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Improved Protocol for Indoline Synthesis via Palladium-Catalyzed Intramolecular C(sp^2)–H Amination

Gang He, Chengxi Lu, Yingsheng Zhao, William A. Nack, and Gong Chen*

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

guc11@psu.edu

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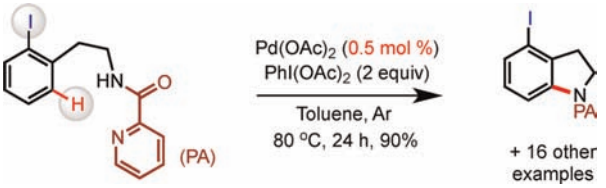
ABSTRACT



An efficient method has been developed for the synthesis of indoline compounds from picolinamide (PA)-protected β-arylethylamine substrates via palladium-catalyzed intramolecular amination of *ortho*-C(sp^2)–H bonds. These reactions feature high efficiency, low catalyst loadings, mild operating conditions, and the use of inexpensive reagents.

Indolines are found in many natural products and pharmaceuticals, and the chemical synthesis of indolines has attracted the attention of generations of organic chemists.[1] For example, intramolecular C–N cross-coupling reactions have been successfully applied for the indoline synthesis.[2] More recently, considerable effort has been invested in obviating the prefunctionalization step, required for indoline synthesis by conventional coupling strategies, through direct functionalization of C–H bonds of arenes or alkyl chains.[3] A number of indoline synthesis protocols based on C–H functionalization strategies have emerged over the past few years.[4,5] Despite conceptual innovation, the synthetic utility of these C–H functionalization methods remains underdeveloped, limiting application in organic synthesis. Practical C–H functionalization protocols are still in great demand.[6] Herein, we report our latest development on the palladium-catalyzed picolinamide-directed

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(2) Selected examples of indoline synthesis via metal-catalyzed cross-coupling reactions: (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428. (c) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231–234. (d) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311–2314. (e) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721–2724.

(3) For an excellent review on N-heterocycle synthesis via C–H functionalization, see: Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883.

(4) Selected examples of indoline synthesis via Pd-catalyzed C(sp^3)–H functionalization: (a) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759–1762. (b) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438–7441. (c) Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 2238–2242. With C(sp^2)–H functionalization: (d) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066–10067.

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intramolecular C−H amination reaction for the synthesis of indolines.

The picolinamide (PA) group, first introduced by the Daugulis laboratory in 2005,[7] has demonstrated excellent directing abilities for a number of C−H functionalization reactions.[8] Recently, our laboratory[8d] as well as that of Daugulis[9] independently reported that picolinamide substrates can undergo intramolecular amination reactions at the δ-C−H position to afford five-membered pyrrolidine and indoline products under the catalysis of $Pd(OAc)_2$. An illustrative example is the cyclization of the β-phenylethylamine substrate **1** at the δ-C(sp^2)−H bond to form the indoline product **2** (Table 1). $PhI(OAc)_2$ was found to be the best oxidant for the reaction (entries 1−10).

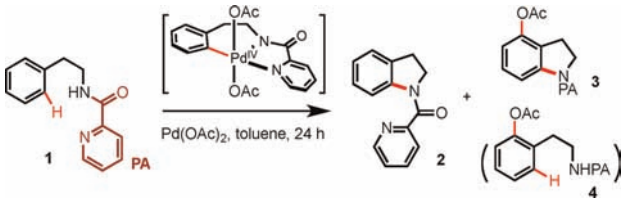
In comparison with the Daugulis protocol[9] and Yu's pioneering triflamide-mediated reaction system,[10] the cyclization of **1** to form **2** proceeds under notably mild operating conditions and in good yield. Encouraged by the promising synthetic utility of this indoline synthesis method, we carried out a new round of study. Further work on this reaction system led us to several notable conclusions and optimizations.

While the PA-directed intramolecular amination of δ-C(sp^3)−H bonds requires a reaction temperature of 110 °C, we found that amination of δ-C(sp^2)−H bonds could be performed at a considerably lowered reaction temperature. Cyclization of substrate **1** proceeds smoothly at 60 °C in toluene using 5 mol % of $Pd(OAc)_2$ catalyst under air to afford **2** in >80% yield; this yield is slightly improved when compared with the same reaction performed at 100 °C (entries 10 and 11). Compound **3** was isolated as the major side product, presumably resulting from cyclization of acetoxylated byproduct **4**. While high reaction temperature accelerates the reaction rate, it also promotes undesired side reactions such as the competing acetoxylation pathway and results in generally diminished chemoselectivity. The cyclization reaction also proceeds at room temperature at a slower rate; a comparable yield of **2** was obtained with 10 mol % of $Pd(OAc)_2$ and extended reaction time (6 days, Ar, entry 23).

