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Regioselective Palladium-Catalyzed Arylation of 2-Furaldehyde

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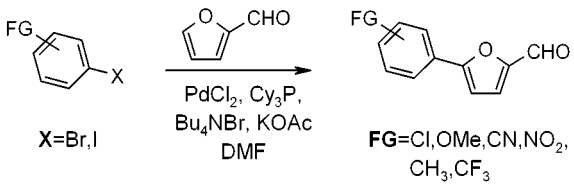
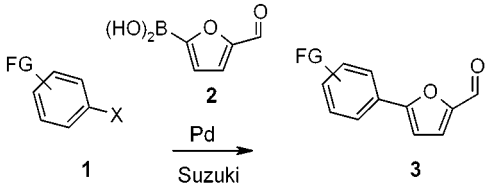
ABSTRACT



An efficient regioselective method for the direct arylation of 2-furaldehyde to provide a range of π-diverse 5-aryl-2-formylfuran derivatives is described. The method employs functionalized aryl halides and a catalytic amount of palladium(II) chloride under relatively mild conditions.

The literature is replete with compounds containing furanyl[1] and bis-furanyl motifs including septamycin and compounds isolated from *Annona squamosa*.[2] Indeed, simple substituted furfurals alone often exhibit activity of biological significance.[3] A mild and efficient method for the direct functionalization of furfural would therefore be of benefit. Our interest in this area stems from the need to prepare 5-arylfurfurals on scale. The arylfuran motif serves as a template for the divergent preparation of analogues in an ongoing medicinal chemistry program. Previously, our strategy relied on the use of a Suzuki[4] coupling of boronic acid **2** (Scheme 1) with a variety of aryl halides. Though the boronic acid is

Scheme 1



commercially available, the cost is prohibitive for large-scale preparations.

We were interested, therefore, in developing a catalytic method for the regioselective arylation of 2-furaldehyde, a reagent for which the cost is commensurate with common organic solvents. Current approaches for direct functionalization of 2-furaldehyde at the 5 position involve electrophilic methods such as Friedel−Crafts alkylations[5] or copper(II)-catalyzed decomposition of diazonium salts[6] (Meerwein arylation) among others. The use of many cross-coupling reactions involving organometallic species are precluded because of competitive reactions with the carbonyl. However, furfural has been used as the nucleophilic coupling partner by protecting the aldehyde in situ with subsequent metalation.[7]

Electrophilic reactions with 2-furaldehyde often exhibit a high degree of regioselectivity.[5] The need to develop a regioselective and catalytic arylation reaction naturally led to the consideration of an appropriately tuned electrophilic palladium species.

The palladium-catalyzed coupling of aryl halides and triflates with alkenes (Heck Reaction)[8] has undergone a number of significant developments since its inception over 30 years ago. Recent attention led to mechanistic insights[9] and to the development of useful additives[10] and highly active palladium catalysts.[11] The wide range of alkenes which undergo the Heck reaction is particularly noteworthy, including electron-deficient alkenes, acrylates, conjugated enones and nitriles, unactivated alkenes, and electron-rich enol ethers and enamides.[9] Similarly, palladium-catalyzed arylations/vinylations have been successfully applied in the function-

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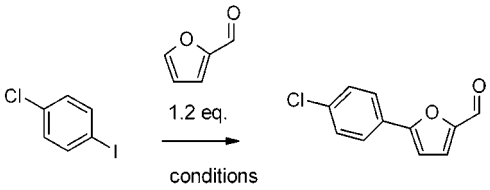
alization of furans,[12] dihydrofurans,[13] thiophenes,[13] azoles, and oxazoles,[14] among others. Additionally, functionalization of 2-furaldehyde has been achieved through oxidative coupling[15] using stoichiometric amounts of $Pd(OAc)_2$; however, homocoupling and lack of regioselectivity render these conditions problematic. Indeed, palladium-mediated dimerization of furfural has been used preparatively.[15]

In an effort to evaluate the overall feasibility of the reaction, we evaluated a number of parameters in preliminary experimentation including bases, solvents, additives, catalysts, and phosphines at two levels using a half-factorial design (16/32 experiments, Table 1).[16] Generally, conversions

Table 1. Screening Factors



base (2 equiv)	solvent	additive (1 equiv)	catalyst (5 mol %)	phosphine (10 mol %)
KOAc	DMA	Bu_4NBr	$PdCl_2$	none
N,*N*-diisopropyl-ethylamine	CH_3CN	CuI	$Pd(OAc)_2$	(*o*-tolyl)$_3$P

were low and ranged from 0 to 41%. Analysis of the data clearly showed selection of base as the major factor influencing percent conversion. Remarkably, KOAc gave a 9-fold increase vs *N*,*N*-diisopropylethylamine as an average over all 16 reactions. Similarly, $PdCl_2$ produced almost a 2-fold increase in conversion with respect to $Pd(OAc)_2$. Homocoupling was a deleterious side reaction and thus reduced significantly the amount of arylfurfural. Further analysis of the data revealed an 8-fold increase on average in the amount of homocoupling when using *N*,*N*-diisopropylethylamine over KOAc as a base. Additionally, the absence of phosphine ligand resulted in a 1.5-fold increase in the amount of homocoupling.

