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ortho-Arylation of Benzamides

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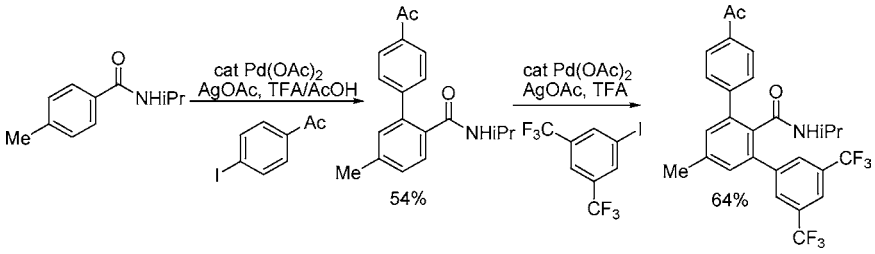
ABSTRACT



A simple method for the direct *ortho*-arylation of benzoic acid amides has been developed. The palladium-catalyzed reactions proceed in trifluoroacetic acid and require the presence of stoichiometric silver acetate. This presents an alternative to the currently used *ortho*-lithiation strategies for the synthesis of arylated benzoic acid derivatives.

Polyaryl units are common among natural products as well as other important substances. As a consequence, formation of aryl−aryl bonds has attracted a lot of attention.[1] The stoichiometric, copper-promoted aryl−aryl bond formation was pioneered by Ullmann over a hundred years ago.[2] More recently, reactions developed by Stille, Kumada, and Suzuki have found wide application in organic synthesis.[3] These reactions can be generalized as a coupling of a C−Y bond (Y = SnR_3, Stille; MgX, Kumada; $B(OH)_2$, Suzuki) with a C−X bond where X = halogen or triflate. Quite often such functionalized starting materials are not available and have to be prepared. Replacement of one or both of these functional groups with C−H bonds would result in shorter synthetic sequences.

Transition-metal-catalyzed C−H activation processes have lately been shown to be effective for C−H/C−X coupling sequences.[4] The stoichiometric version of this reaction was pioneered by Tremont more than 20 years ago.[4a] Since then, it has been shown that many arenes containing a directing group can be arylated by aryl halides, boronates, stannanes, or aryliodonium salts under palladium, ruthenium, or rhodium catalysis. Ruthenium catalysis is mostly limited to arylation of arenes containing a strong directing group, for example, pyridines, imines, or oxazolines.[4b−d] However, there are examples of aromatic ketone *ortho*-arylation by arylboronates.[4e] Rhodium complexes have been shown to catalyze the arylation of arylpyridines, phenols, and electron-rich heterocycles.[4f−h] The most general arylation methods have been developed based on Pd catalysis. A number of compounds containing a directing group can be arylated. The reaction of 2-arylpyridines, 8-methylquinoline, and other nitrogen heterocycles with diphenyliodonium salts under Pd(II) catalysis has been studied by Sanford.[4i] Phenols and naphthols can be arylated in *ortho* or *peri* positions if treated with $ArBr/Pd(OAc)_2/Cs_2CO_3$ in DMF or xylene at elevated temperatures.[4j,k] We have shown that pyridines, acylated

(1) For a review, see: Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174.

(3) For reviews, see: (a) Suzuki, A. *Chem. Commun.* **2005**, 4759. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (c) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201. (d) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.

(4) (a) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123. (c) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113. (d) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783. (e) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (f) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439. (g) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (h) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35. (i) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (j) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961. (k) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (l) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (m) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. (n) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

