Published in final edited form as:
J Am Chem Soc. 2012 January 11; 134(1): 7–10. doi:10.1021/ja210959p.

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

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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 last few years, significant advances have been made in 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-*t*-butylbenzenes by using aryl amines as 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 *t*-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] 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.

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

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ASSOCIATED CONTENT

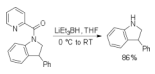
Supporting Information Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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 total synthesis of Celogentin C.[10a] Picolinic acid directing group has also been used by Chen in 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 C-H activation in δ-positions would be possible, oxidation of the palladacycle **2** to form a high-valent palladium species followed by C-N reductive elimination would afford a pyrroline derivative **3**. 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 oxidant capable of converting palladium to a higher oxidation state followed by reductive elimination that would afford 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 good yields (entries 1–5). Chloro substitution on aromatic ring is tolerated (entry 2), as is ester on indoline (entry 3). 2,2-Diphenylethylamine picolinamide is cyclized in a good yield affording 3-phenylindoline (entry 4). 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 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). *t*-Octylamine picolinamide is cyclized in a good yield (entry 7), and 3,3-dimethylbutylamine derivative affords the product in moderate yield (entry 8). Leucine picolinamide gives 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). 2-*t*-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, 14). Reasonable functional group tolerance is observed, with *t*-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.



(1)

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, picolinamide directing group is essential for achieving cyclization. (Scheme 4). Second, 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 cyclization product, showing that 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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.

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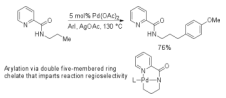
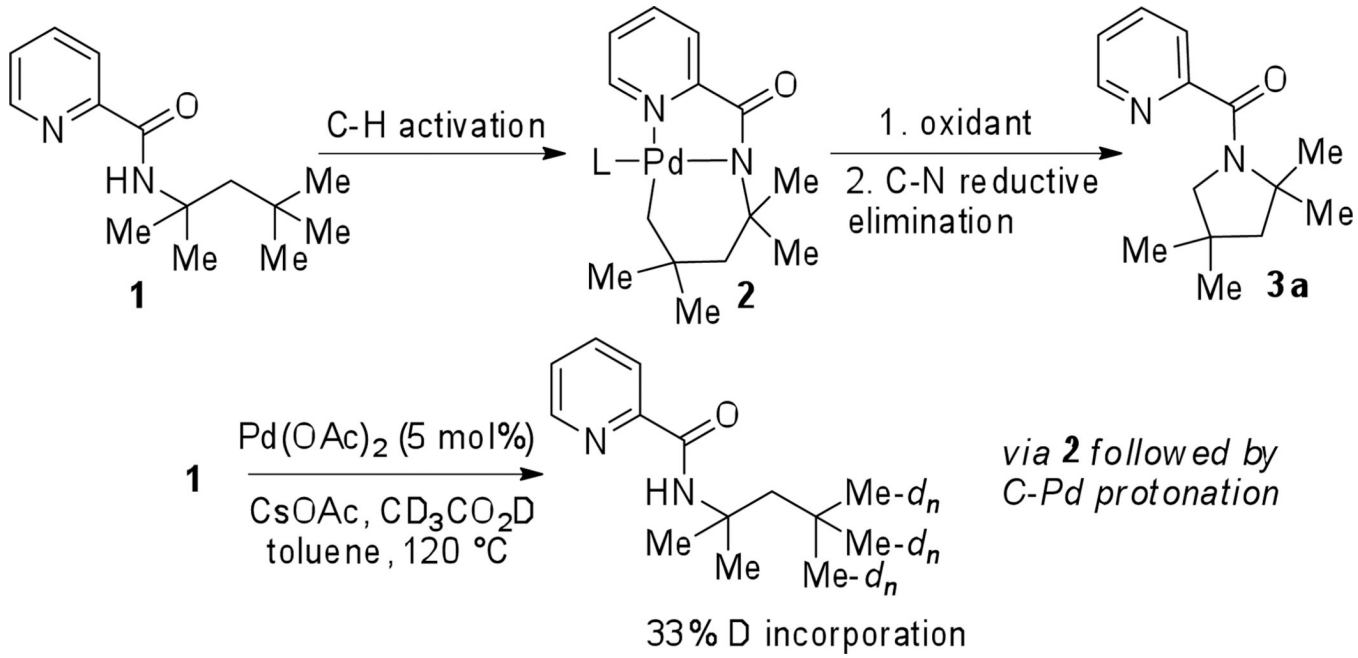
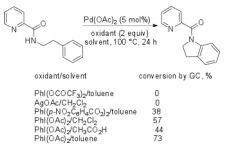


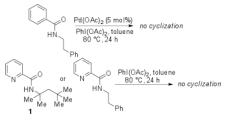
Scheme 1.
Picolinic Acid Directing Group



