JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Heterocycle Synthesis via Direct C−H/N−H Coupling

Enrico T. Nadres and Olafs Daugulis*

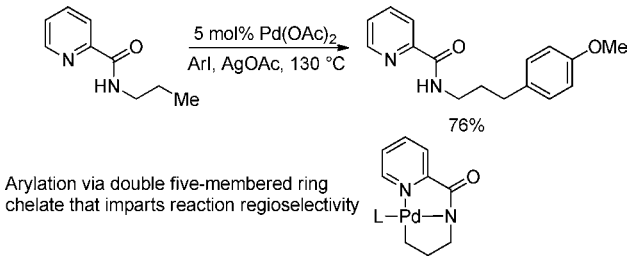
Department of Chemistry, University of Houston, Houston, Texas 77204-5003, United States

Supporting Information

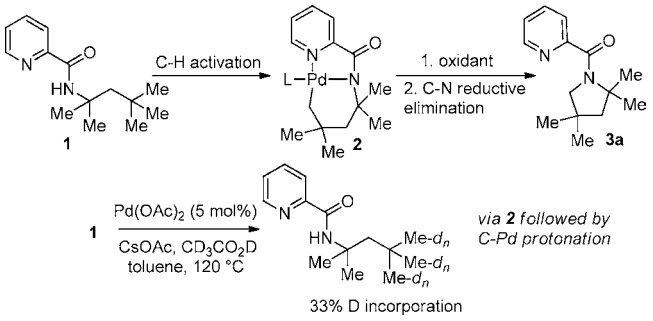
ABSTRACT: A method for five- and six-membered heterocycle formation by palladium-catalyzed C−H/N−H coupling is presented. The method employs a picolinamide directing group, $PhI(OAc)_2$ oxidant, and toluene solvent at 80−120 °C. Cyclization is effective for sp^2 as well as aliphatic and benzylic sp^3 C−H bonds.

Transition-metal-catalyzed functionalization of carbon−hydrogen bonds is a topic of recent intense interest. During the past few years, significant advances have been made in the conversion of C−H bonds to C−C and C−O functionalities.[1] However, direct non-nitrene amination reactions are rare. Most of the reports demonstrate functionalization of either sp^2 or activated (benzylic) sp^3 C−H bonds.[2a−k] Only a few papers describe palladium-catalyzed amination of alkane C−H bonds. Functionalization of methyl groups adjacent to quartenary centers is described in most cases. An early paper by Sames describes amino acid cyclization under platinum catalysis.[3a] Glorius has developed an elegant method for intramolecular, palladium-catalyzed amination of unactivated sp^3 C−H bonds that results in the formation of indolines.[3b] The reaction proceeds by an oxidative coupling of an amide NH with a $C(sp^3)$−H bond that is the most straightforward way for generating a N−C bond. A stoichiometric Ag(I) oxidant was employed, and no examples of pyrrolidine formation were presented. Buchwald has shown that palladium-catalyzed intermolecular amination of 2-bromo-*tert*-butylbenzenes by using aryl amines as a nitrogen source is possible. In this example, an *ortho*-$C(sp^2)$−Br bond is used as an internal oxidant.[4] In two examples, palladium-catalyzed formation of indolines has been accomplished by C−Br/sp^3 C−H coupling.[5] In these cases, functionalization of C−H bonds that are not part of *tert*-butyl groups is also possible. Several examples describe the formation of indolines or carbazoles by a $C(sp^2)$−H/NH coupling.[6a−c,e] Notably, Yu has demonstrated palladium-catalyzed *N*-triflated phenethylamine conversion to indolines by employing a range of oxidants.[6a] Buchwald and Gaunt have formed carbazoles from 2-arylanilines by employing palladium catalysis and O_2/$Cu(OAc)_2$ or $PhI(OAc)_2$ oxidants.[6b,c] Copper-catalyzed and transition-metal-free synthesis of carbazoles has been reported.[2i,k] Hofmann−Löffler reaction is a classical way to form pyrrolidines.[6f,g] A picolinamide directing group has been used for acetoxylation of sp^2 C−H bonds.[6d] A general method for C−H/N−H bond coupling that could utilize both sp^2 and sp^3 C−H bonds has not yet been disclosed. We report here a method for picolinamide auxiliary assisted, palladium-catalyzed pyrrolidine, indoline, and isoindoline synthesis by a C−H/N−H coupling.

