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Palladium-Catalyzed Arylation of Electron-Rich Heterocycles with Aryl Chlorides

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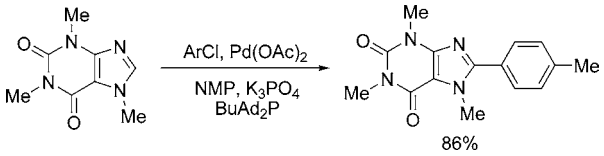
ABSTRACT



Palladium-catalyzed C–H activation: cheap aryl chlorides can now be used for the arylation of a wide variety of electron-rich heterocycles. The key to the success of this reaction is the use of a bulky, electron-rich phosphine ligand. No copper additives are needed.

The formation of carbon−carbon bonds is perhaps one of the most important reactions in organic chemistry. Currently, the most developed methods for forming sp^2 carbon−carbon bonds involve transition-metal-catalyzed cross-coupling reactions between Ar−M (M = SnR_3, $B(OR)_2$, MgX) and Ar−X (X = halogen, sulfonate).[1] Quite often, these functionalized starting materials are either expensive or have to be prepared in several steps. Regioselective conversion of C−H to C−C bonds would result in shortening of synthetic schemes by allowing the use of readily available starting materials.[2]

The goal of this work was to develop a general method for intermolecular electron-rich heterocycle arylation by aryl chlorides. The pioneering work in this field was performed by Ohta and co-workers.[3] They demonstrated that indoles, furan, thiophene, benzofuran, and benzothiophene can be arylated under palladium catalysis. Subsequently, other groups have extended this methodology to the arylation of a number of heterocycles by using palladium or rhodium catalysis.[4] However, this methodology still suffers from some deficiencies. First, for some heterocycles to be successfully arylated, stoichiometric amounts of copper salt additives are necessary.[4a,h,l] Second, most methods allow the arylation of only a few types of heterocycles thus limiting the scope of the methodology. Third, in most cases, either aryl bromide or aryl iodide reagents are used. Cheaper and generally more available aryl chlorides have been used only rarely,[4f] and

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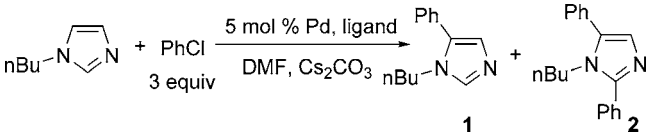
their use often is limited to activated substrates, for example, chloropyrazines.[3] We report here a general method for the intermolecular arylation of electron-rich, five-membered heterocycles by aryl chlorides.

The screening reactions were performed with respect to the solvent, base, and palladium source (see Supporting Information for the details). The oxidative addition of ArCl to Pd(0) usually requires a bulky, electron-rich phosphine, a secondary phosphine oxide, or an N-heterocyclic carbene (NHC).[5] Optimization revealed that neither phospine oxide nor NHC ligands are effective. Electron-rich, bulky butyldi-1-adamantylphosphine[6] and *tert*-butyldicyclohexylphosphine afforded the best results, and the former was chosen because of cost considerations (Table 1). Among the bases screened,

Table 1. Ligand Optimization[a]



entry	ligand, 10 mol %	% of **1**	% of **2**
1	nBuAd$_2$P	40	12
2	tBu$_2$bP-P[b]	20	6
3	tBuCy$_2$P	45	16
4	IPr-HCl[c] (5 mol %) + K^{t}BuO (10 mol %)	12	4
5	Ad$_2$POH	10	3

[a] Conditions: 5 mol % of Pd(OAc)$_2$, 2 equiv of Cs_2CO_3, MS 3 Å, dry DMF, stir for 15 min at rt and then for 16 h at 125 °C. [b] 2-(Di-*tert*-butylphosphino)biphenyl. [c] 1,3-Bis-(2,6-di-*iso*-propylphenyl)-4,5-dihydroimidazolium chloride.

use of CsOAc, CsF, K_3PO_4, K_2CO_3, and Cs_2CO_3 resulted in reasonable conversions to the product. Potassium phosphate afforded somewhat better selectivity for monoarylation, is cheaper than the cesium salts, and was used in all subsequent reactions. Evaluation of palladium sources revealed that palladium acetate is superior to all other choices. Optimization with respect to solvent showed that the reaction proceeds best in NMP. The optimized conditions thus include NMP solvent, K_3PO_4 base, butyldi-1-adamantylphosphine ligand, and Pd(OAc)$_2$ catalyst.

A variety of electron-rich heterocycles can be arylated using this methodology (Table 2). Thiophene and benzothiophene are reactive (entries 1−3). Both 1,2- and 1,3-oxazole derivatives can be arylated (entries 4 and 6−8). Benzofuran is diarylated in a reasonable yield (entry 5). Thiazole and benzothiazole arylation is also successful (entries 9−12). In 2-substituted thiazoles, the aryl group is introduced next to sulfur (entries 11 and 12). 1-*n*-Butylimidazole is arylated in the 5-position, with some diarylation product also formed (entry 13). 1-Methyl-1,2,4-triazole is selectively arylated in the 5-position (entry 14). Caffeine is very reactive, and some of the products are of interest as