Phosphines have been used in cross-coupling reactions to promote transmetalation and thereby reduce homocoupling.[17] In Heck-type reactions, elimination of the hydridopalladium halide intermediate is reversible.[8] Phosphines have been used to prevent or slow the re-addition of the hydridopalladium complex to the double bond.[9] The use of phosphines to promote oxidative addition of aryl halides to palladium is well-known; however, in this particular reaction, alkene insertion is arguably the step with the most significant energy barrier. To suggest the role phosphine might play in alkene insertion for this reaction would be purely speculative; however, examination of a range of sterically and electronically diverse phosphines was warranted.

Using a statistically driven approach, an array of solvents, catalysts, and ligands was explored with iodochlorobenzene again as a common substrate. Five phosphines, three catalysts, and three solvents were selected for additional study. Solvents were selected in part by the diversity of their physical properties.[18]

A complete factorial design involved 45 combinations; however, the number of experiments was reduced to 30 in such a way that information could still be statistically interpreted.[19] This permitted a broad exploration of the parameter space and highlighted synergies that a traditional vary-one-factor-at-a-time approach might have overlooked. Figure 1 displays results from the 30 reactions. For this study

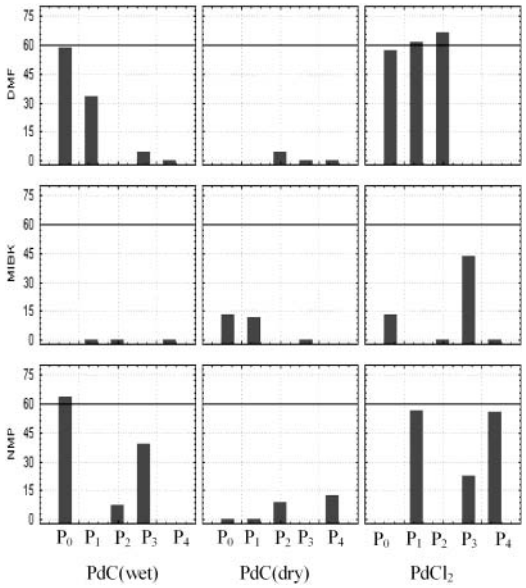


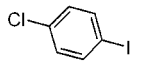
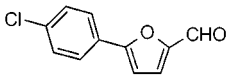
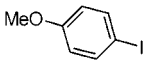
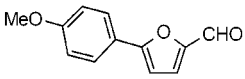
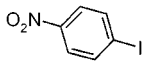
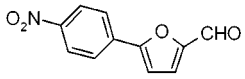
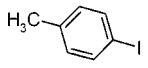
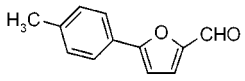
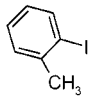
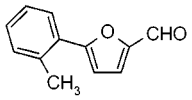
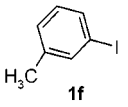
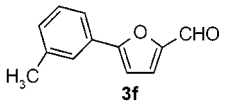
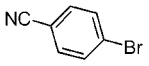
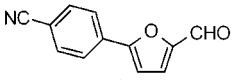
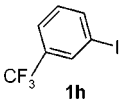
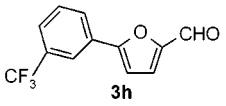
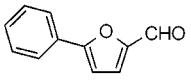
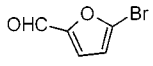
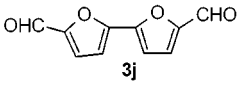
Figure 1. Conversion (%). Data points shown (30/45) reflect a statistically balanced design. All experiments were preformed with 1 equiv of Bu_4NBr, 2 equiv of KOAc, and 3 equiv of 2-furaldehyde. Solvents: DMF, 4-methyl-2-pentanone (MIBK), NMP. Catalysts: $PdCl_2$, 5% Pd/C (wet and dry). Phopshine ligands: P_0 = none, P_1 = (2-furyl)$_3$P, P_2 = Cy_3P, P_3 = (*o*-tol)$_3$P, and P_4 = (*t*-bu)$_3$P. Conversion is defined from HPLC areas at the 6 h time-point: 100-(product/product + starting material + homocoupling; 220 nm).

the amount of 2-furaldehyde was increased to 3 equiv in an effort to further minimize homocoupling.