Scheme 1. Picolinic Acid Directing Group



Scheme 2. Activation of C−H Bonds in δ-Positions

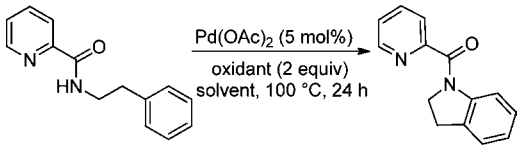


In 2005, we reported the *β*-arylation of carboxylic acid and *γ*-arylation of amine derivatives by employing an 8-aminoquinoline or picolinic acid auxiliary, catalytic $Pd(OAc)_2$, stoichiometric AgOAc, and an aryl iodide coupling partner (Scheme 1).[7] Subsequently, a number of auxiliaries were investigated for carboxylic acid *β*-arylation and it was shown that silver salts can be replaced by simple inorganic bases.[8] Several other groups have used this methodology for synthetic purposes. Corey has used the 8-aminoquinoline auxiliary to arylate sp^3 C−H bonds in amino acid derivatives.[9] Chen has employed the methodology in the total synthesis of Celogentin C.[10a] The picolinic acid directing group has also been used by Chen in the arylation of *γ*-positions of amines culminating in the synthesis of obafluorin.[10b] Total syntheses of piperarborenines were recently reported by Baran by employing a 2-thiomethylaniline directing group.[10c] The arylation reactions proceed via a favored double five-membered ring chelate (Scheme 1). If it was possible for C−H activation in *δ*-positions to occur, oxidation of the palladacycle **2** to form a high-valent palladium species followed by C−N reductive elimination would afford a

Received: November 21, 2011
Published: December 29, 2011

   dx.doi.org/10.1021/ja210959p | J. Am. Chem.Soc. 2012, 134, 7−10

Scheme 3. Optimization of Oxidant



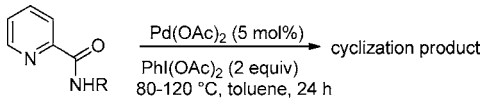
oxidant/solvent	conversion by GC, %
$PhI(OCOCF_3)_2$/toluene	0
$AgOAc/CH_2Cl_2$	0
$PhI(p\text{-}NO_2C_6H_4CO_2)_2$/toluene	38
$PhI(OAc)_2/CH_2Cl_2$	57
$PhI(OAc)_2/CH_3CO_2H$	44
$PhI(OAc)_2$/toluene	73

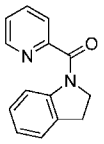
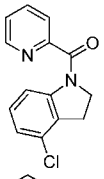
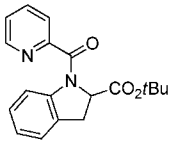
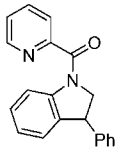
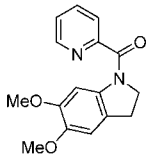
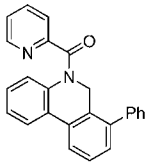
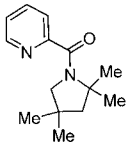
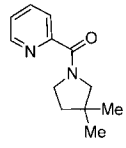
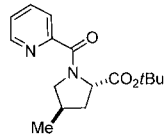
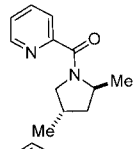
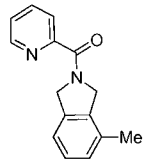
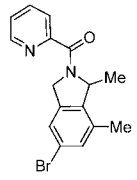
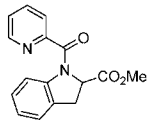
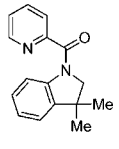
pyrroline derivative **3** (Scheme 2). Treatment of **1** with 5% $Pd(OAc)_2$ in toluene/CD_3CO_2D at 120 °C showed 33% deuterium incorporation at the terminal methyl groups. No other C−H bonds were deuterated. Hence, C−H δ-activation is possible by employing a picolinic acid directing group.[3b,11,12]