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



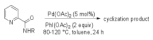
Scheme 3.
Optimization of Oxidant

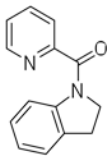
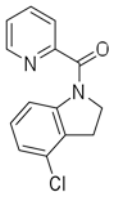
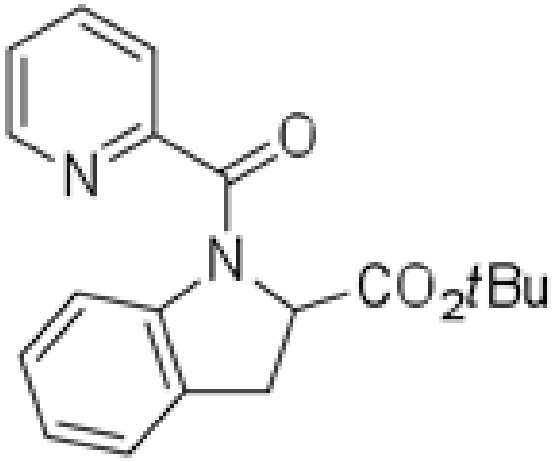
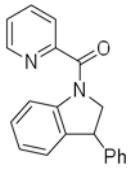
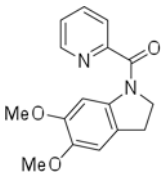


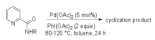
Scheme 4.
Control experiments

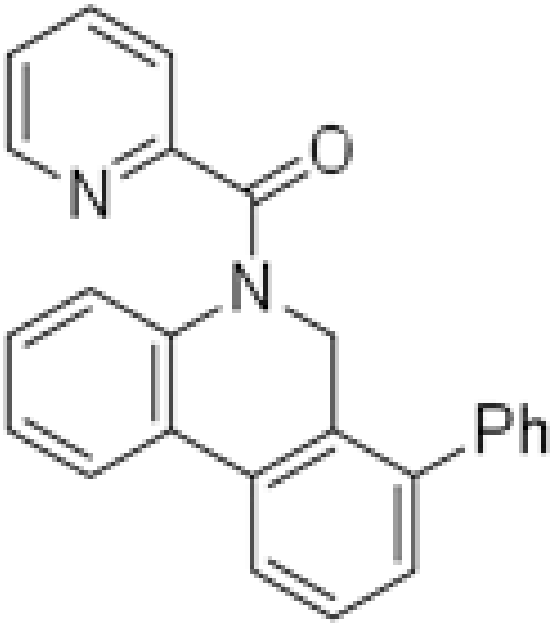
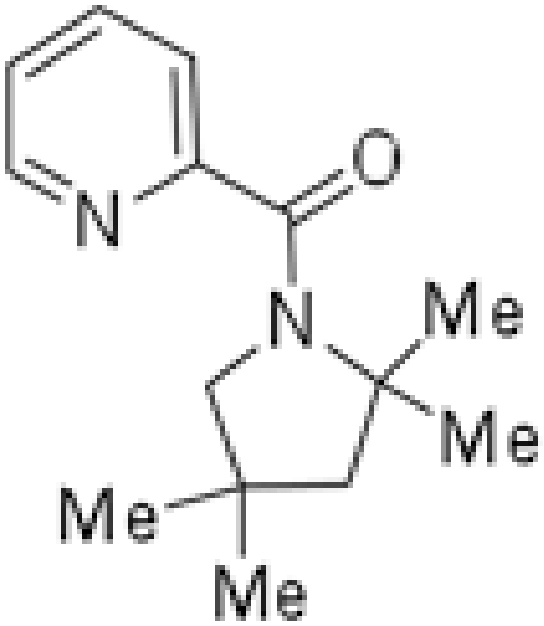
Table 1

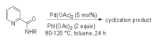
Cyclization of aryl and alkyl picolinamides[a]



entry	R	cyclized product	yield, %
1	2-phenylethyl		80
2	2-chlorophenylethyl		80
3	1-(CO_2tBu)-2-phenylethyl		77
4	2,2-diphenylethyl		76
5[b]	3,4-dimethoxyphenylethyl		16



entry	R	cyclized product	yield, %
6[c]	2,6-diphenylbenzyl		86
7	2,2,4-trimethylpent-2-yl		88