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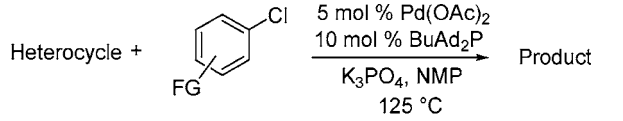
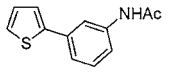
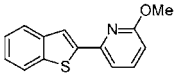
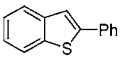
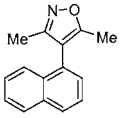
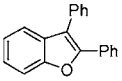
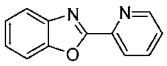
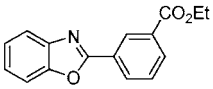
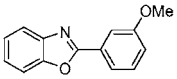
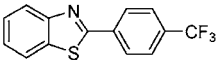
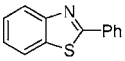
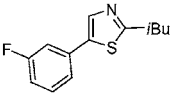
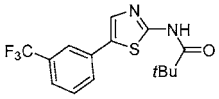
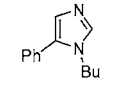
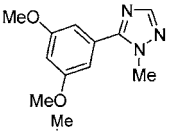
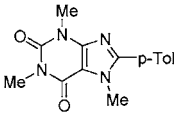
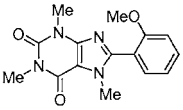
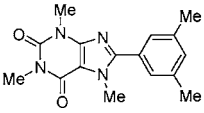
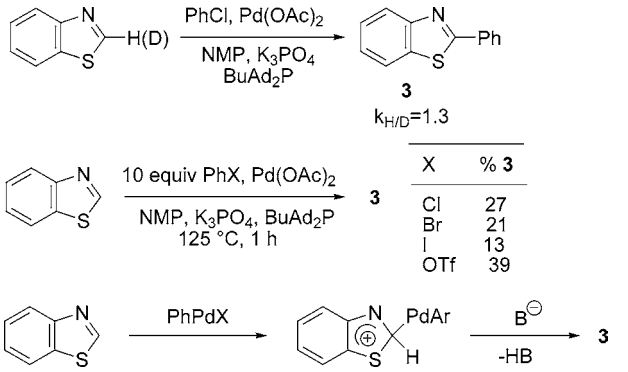
Table 2. Heterocycle Arylation by Aryl Chlorides[a]



entry	heterocycle	FG	product	yield
1[b]	Thiophene	3-NHAc		54%
2	Benzothiophene	c		72%
3	Benzothiophene	H		63%
4	3,5-Dimethyl-isoxazole	d		76%
5[e]	Benzofuran	H		68%
6	Benzoxazole	f		67%
7	Benzoxazole	3-CO_2Et		84%
8	Benzoxazole	3-OMe		58%
9	Benzothiazole	4-CF_3		82%
10	Benzothiazole	H		84%
11	2-Isobutyl-thiazole	3-F		83%
12	2-Pivaloylamino-thiazole	3-CF_3		79%
13[g]	1-Butylimidazole	H		52%
14	1-Methyl-1,2,4-triazole	3,5-$(MeO)_2$		76%
15	Caffeine	4-CH_3		86%
16	Caffeine	2-OMe		71%
17	Caffeine	3,5-Me_2		77%

[a] Substrate (1 equiv), ArCl (1.5 equiv), K_3PO_4 (2 equiv), Pd(OAc)$_2$ (5 mol %), 10 mol % of nBuAd$_2$P, 24 h at 125 °C. Yields are isolated yields. See the Supporting Information for details. [b] Thiophene (3 equiv), chloroarene (1 equiv). [c] 2-Chloro-6-methoxypyridine. [d] 1-Chloronaphthalene. [e] Benzofuran (1 equiv), chloroarene (3 equiv). [f] 2-Chloropyridine. [g] 2,5-Diphenylated derivative also isolated in 13% yield.

Scheme 1. Mechanistic Considerations



adenosine receptor antagonists (entries 15−17).[7] If C−H activation methodology is not used, the synthetic sequences leading to these compounds require several steps instead of a single step.[7] Amide substitution is tolerated on both aryl chloride and the heterocycle (entries 1 and 12), and the N−H bond is not arylated.[8] Chlorobenzoic acid esters can also be used (entry 7). 2-Chloropyridines are reactive (entries 2 and 6), and the products of these arylations may find use as chelating ligands. Both electron-rich and electron-poor aryl chlorides can be used; however, as expected, electron-poor chlorides are more reactive. Some steric hindrance is tolerated on the heterocycle (entry 4) and aryl chloride (entry 16). Arylation of *N*-methylindole under the standard conditions resulted in low conversion (ca. 20%).

We have performed some preliminary mechanistic investigations of the arylation. The qualitative arylation mechanism is presented in Scheme 1. The deuterium isotope effect for the arylation of benzothiazole was found to be 1.3 (Scheme 1). Isotope effect values of this magnitude are often observed for aromatic electrophilic substitution reactions.[9] Additionally, the regiochemistry of 1-*n*-butylimidazole arylation is consistent with that observed in electrophilic substitution.[10] As a consequence, we favor the electrophilic substitution mechanism proposed by Miura for the arylation of thiazoles and imidazoles;[4a] an analogous mechanism was proposed by Gevorgyan for the arylation of indolizines.[4b] The observed counterion effect is also interesting. The reactions are the fastest for triflates. Somewhat slower reactions are observed for chlorides; bromides and iodides react the slowest. Because the oxidative additions to Pd(0) are normally the fastest for iodides, it is clear that the oxidative addition of the C−Cl bond is not the rate-determining step. Additionally, the leaving group is unlikely to act as a base in proton removal because compounds containing the weakest base, triflate, react the fastest. It has to be stated that the arylation of such different heterocycles does not necessarily proceed by exactly the same mechanism. Certain Rh-catalyzed heterocycle arylations proceed via Rh carbene intermediates.[4o]

In conclusion, we have developed a new, efficient, and general electron-rich intermolecular heterocycle arylation process based on C−H activation. This is the first general method for heterocycle arylation with aryl chlorides. Electrophilic substitution is the most likely mechanism for this reaction.

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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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