Subsequent reaction steps require an oxidant capable of converting palladium to a higher oxidation state followed by reductive elimination that would afford a cyclized product and regenerate the Pd(II) catalyst. Several oxidants were investigated, and the best results were obtained by employing $PhI(OAc)_2$ in toluene (Scheme 3).

Cyclization results are presented in Table 1. Direct sp^2 C−H/N−H coupling is possible, generating indolines in fair to

Table 1. Cyclization of Aryl and Alkyl Picolinamides[a]



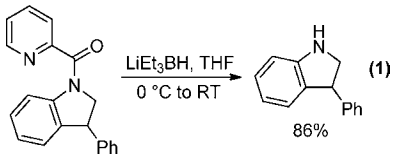
entry	R	cyclized product	yield, %
1	2-phenylethyl		80
2	2-chloro-phenylethyl		80
3	1-(CO_2tBu)-2-phenylethyl		77
4	2,2-diphenyl-ethyl		76
5[b]	3,4-dimeth-oxyphenylethyl		16
6[c]	2,6-diphenyl-benzyl		86
7	2,4,4-trimethyl-pent-2-yl		88
8[d]	3,3-dimethyl-butyl		40
9[d,e]	1-CO_2tBu-3-methylbutyl		36
10[f]	4-methyl-pent-2-yl		59
11[d]	2,6-dimethyl-benzyl		68
12[d]	2,6-dimethyl-4-bromo-α-methyl-benzyl		42
13	1-(CO_2Me)-2-phenylethyl		67
14[g]	2-t-butylphenyl		36

[a]Yields are isolated yields. See Supporting Information for details. [b]5,6-Dimethoxyindole picolinamide (18%) and 2-acetoxy-4,5-dimethoxyphenethylamine picolinamide (59%) also isolated. [c]7-Phenylphenanthridine (7%) also isolated. [d]Toluene/acetonitrile solvent. [e]Trans/cis ratio 9/1. [f]>10/1 trans/cis. [g]Toluene/DMF solvent. Entries 1, 3−7, 13 were run at 80 °C; 2, 9 at 100 °C, and 10−12, 14 at 120 °C.

dx.doi.org/10.1021/ja210959p | J. Am. Chem.Soc. 2012, 134, 7−10

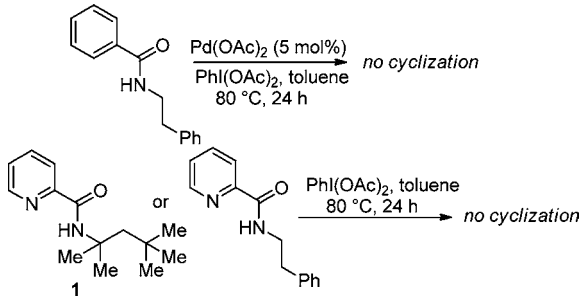
good yields (entries 1−5, 13). Chloro substitution on an aromatic ring is tolerated (entry 2), as is ester on indoline (entries 3, 13). 2,2-Diphenylethylamine picolinamide is cyclized in a good yield affording 3-phenylindoline (entry 4). A low yield is observed for cyclization of 3,4-dimethoxyphenetylamine picolinamide (entry 5). In addition to the cyclized product, the corresponding indole and sp^2 C−H bond acetoxylation products are obtained. Interestingly, formation of a six-membered ring structure is also possible in a good yield (entry 6), showing that cyclopalladation via a seven-membered ring is feasible.[3b,12] In addition to a dihydrophenanthridine derivative, a minor amount of 7-phenylphenanthridine was also isolated.

