Scheme 1B).[6,17b,19]

Scheme 2. Revomal of the PA Group



Removal of the PA group from functionalized products has been demonstrated in our previous report.[9] For example, compound **44** reacts with Boc_2O at rt and can then be cleaved with NaOMe/MeOH to give the Boc protected product **55** in excellent yield (Scheme 2).

In summary, we have developed a new method to prepare *ortho*-alkenylated and alkynylated benzylamine products via Pd-catalyzed $C(sp^2)$−H functionalization reactions. A broad substrate scope for benzylamine picolinamide has been demonstrated; cyclic vinyl iodides, 2-iodostyrenes, and acetylene bromide substrates can be effectively utilized as coupling partners. This method features generally high efficiency, inexpensive reagents, and convenient operating conditions. We are currently engaged in further mechanistic studies and application of this method to organic synthesis.

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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.

(13) For selected reviews on carboxylate ligands in transition-metal-catalyzed C−H functionalization reactions, see: (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118–1126. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. Weakly basic conditions might allow for the protonolysis of the PA/Pd complex, thus resulting in the release of the functionalized product.

(14) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414–3417. The functional role of *o*PBA in this reaction system remains elusive. In comparison with PivOH, *o*PBA provides marginally but consistently better performance in terms of reaction rate and yield.

(15) We observed marked inhibition by O_2 in our Pd-catalyzed, PA-directed, $PhI(OAc)_2$-mediated intramolecular C−N cyclization reaction; see ref 11b.

(16) Cyclic vinyl iodides can be readily prepared from the corresponding ketone precursors, see Supporting Information.

(17) For studies on C−H alkynylation reactions by Chatani, see: (a) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250–3252. (b) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984–12986. (c) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354–357. For other selected examples of C−H alkynylation reactions, see: (d) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528–8529. (e) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742–7743.

(18) For selected reviews on Pd^{IV} chemistry, see: (a) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83–90. (b) Xu, L.; Li, B.; Yang, Z.; Shi, Z. *Chem. Soc. Rev.* **2010**, *39*, 712–733. (c) Racowski, J.; Sanford, M. S. *Top. Organomet. Chem* **2011**, *53*, 61–84. Well charaterized oxidative addition of vinyl halides to Pd^{II} to form vinyl Pd^{IV} intermediates is extremely rare in the literature.

(19) For an elegant study on β-heteroatom elimination, see: Zhu, G.; Lu, X. *Organometallics* **1995**, *14*, 4899–4904. This mechanism seems well-suited to explain the unique reactivity of cyclic vinyl iodide substrates in this reaction system. The migratory insertion product **54** is well set-up for the subsequent antiperiplanar β-I elimination, followed by the regeneration of Pd^{II} species. Such elimination is less favored in the acyclic substrates where β-H elimination would compete and possibly lead to undesired decomposition to Pd black.

The authors declare no competing financial interest.