We observed that O_2 has a pronounced inhibitory effect on the cyclization reaction, particularly with lower catalyst loading or at lower reaction temperatures (e.g., 2 mol % of $Pd(OAc)_2$, 60 °C, entries 12 and 13). This contrasts with our previously reported PA-directed C(sp^2)−H alkylation reaction with alkyl halides, where O_2 demonstrated a promoting effect.[8c,11] The reaction proceeds most efficiently under an argon atmosphere and without the use of any additives (entry 14). Under an air atmosphere, addition of carboxylic acid additives such as PivOH and AdOH restores the desired reactivity to a useful level of 75−80% (entries 16 and 18).

In comparison with many of the known C−H functionalization protocols, low catalyst loading was required for this cyclization reaction to proceed. Excellent results were obtained with 2 mol % of $Pd(OAc)_2$ at 60 °C for 24 h (general condition A, entry 14) or with 0.5 mol % of $Pd(OAc)_2$ at 80 °C for 24 h (general condition B, entry 21). We reason that, unlike the secondary amide starting

Table 1. Indoline Synthesis via Pd-Catalyzed Intramolecular Amination of C(sp^2)−H Bonds



entry	$Pd(OAc)_2$ (mol %)	additives (equiv) / atmosphere	T (°C)	yield (%)[a] 2	3
1	5	AgOAc (2), air	100	<2	<2
2	5	$Cu(OAc)_2$ (2), air	100	<2	<2
3	5	$Ce(SO_4)_2$ (2), air	100	<2	<2
4	5	$K_2S_2O_8$ (2), air	100	<2	<2
5	5	oxone (2), air	100	<2	<2
6	5	F(+)[b], air	100	<2	<2
7	5	BQ (2), air	100	7	<2
8	5	$PhI(OCOCF_3)_2$ (2), air	100	<2	<2
9	5	$PhI(OPiv)_2$ (2), air	100	78	8
10	5	$PhI(OAc)_2$ (2), air	100	80	10
11	5	$PhI(OAc)_2$ (2), air	60	85	7
12	2	$PhI(OAc)_2$ (2), air	60	64	6
13	2	$PhI(OAc)_2$ (2), O_2 (1 atm)	60	37	<2
14	2	$PhI(OAc)_2$ (2), Ar	60	90 (88[c])	6
15	2	$PhI(OAc)_2$ (2) + AcOH (2), air	60	70	9
16	2	$PhI(OAc)_2$ (2) + PivOH (2), air	60	75	9
17	2	$PhI(OAc)_2$ (2) + TFA (2), air	60	<2	<2
18	2	$PhI(OAc)_2$ (2) + AdOH (2), air	60	79	6
19	2	$PhI(OAc)_2$ (2) + Py (2), air	60	<2	<2
20	1	$PhI(OAc)_2$ (2), Ar	60	84 (2 d)	8
21	0.5	$PhI(OAc)_2$ (2), Ar	80	82 (80[c])	16
22	0.1	$PhI(OAc)_2$ (2), Ar	80	47	10
23	10	$PhI(OAc)_2$ (2), Ar	rt	85 (6 d)	5

[a] All screening reactions were carried out in a 20 mL glass vial with a PTFE-lined cap on a 0.4 mmol scale; yields are based on ^1H NMR analysis of the reaction mixture. [b] 1-Fluoro-2,4,6-trimethylpyridinium triflate. [c] Isolated yield on a 1.0 mmol scale.

(6) Selected reviews on practical C−H functionalization methods: (a) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (b) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885–1898. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115.

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

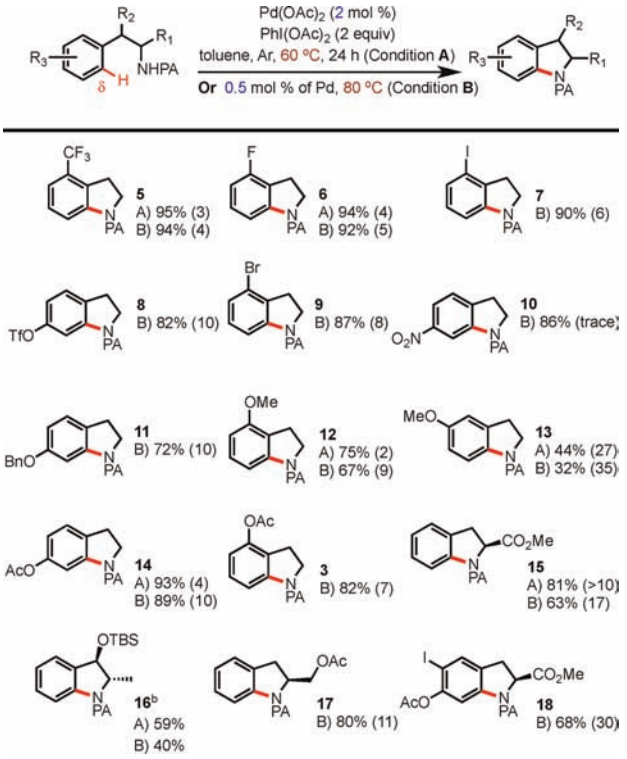
(8) (a) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958–961. (b) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192–5196. (c) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850–4853. (d) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3–6. (e) Zhang, S. Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313–7316. (f) Zhao, Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* 2012, DOI: 10.1021/ol301214u. (g) Gou, F. R.; Wang, X. C.; Huo, P. F.; Bi, H. P.; Guan, Z. H.; Liang, Y. M. *Org. Lett.* **2009**, *11*, 5726.

