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Direct Palladium-Catalyzed *Ortho*-Arylation of Benzylamines

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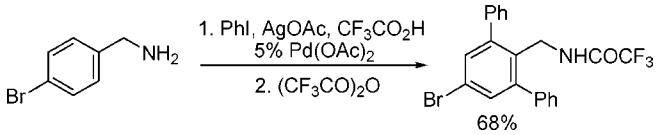
ABSTRACT



Unsubstituted benzylamines and *N*-methylbenzylamine can be *ortho*-arylated under palladium catalysis at 130 °C. The reactions require the presence of trifluoroacetic acid and silver acetate.

Probably the most ubiquitous functional group in organic chemistry is the C−H bond. The use of this group in selective organic transformations offers advantages with respect to the length of synthetic transformations and the availability of starting materials. As a consequence, the development of selective C−H bond functionalization has become a topic of intense interest.[1] Despite many recent successes, there are still problems with respect to the selectivity and generality of such processes. Only a handful of examples of unactivated (not benzylic or α to heteroatoms) sp^3 C−H bond conversions to C−C bonds have been demonstrated in the literature.[2] An improvement in the generality of intermolecular C−H activation reactions is desirable. There are a few substrate classes where remarkable achievements in this method have been demonstrated. For example, electron-rich heterocycles can be both arylated and alkenylated under a variety of conditions, allowing direct functionalization of these important substrates.[3] Additionally, pyridines, oxazolines, anilides, and phenols are among substrates that may be arylated or otherwise functionalized.[4] Recently, several examples of the alkylation or arylation of compounds without strong directing groups have been demonstrated.[5] We have developed a widely applicable method that allows the arylation of various substrates functionalized with directing groups.[6] The reactions involve heating of an aryl iodide, the substrate, and silver acetate in a carboxylic acid or without solvent. Unique functional group tolerance is observed; bromide is always tolerated, and occasionally even iodide substituents are compatible with the reaction conditions. Acylated anilines,[6a] 2-aryl-, and alkylpyridines[6b] have been shown to be reactive under these conditions. If an additional

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pyridine or quinoline chelating group is present, then even sp^3 C−H bonds are reactive.[6c] This method was recently used for the synthesis of modified amino acid derivatives.[7]

On the other hand, the selective, palladium-catalyzed *ortho*-arylation of benzylamines has yet to be demonstrated. Reaction sequences leading to such compounds currently require multiple steps, involving lithiation/boronation/cross-coupling.[8] We report here the direct *ortho*-arylation of benzylamines by aryl iodides under palladium catalysis.

Although the *ortho*-palladation of *N*,*N*-dialkylbenzylamines is well-known,[9] the palladation of NH-containing benzylamines is much less common.[10] We wished to determine if these compounds could be *ortho*-arylated using our method; we note that the corresponding lithiation chemistry would be difficult in this case due to acidic NH protons. Given the solvent dependence of the previously reported arylations,[6a,b] acetic and trifluoroacetic acids were tested in the reaction of (*R*)-α-methylbenzylamine and iodobenzene. The reaction was fast in trifluoroacetic acid, and a slower process resulting in the formation of a mixture of mono- and diarylation products was observed in acetic acid. Importantly, the amount of acid strongly influenced the results. Specifically, the reactions were the fastest when about 5 equiv of trifluoroacetic acid was used. In only one case were sp^3 C−H bonds found to be reactive; 2-amino-3,3-dimethylbutane was arylated by *p*-tolyl iodide, leading to a mixture of mono- and diarylation products. It was not possible to obtain selectively either the mono- or the diarylated amine, and out of many alkylamines, only this substrate was reactive. The attempted arylation of amines possessing *β*-hydrogen substituents led to the immediate formation of Pd(0), presumably by facile *β*-hydride elimination from the palladated intermediate. Consequently, we concentrated our efforts on the arylations of benzylamines.

Analysis by GC-MS of the products formed from the arylation of benzylamine revealed that, besides the expected diarylation product, some (ca. 10%) of the *N*-trifluoroacetylated derivative was formed (Scheme 1). *N*-Methylbenzylamines were not trifluoroacetylated under these conditions. A control experiment was performed to verify that benzylamine trifluoroacetamides are not the species arylated in the reaction mixture. Thus, *N*-trifluoroacetylbenzylamine was reacted with iodobenzene under the usual conditions. No reaction was observed. To simplify the isolation procedure, the reaction mixtures were treated with trifluoroacetic anhydride (for unsubstituted benzylamines) or acetic anhydride/triethylamine (for *N*-methyl derivatives).

