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Catalytic Coupling of C–H and C–I Bonds Using Pyridine As a Directing Group

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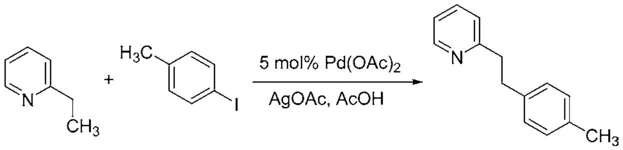
ABSTRACT



A method for the palladium-catalyzed arylation of pyridines and pyrazoles has been developed. Both aliphatic and aromatic C–H bonds may be functionalized using this method. A bromo substituent is tolerated on the aryl iodide coupling component.

The combination of selective, catalytic activation of C−H bonds with functionalization to form C−C bonds is an important goal for organometallic chemistry.[1] The utilization of a C−H bond as a functional group allows one to use cheap and readily available starting materials for organic synthesis, shorten reaction sequences, and obtain compounds that are difficult to synthesize using conventional methods.

Ideally, one would want to couple two C−H bonds to form a functionalized product ($R-H + R'-H \rightarrow R-R'$).[2] However, this process is often unfavorable thermodynamically, and given the potentially large number of C−H bonds in both reactants, achieving the desired regioselectivity of coupling is problematic. The coupling of aryl(alkyl) halides with C−H bonds is viable, but this variation has not been extensively investigated. Palladium-promoted ortho alkylation of imines and acetanilide derivatives by alkyl iodides has been described.[3] Both sp^2 and sp^3 C−H bonds of various heterocycles have been arylated α to the heteroatom under Rh or Pd catalysis.[4] Benzanilides have been arylated on the benzoic acid moiety under Pd(0)−Pd(II) catalytic cycle conditions.[5] Arylation of phenols in the ortho position has been achieved using Rh(I) catalysts.[6] Unfunctionalized arenes may be reacted with aryl iodides under Ir catalysis, and aromatic ketones and imines have been shown to ortho arylate using Ru catalysis.[7] 2-Arylpyridines have been arylated by arylstannanes under Rh catalysis[8] or by aryl bromides under Ru catalysis.[9] Recently, Sanford and coworkers have shown that sp^2 and activated sp^3 (benzylic) C−H bonds in pyridines can be arylated by aryliodonium salts under Pd catalysis.[10]

We have recently demonstrated a highly efficient catalytic procedure for the ortho arylation of substituted anilides

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[1] Reviews: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (d) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

[2] (a) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (b) Dasgupta, R.; Maiti, B. R. *Int. Eng. Chem. Proc. Des. Dev.* **1986**, *25*, 381.

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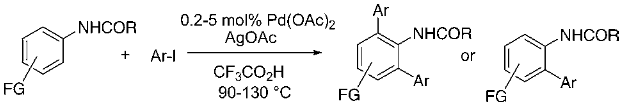
Scheme 1. Anilide Arylation

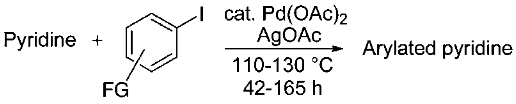


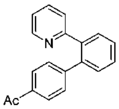
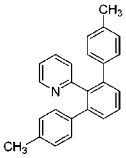
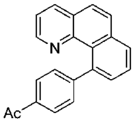
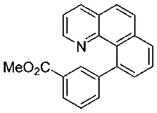
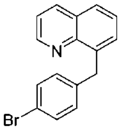
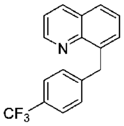
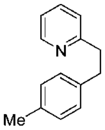
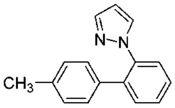
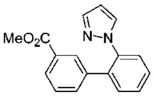
(Scheme 1).[11] This method allows up to 1000 turnovers/Pd and a unique functional group tolerance: bromide is tolerated on both coupling partners, and iodide is tolerated on the anilide. We have verified that this method allows the arylation of other arenes that contain ortho-directing groups. We report here the palladium-catalyzed arylation of sp^3 and sp^2 C−H bonds in substituted pyridines by aryl iodides.