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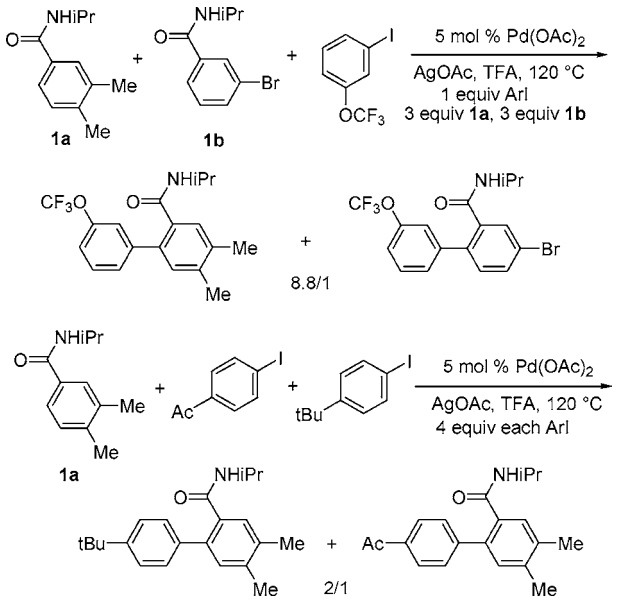
anilines, 8-aminoquinoline benzamides, and benzylamine picolinamides can be arylated by aryl iodides, presumably under Pd(II)−Pd(IV) catalytic cycle conditions.[4l−n] A number of palladium-catalyzed arylations have been shown to be initiated by oxidative addition of a C−X bond to Pd(0).[5] Various heterocycles may also be arylated α to the heteroatom.[6]

Our attention was drawn to two observations. First, Miura and co-workers have demonstrated that benzoic acid phenylamides can be arylated by aryl bromides or triflates.[7] The reactions proceed in DMF or toluene and require the presence of a cesium base. The coordination of an amide anion to an intermediate palladium species is necessary for the *ortho*-palladation/aryl transfer step to occur. Most likely the reaction proceeds by a Pd(0)−Pd(II) mechanistic pathway. With the exception of Miura's work, direct palladation of simple benzamides has not been observed. Second, there is a certain similarity between the *ortho*-lithiation[8] and *ortho*-palladation chemistry.[9] Many compounds that may be lithiated can also participate in palladation/functionalization sequences. If the analogies hold, then the *ortho*-palladation/arylation sequence may be applicable for simple benzoic acid amides just as this sequence works for anilide derivatives.[4l] If the reaction would proceed by a Pd(II)−Pd(IV) catalytic cycle, then increased functional group tolerance might be observed. Compared to our previous method for benzoic acid amide arylation, an expensive 8-aminoquinoline auxiliary would not be required.[4n] We report here a method for direct *ortho*-arylation of benzoic acid isopropylamides.

A short optimization was carried out to determine which benzoic acid amides are the most suitable for the arylation. Unsubstituted amides and methylamides gave inferior yields and conversions; *tert*-butylamides were unstable under the optimization conditions in trifluoroacetic acid. The arylation of propylamides and isopropylamides worked well. All subsequent reactions were carried out with isopropylamides. The reactions proceed both in acetic and trifluoroacetic acids but are faster in trifluoroacetic acid.

Faster reactions, as expected for an electrophilic C−H activation,[10] are observed for electron-rich benzamides. A competition experiment was carried out by reacting a mixture of 3,4-dimethylbenzoic acid isopropylamide (**1a**) and 3-bromobenzoic acid isopropylamide (**1b**) with 3-trifluoromethoxyphenyl iodide (Scheme 1). After complete consumption

Scheme 1. Competition Experiments



of ArI, an 8.8:1 ratio of arylated **1a**/arylated **1b** was observed. As seen for other catalytic reactions proceeding by a Pd(II)−Pd(IV) mechanism,[4l−n] electron-rich aryl iodides react faster. A qualitative competition experiment was performed by reacting **1a** with a mixture of 4-*tert*-butylphenyl iodide and 4-iodoacetophenone (Scheme 1). At about 70% conversion, a 2:1 ratio of 4-*tert*-butylphenylated/4-acetylphenylated products was observed. The aryl iodide enters the catalytic cycle at the stage of oxidative addition to Pd(II), which is most likely the rate-determining step. This step must be faster for electron-rich aryl iodides.

Both electron-rich (entries 1−3, 7, 8, 10, Table 1) and moderately electron-poor (entries 4−6) amides are reactive. *meta*-Substituted benzamides are monoarylated (entries 1−5, 7, 8), whereas the benzoic acid and 4-methylbenzoic acid amides can be either monoarylated (entry 10) or diarylated (entry 9) depending on reaction time and solvent. It is possible to introduce two different aryl groups onto the aromatic ring by sequential arylation. This is demonstrated by first reacting **1f** with 4-iodoacetophenone, producing monoarylated product in 54% yield (entry 10). This reaction was run in an acetic acid/trifluoroacetic acid mixture that is advantageous if selective monoarylation is desired. The product was subsequently arylated by 3,5-bis(trifluoromethyl)-iodobenzene to give the diarylated product in 64% yield (entry 11). An interesting byproduct was isolated in 7% yield in the latter reaction (Figure 1). An additional aryl substituent was introduced *ortho* to the acetyl group.