Scheme 1. Trifluoroacetamide Formation

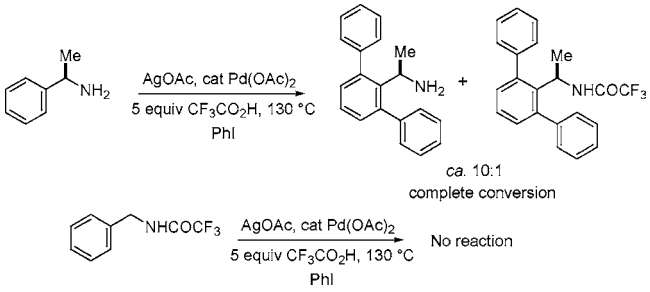
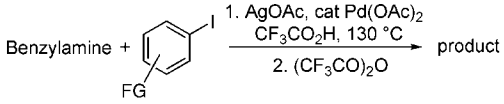
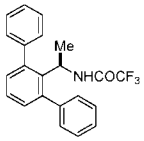
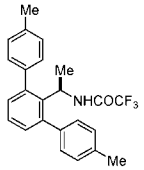
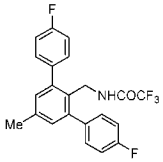
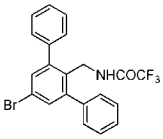
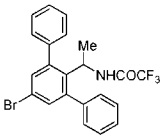
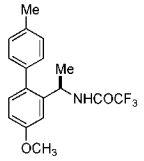
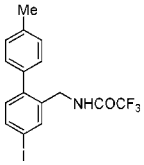


Table 1. Arylation of Benzylamines[a]



entry	benzylamine	FG	product	yield
1	(*R*)-α-Methylbenzylamine (**1a**)	H		72%
2	**1a**	4-Me		83%
3	4-Methylbenzylamine (**1b**)	4-F		67%
4	4-Bromobenzylamine (**1c**)	H		68%
5	α-Methyl-4-bromobenzylamine (**1d**)	H		61%
6	(*R*)-α-Methyl-3-methoxybenzylamine (**1e**)	4-Me		78%
7	3-iodobenzylamine (**1f**)	4-Me		52%

[a] Benzylamine (1 equiv), ArI (10 equiv), AgOAc (2.4 equiv), $Pd(OAc)_2$ (5 mol %), CF_3CO_2H (5 equiv), 1.5−4 h. Yields are isolated yields. See the Supporting Information for details.

Using GC standards, we found that the reactions proceed in almost quantitative yields. However, upon attempted

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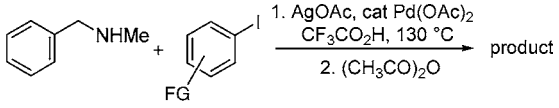
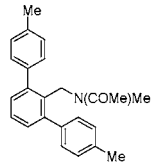
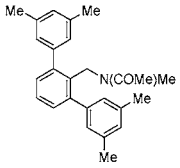
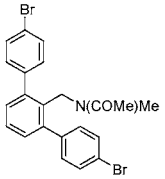
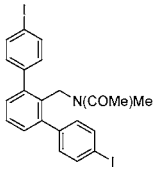
Table 2. Arylation of *N*-Methylbenzylamine[a]



entry	FG	product	yield
1	4-Me		66%
2	3,5-Me_2		77%
3	4-Br		60%
4	4-I		49%

[a] *N*-Methylbenzylamine (1 equiv), ArI (10 equiv), AgOAc (2.4 equiv), $Pd(OAc)_2$ (5 mol %), CF_3CO_2H (5 equiv), 1−2 h. Yields are isolated yields. See the Supporting Information for details.

chromatography of the trifluoroacetamides, variable yields as low as 30% were observed. Reproducible yields were, however, obtained upon treatment of trifluoroacetamides with transition-metal scavenging resins before chromatography. The acetylated *N*-methylbenzylamines did not require such treatment.

The reactions proceed well with both electron-rich and moderately electron-poor (Table 1, entries 4, 5, 7) benzylamines. As expected, the reactions are faster for electron-rich benzylamines. A competition experiment was carried out by reacting *N*-methylbenzylamine with a mixture of 4-iodotoluene and 4-iodobromobenzene. Approximately equal reactivity was observed (see Supporting Information for details). This feature is distinct from the usual Pd(0)−Pd(II) catalytic cycles where electron-poor aryl halides are more reactive. For unsubstituted or 4-substituted benzylamines, clean 2,6-diarylation is observed. Benzylamines substituted at the 3-position are monoarylated (examples 6 and 7). As in the case of pyridine and anilide arylation, bromine is tolerated on the substrate (entries 4 and 5), and even iodide is compatible with the reaction conditions, although in this case the yield is somewhat reduced (entry 7).

N-Methylbenzylamine is also arylated successfully under the optimized reaction conditions (Table 2). The reactions are somewhat faster than in the case of unsubstituted benzylamines. Because trifluoroacetylation of products was not observed in these reactions, the arylated amines were acetylated to facilitate the isolation. An X-ray structure of the product of entry 3 in Table 2 was obtained (see Supporting Information for details).

In conclusion, we have developed a useful method for the direct *ortho*-arylation of benzylamines and *N*-methylbenzylamine. The reactions require a slight excess of silver acetate, about 5 equiv of trifluoroacetic acid, and temperatures of 130 °C. This presents a shorter and more convenient alternative to our previously reported methodology that requires a picolylamide directing group for benzylamine arylation and is successful only for primary amine derivatives.[6c]

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Supporting Information Available: Detailed experimental procedures, characterization data for new compounds, and X-ray data for Table 2, entry 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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