We initially attempted reactions at 80 °C and found this temperature to be completely ineffective, therefore necessitating an increase to 110 °C in order to obtain reasonable conversion rates. Consistent with Jeffery's observations,[10] the palladium(0) catalyst preformed well in both DMF and NMP in the absence of phosphine ligand when Bu_4NBr was used as the additive. Similarly, Jeffery observed pronounced effects from water, either beneficial or detrimental. A marked effect is also seen here when comparing wet Pd/C vs dry. Clearly $PdCl_2$ with DMF produced promising results with and without added ligand. Ultimately, Cy_3P was carried forward because it worked well for other substrates under investigation. In a number of cases, low conversions were still the direct result of extensive homocoupling.[16] We later found that this could be avoided altogether or minimized (<10%) with the slow addition of the aryl halide via syringe

pump over 10 h to an excess of 2-furaldehyde (10 equiv). While this excess is clearly not required for all substrates as evidenced by some of the high conversions shown in Figure 1, we chose to apply this protocol to a number of diverse substrates to establish the scope of the transformation (Table 2). The reaction worked well with sterically hindered

Table 2. [a] Synthesis of 5-Substituted Arylfurfurals from Aryl Halide (**1**) and 2-Furaldehyde (**2**)

1	 **1a**	 **3a**	87
2	 **1b**	 **3b**	75
3	 **1c**	 **3c**	88
4	 **1d**	 **3d**	71
5	 **1e**	 **3e**	68
6	 **1f**	 **3f**	67
7	 **1g**	 **3g**	71
8	 **1h**	 **3h**	60
9	 **1i**	 **3i**	70
10	 **1j**	 **3j**	64

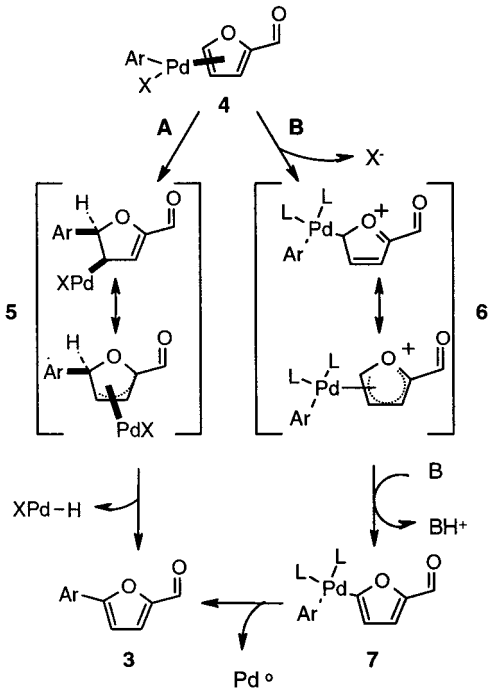
[a] A solution of aryl halide (2.1 mmol) in DMF (3 mL) was added to a degassed mixture of palladium(II) chloride (5 mol %), KOAc (4.2 mmol), Bu_4NBr (2.1 mmol), and Cy_3P (10 mol %) in DMF (18 mL) at 110 °C over 10 h. [b] Isolated yields.

substrates (entry 5), electron-rich (entries 2, 4−6), and electron-deficient (entries 1, 3, 7, 8, 10) aryl halides.

Additionally, there was little effect of substitution pattern of the aryl halide (entries 4−6) with respect to yield or regioselectivity. The method worked well for aryl bromides or aryl iodides and was tolerant of a range of functional groups. We did, however, attempt to couple 2-bromopyridine using these conditions and detected only starting material by HPLC. While this reaction appears to be general with regard to 2-furaldehyde, application to furan, furan carboxylates, and other substituted furans is under investigation.

Mechanistically, this transformation proceeds arguably through a palladium(II) π -complex (Scheme 2). Whether

Scheme 2



this reaction progresses through a traditional Heck-type mechanism (path A) or through formation of a divinyl palladium(II) intermediate (**7**) is not clear. Precedence for electrophilic palladium(II) species (path B) is well documented.[20] Alternatively, insertion of the alkene (path A) would necessarily give the *syn* aryl palladium(II) intermediate **5**; however, elimination would require as previously suggested by Grigg[18a] and co-workers, a stereopermutation or a *trans* elimination of XPdH. Though the alternative pathway seems more plausible, this cannot be ruled out. The regioselectivity is best explained with conjugated resonance-

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stabilization derived from electrophilic attack at the 5-position (intermediate **6**) which is not achievable from attack at either the 2- or 3-position.

In summary, we have developed a general protocol for the mild and regioselective arylation of 2-furaldehyde using palladium catalysis. We are currently investigating, and will report in due course, the application of this methodology to a more complex substrate that is in development as an anticancer agent.

Acknowledgment. We thank Jon Williams and Paul McAllister for assistance with GC/MS and Statistica software, respectively.

Supporting Information Available: Experimental procedures and characterizations for compounds **3a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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