The reactions proceed well with electron-poor aryl iodides. Electron-rich aryl iodides (entry 1) react faster but are more susceptible to side reactions. For example, use of *p*-methoxyphenyl iodide in the arylation of **1a** resulted in

(5) (a) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (b) Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857. (c) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2. (d) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (e) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.

(6) (a) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (c) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (d) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (e) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

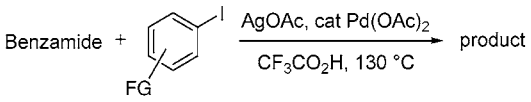
(7) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655.

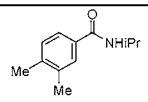
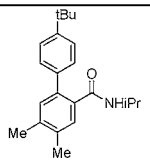
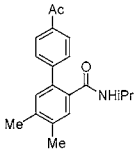
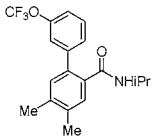
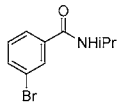
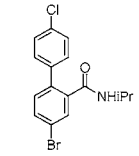
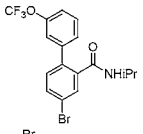
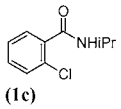
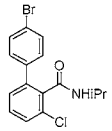
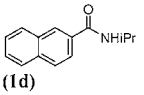
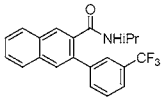
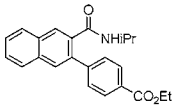
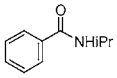
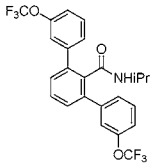
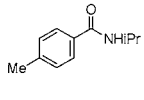
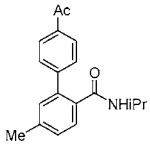
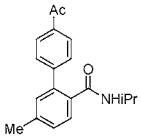
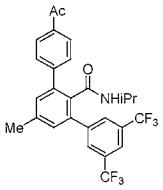
(8) (a) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(9) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527.

(10) (a) Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416. (b) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Organomet. Chem.* **1991**, *406*, 309.

Table 1. Benzoic Acid Isopropylamide Arylation[a]

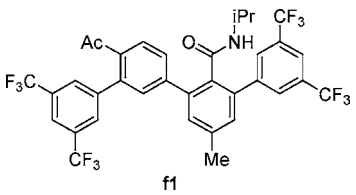


entry	benzamide	FG	product	yield
1	 **(1a)**	4-tBu		79%
2	**1a**	4-Ac		57%
3	**1a**	3-OCF_3		96%
4	 **(1b)**	4-Cl		79%
5	**1b**	3-OCF_3		84%
6	 **(1c)**	4-Br		59%
7	 **(1d)**	3-CF_3		61%
8	**1d**	4-CO_2Et		58%
9	 **(1e)**	3-OCF_3		73%
10[b]	 **(1f)**	4-Ac		54%
11[c]	 **(1g)**	3,5-$(CF_3)_2$		64%

[a] Amide (1 equiv), ArI (2.3−4 equiv), AgOAc (1.5 equiv per introduced Ar), $Pd(OAc)_2$ (5 mol %), trifluoroacetic acid solvent (0.7 mL per mmol amide), 0.5−5 h. Yields are isolated yields. See Supporting Information for details. [b] Acetic/trifluoroacetic acid mixture (4:1) as solvent. [c] Byproduct **f1** isolated in 7% yield.

incomplete reaction and substantial protodeiodination of aryl iodide. Thus, more optimization is needed if electron-rich ArI is used.

In conclusion, we have developed a new and convenient method for the *ortho*-arylation of benzamides. This method is complementary to existing lithiation/ boronation/cross-coupling methods and offers advantages with regards to the number of synthetic steps and in cases where base-sensitive substrates are used. However, the lithiation strategies are likely preferred if acid-sensitive substrates are used because our method requires the use of trifluoroacetic acid as solvent.



f1

Figure 1. Byproduct in the arylation of **1g**.

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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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