(9) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7–9.

(10) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.

(11) One possible explanation for this observed inhibition involves O_2 reversibly binding the Pd^{II} palladacycle intermediate. Such an interaction would presumably hamper the subsequent $Pd^{II/IV}$ oxidation by $PhI(OAc)_2$. More detailed studies will be published in the future.

Table 2. Substrate Scope of β-Arylethylamine Substrates[a]



[a] Yields based on isolated products on a 1.0 mmol scale. Acetoxylated product yields are shown in parentheses. [b] The remaining mass balance consisted mainly of starting material.

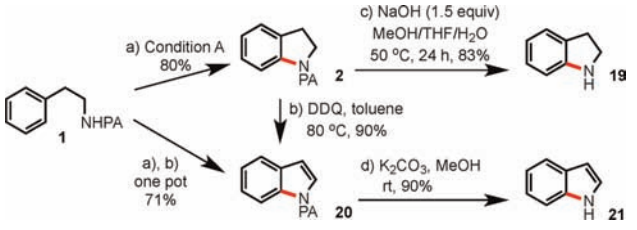
material, the tertiary amide product has little affinity for the catalytic Pd^{II} species, lessening competition for the catalytic pathway. We also noted the reaction mixture remained a transparent yellow solution during the course of the reaction; Pd black precipitate was rarely observed.

A range of β-arylethylamine substrates were then cyclized under the newly optimized conditions (Table 2). In general, electron-deficient substrates (**5**, **6**, **8**, and **10**) were cyclized in excellent yield along with small amounts (< 10%) of undesired acetoxylated products. The reactions of substrates bearing electron-donating functional groups like OBn (**11**) and OMe (**12**) were found to be slightly less selective. In particular, we noted that substrates bearing electron-donating groups para to the targeted C−H bond (e.g., **13**) gave considerably diminished yield of cyclized product, with increased amounts of acetoxylated side products. This acetoxylation side reaction is much less prominent with electron-deficient substrates (e.g., **5** and **6**)

Excellent regioselectivity at the least sterically hindered position was observed in substrates bearing two inequivalent *ortho*-C−H bonds (**18**). Common functional groups such as esters, acetyls, and TBS protecting groups were tolerated (**15**–**18**). Furthermore, we were pleased to observe that OTf, halogen groups including Br and even *ortho*-I[12] groups of arenes were preserved under these reaction conditions (**7**–**9** and **18**). This unique blend of reactivity and functional group compatibility may be due to suppressed formation of undesired Pd^0 species under the optimized reaction conditions with low catalyst loading and relatively low reaction temperature. Finally, α- and β-substituted arylethylamine substrates could provide densely functionalized indoline products in variably diminished yield (**15**–**18**).[13]

The PA group used in this indoline synthesis can be considered a protecting group as it can be readily removed under mild conditions from the cyclized product. For example, treatment of compound **2** with 1.5 equiv of NaOH in MeOH/THF/H_2O at 50 °C gave indoline **19** in excellent yield (Scheme 1). PA-protected indoline **2** was also readily oxidized by DDQ to form the indole product **20** in high yield. The cyclization and oxidation steps can be carried out sequentially in one pot. The PA group of the resulting indole **20** was easily removed under mildly basic conditions to give free indole **21**.

Scheme 1. Further Transformations



The PA-directed intramolecular C(sp^2)−H amination reaction likely proceeds through a $Pd^{II/IV}$ catalytic cycle by a sequence of C−H palladation, $Pd^{II/IV}$ oxidation, and C−N reductive elimination (Scheme 2A).[14,15] However, our efforts to obtain a palladacycle intermediate have been unsuccessful. The *ortho*-C−H bond of substrate **22** was readily deuterated under the catalysis of $Pd(OAc)_2$ by AcOD, providing **23**. A primary kinetic isotope effect (~3.1) was observed in the cyclization of **22** and **23** under general condition A.