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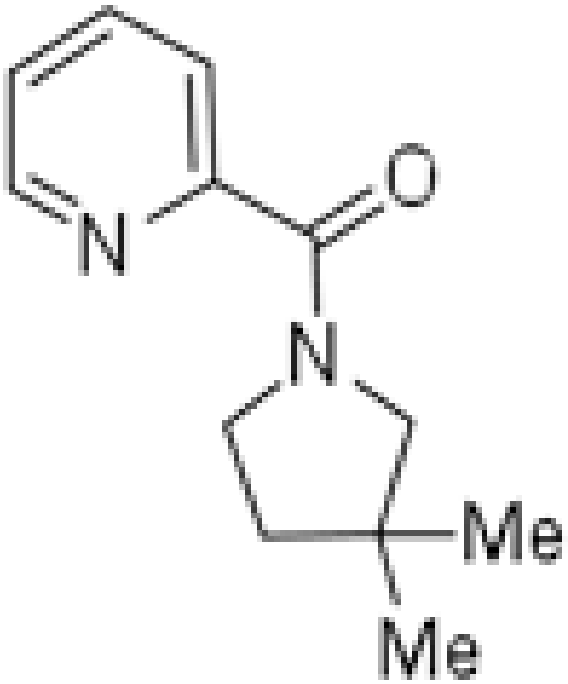
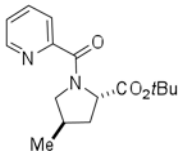
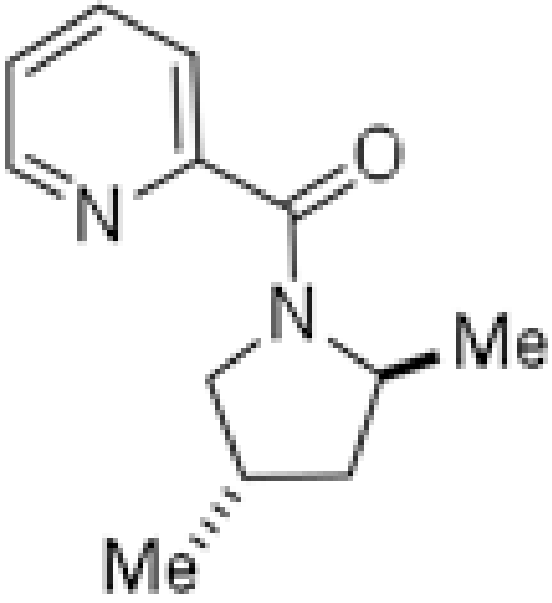
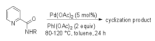
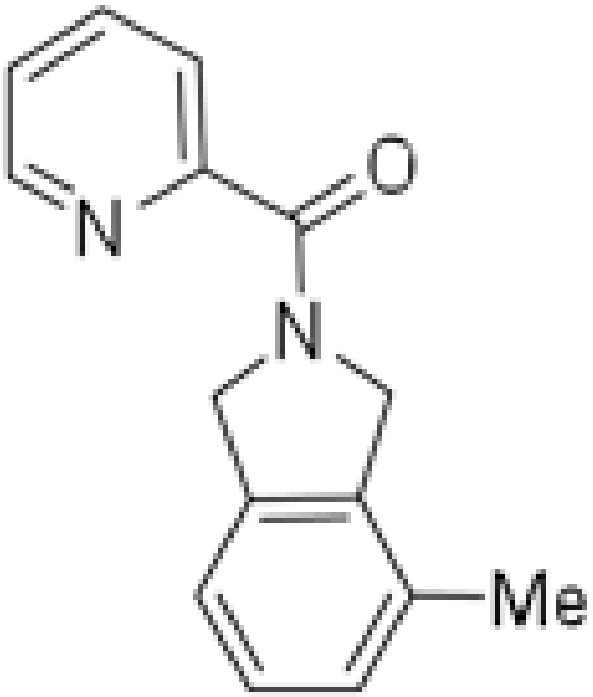
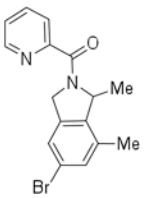
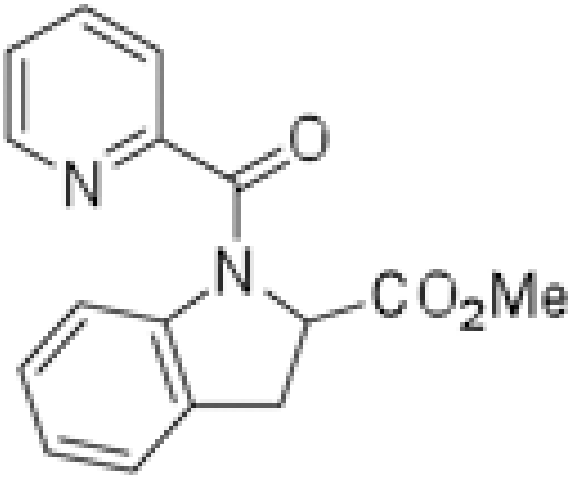
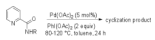
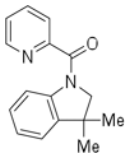
8[d]	3,3-dimethylbutyl		40
9[d,e]	2-CO_2tBu-3-methylbutyl		36
10[f]	4-methyl-pent-2-yl		59



entry	R	cyclized product	yield, %
11[d]	2,6-dimethylbenzyl		68
12[d]	2,6-dimethyl-4-bromo-α-methylbenzyl		42
13	1-(CO_2Me)-2-phenylethyl		67



entry	R	cyclized product	yield, %
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] Tolene/DMF solvent. Entries 1, 3–7, 13 were run at 80 °C; 2, 9 at 100 °C, and 10–12, 14 at 120 °C.