The initial screening reactions were carried out with respect to the solvent. Two distinct cases were observed. As a typical substrate, 2-phenylpyridine (**1a**) was reacted with iodobenzene in the presence of catalytic $Pd(OAc)_2$ and stoichiometric AgOAc. The reaction was slow in DMF, trifluoroacetic acid, chlorobenzene, and *tert*-butyl alcohol. In contrast, a relatively fast reaction was observed in acetic and propionic acids, which were chosen as solvents for most of the substrates. In the case of 8-methylquinoline (**1c**), the reactions were substantially faster (3,5-dimethyliodobenzene was used for screening), and the use of acetic acid led to the formation of a mixture of compounds presumably containing polyarylation products and materials resulting from the partial oxidation of the intermediates.[12] In DMF, methanol, and chlorobenzene, the reaction was very slow, but in *tert*-butyl alcohol, selective monoarylation was observed.

Virtually any pyridines that can be palladated may be arylated by using this method (Table 1). Bromide is tolerated on the aryl group (entry 5), which is problematic when conventional Pd(0)−Pd(II) coupling methods are used. This approach thus allows the construction of scaffolds that may be functionalized further using conventional Pd(0) coupling processes. The arylation proceeds well with both electron-rich iodides (entries 2, 7, and 8) and moderately electron-poor iodides (entries 3−5 and 9). In the case of strongly electron-poor iodides, the reactions become slow and proceed only with the most reactive substrates (entry 6). This method allows the functionalization of not only aromatic but also benzylic (entries 5 and 6) and unactivated sp^3 (entry 7) C−H bonds. If more than one substitution is possible, either selective monoarylation (entry 1) or diarylation (entry 2) can be achieved by varying the reaction time. In both cases, a 5/1 ratio of ArI/pyridine was used, and initially selective (ca. 4:1 for entry 2) formation of the monoarylation product was observed by GC. At longer reaction times, diarylation product is formed. For aliphatic C−H bonds, only selective monoarylation can be achieved. 2-*tert*-Butylpyridine and 2-propylpyridine arylation produced a mixture of products, and selective monosubstitution was not achieved under the conditions investigated. 1-Phenylpyrazole was also arylated under these reaction conditions (entries 8 and 9).

Table 1. Arylation of Substituted Pyridines



entry	pyridine	FG	arylated pyridine	yield
1	2-Phenylpyridine (**1a**)	4-Ac		73%
2	**1a**	4-Me		80%
3	7,8-Benzoquinoline (**1b**)	4-Ac		74%
4	**1b**	3-CO_2Me		60%
5	8-Methylquinoline (**1c**)	4-Br		74%
6	**1c**	4-CF_3		69%
7	2-Ethylpyridine (**1d**)	4-Me		51%
8	1-Phenylpyrazole (**1e**)	4-Me		61%
9	**1e**	3-CO_2Me		59%

[a] Pyridine (1 equiv), ArI (3−5 equiv), AgOAc (1−3 equiv), $Pd(OAc)_2$ (3−5 mol %). Solvent: acetic acid (entries 1, 2, 4, and 7−9), propionic acid (entry 3), or *tert*-butyl alcohol (entries 5 and 6). Yields are isolated yields. See Supporting Information for details.

Currently, only a speculative discussion of the reaction mechanism is possible. As in the case of anilide arylation,[11] reactions generally are faster for electron-rich aryl iodides, which is different from the usual Pd(0)−Pd(II) catalytic processes. The most likely reaction mechanism involves

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electrophilic C−H activation by Pd(II) followed by oxidative addition of ArI to form a Pd(IV) intermediate. Reductive elimination of the product followed by iodide exchange for acetate by Ag^+ completes the catalytic cycle. In this regard, isolation of Pd(IV) aryls by Canty and co-workers may be relevant.[13]

In conclusion, we have developed a new arylation procedure for pyridines. This method allows the arylation of both aliphatic and aromatic C−H bonds in pyridines that can be ortho metalated by Pd(II)[14] and exhibits an interesting functional group tolerance: bromide is tolerated on the aryl iodide coupling component.

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

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