The synthetic utility of this C−H amination chemistry was then explored in our effort toward the total synthesis of the natural product betanin (**32**, Scheme 3).[16]

(12) Excellent tolerance for iodo groups on arene substrates is rare in related Pd-catalyzed C−H functionalization literature.

(13) Ring strain associated with the C−N reductive elimination from the six-membered palladacycle intermediate to form the more densely substituted five-membered indoline product might promote the production of the less strained acyclic acetoxylated side products.

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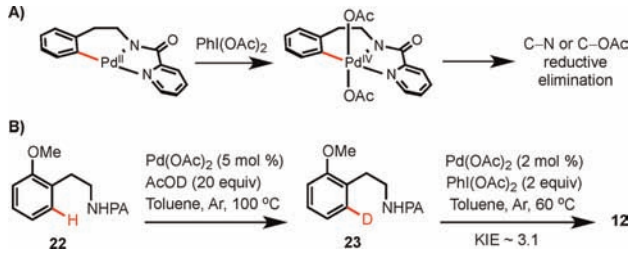
(16) Strack, D.; Vogt, T.; Schliemann, W. *Phytochemistry* **2003**, *62*, 247–269.

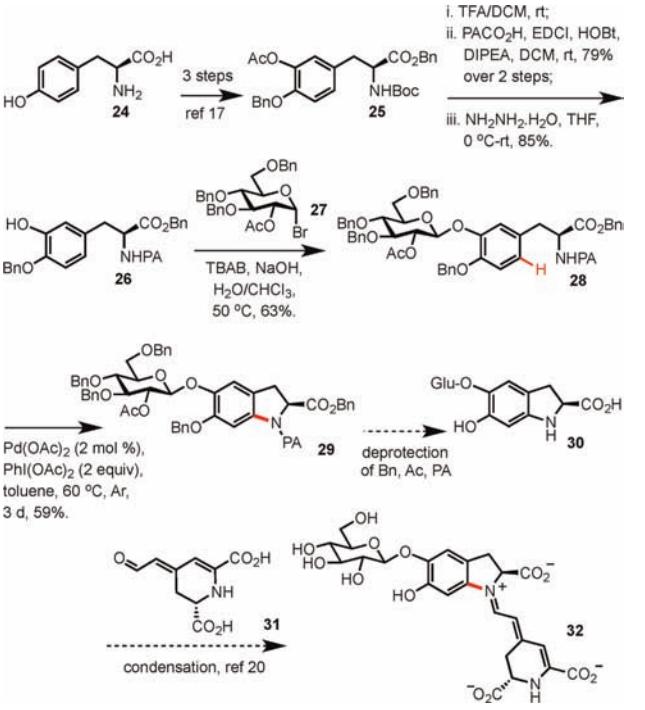
Scheme 2. Preliminary Mechanistic Studies



We envisioned that the indoline core of **30** could be constructed via the PA-directed intramolecular C−H amination reaction in the late stages of synthesis. Dopamine intermediate **25** can be readily prepared from free tyrosine in good yield in three steps based on a known procedure.[17] The Boc group of **25** was then replaced with PA group by standard deprotection and amide coupling. Upon removal of the OAc group, the phenol intermediate **26** was reacted with Bn- and Ac-protected glucosyl bromo donor **27** under a biphasic glycosylation conditions to give glucosylated product **28** in good yield and excellent stereoselectivity.[18] The C−N cyclization reaction provided the desired indoline core **29** in 59% yield under general reaction condition A with extended time (2 mol % of $Pd(OAc)_2$, 60 °C, 3 days).[19] Global deprotection of the protecting groups and final condensation with a suitable betalamic acid partner **31** to furnish the target product is currently under investigation.[20]

In summary, we have developed a practical protocol for the synthesis of indoline compounds from picolinamide-protected β-arylethylamine substrates. This method features high efficiency and functional group tolerance and operates under mild and economical conditions. The PA group serves as a well-behaved amine protecting group for the indoline products and can be easily removed under mildly basic conditions. Finally, the PA group of the indoline product could potentially enable further structural transformation via directed functionalization of neighboring C−H bonds. Development along these lines will be reported in due course.

Scheme 3. Application of Our Effort toward the Synthesis of Betanin



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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.

The authors declare no competing financial interest.

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(18) Zhu, C.; Peng, W.; Li, Y.; Han, X.; Biao, Y. *Carbohydr. Res.* **2006**, *341*, 1047–1051.

(19) An acetoxylated compound was isolated as the major side product. The observed moderate cyclization yield was anticipated due to the *para*-O substitutent of **28**.

(20) A closely related condensation strategy has been successfully demonstrated in Herrmann's synthesis of betalaine using a deglycosylated indoline substrate: Herrmann, K.; Dreiding, A. S. *Helv. Chim. Acta* **1975**, *58*, 1805–1808.