More challenging sp^3 C−H/N−H cyclizations also proceed smoothly (entries 7−12, 14). *tert*-Octylamine picolinamide is cyclized in a good yield (entry 7), and a 3,3-dimethylbutylamine derivative affords the product in moderate yield (entry 8). Leucine picolinamide gives a cyclized product in fair yield (entry 9). 4-Methyl-2-aminopentane picolinamide cyclizes in 59% yield (entry 10). Benzylic sp^3 C−H bonds are also reactive. 2,6-Dimethylbenzylamine picolinamide affords a 4-methylisoindoline derivative (entry 11). A 2,4,6-trisubstituted isoindoline can be obtained if 2,6-dimethyl-4-bromo-α-methylbenzylamine picolinamide is cyclized (entry 12). A 2-*tert*-butylaniline derivative is cyclized in a modest yield (entry 14). For sp^3 C−H bond amination, addition of acetonitrile solvent is sometimes beneficial (entries 8, 9, 11). Reasonable functional group tolerance is observed, with *tert*-butyl and methyl esters (entries 3 and 13) as well as aromatic chloride and bromide substituents (entries 2 and 12) tolerated. The directing group can be removed by $LiEt_3BH$ (eq 1). In general, amination is preferable to acetoxylation which is observed if a six-membered chelate such as **2** cannot be formed. Amination of methylene groups was not successful.



Several control experiments were run to exclude the possibility of other reaction pathways. First, subjecting 2-phenylethylamine benzamide to the cyclization conditions afforded no product. Consequently, a picolinamide directing group is essential for achieving cyclization (Scheme 4). Second,

Scheme 4. Control Experiments



the reaction of phenylethylamine picolinamide and *N*-(2,4,4-trimethylpentan-2-yl)picolinamide with $PhI(OAc)_2$ in toluene at 80 °C did not afford a cyclization product, showing that a palladium catalyst is required.

In conclusion, we have developed a palladium-catalyzed method for pyrrolidine, indoline, and isoindoline formation by a C−H/N−H coupling. The method employs a picolinamide directing group, $PhI(OAc)_2$ oxidant, and toluene solvent at 80−120 °C. Cyclization is effective for sp^2 as well as aliphatic and benzylic sp^3 C−H bonds.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

olafs@uh.edu

■ ACKNOWLEDGMENTS

We thank the Welch Foundation (Grant No. E-1571), National Institute of General Medical Sciences (Grant No. R01GM077635), A. P. Sloan Foundation, and Camille and Henry Dreyfus Foundation for supporting this research.

■ REFERENCES

(1) Reviews: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (h) Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495. (i) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (j) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, 677. (k) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (l) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J* **2010**, *16*, 2654. (m) Catellani, M.; Motti, E.; Della Ca', N.; Ferraccioli, R. *Eur. J. Org. Chem.* **2007**, 4153.

(2) (a) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978. (b) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511. (c) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707. (d) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (e) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (f) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (g) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590. (h) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (i) Cho, S.-H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996. (j) Fan, R.; Pu, D.; Wen, F.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8994. (k) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605. Amination via nitrenoids: (l) Du Bois, J. *Chemtracts* **2005**, *18*, 1. (m) Lu, H.; Subbarayan, V.; Tao, J.; Zhang, X. P. *Organometallics* **2010**, *29*, 389. (n) Ichinose, M.; Suematsu, H.; Yasutomi, Y.; Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 9884.

(3) Amino acid cyclization: (a) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (b) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892.

(4) Pan, J.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8647.

(5) (a) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (b) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438.

(6) (a) Mei, T. S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (b) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (c) Jordan-Hore, J. A.; Johansson, C. C. C.;

Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (d) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726. (e) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738. (f) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 5. (g) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095.

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

(8) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(9) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391.

(10) (a) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958. (b) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (c) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076.

(11) Li, J.-J.; Giri, R.; Yu, J.-Q. *Tetrahedron* **2008**, *64*, 6979.

(12) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.

dx.doi.org/10.1021/ja210959p | *J. Am. Chem.Soc.* 2012, 134, 7−10