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Umpolung Direct Arylation Reactions: Facile Process Requiring Only Catalytic Palladium and Substoichiometric Amount of Silver Salts

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Abstract: An umpolung direct arylation process is described. The reaction requires only a catalytic amount of $Pd(OAc)_2$ and a substoichiometric amount of silver salts, without any external base or ligand to proceed. The directed oxidative insertion of the transition metal followed by the coupling into the C−H bond of an unactivated arene has surprisingly not yet been reported, despite the clear advantages in the ease of starting material synthesis. The reaction is regioselective with regards to the arene partner, and the role of the acetate and carbonate groups has been elucidated. This methodology adds to the very few examples of benzene coupling without the inclusion of electron-withdrawing groups to increase acidity.

The biaryl motif is a privileged structure, omnipresent in many facets of chemistry and biology. These important compounds are key components of many pharmaceutically active reagents, natural products, agrochemicals, dyes, and are of much interest in material and supramolecular sciences.[1] Cross-coupling reactions developed since the 1970s provide powerful tools for the preparation of these scaffolds, and as such, these methods have dominated the way these compounds are synthesized.[2] Despite their remarkable effectiveness, they suffer from several key drawbacks. Most notably, they rely on the synthesis of *pseudo* nucleophile and electrophile starting materials and generate stoichiometric amounts of sometimes toxic metal salts as reaction byproducts. Consequently, these reactions are neither atom- nor time-economical and may negatively contribute to the environment (Figure 1).

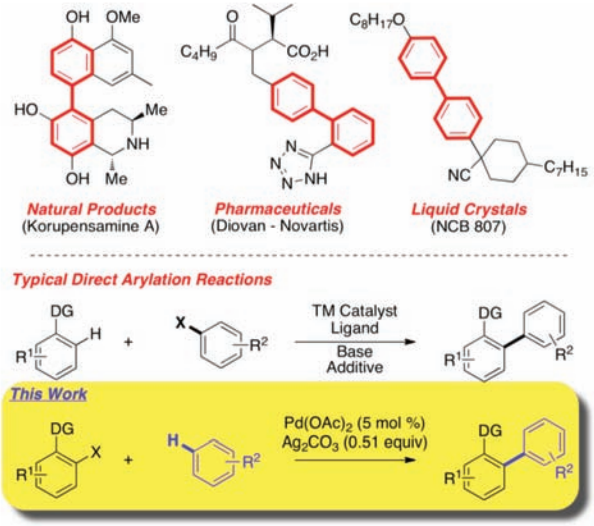
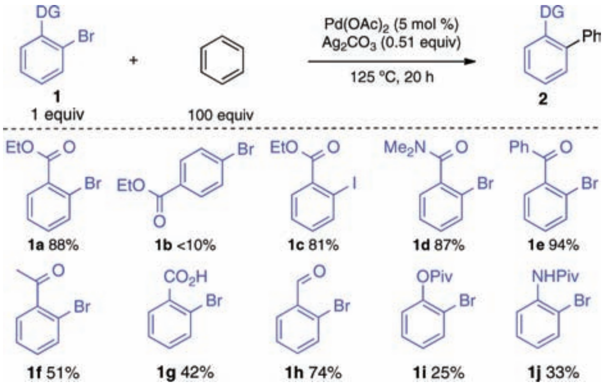


Figure 1. Importance of biaryl compounds and direct methods for their synthesis.

Given these realities, more focus has been dedicated over the past half decade to the development of direct arylation reactions.[3] Through the use of such methodology, the elimination of one, if not both, of the required preactivations on the starting materials is achieved. As such, these transformations are greener, while improving the overall economy of the reaction.[4] Of the direct arylation reactions reported, the most dominant class involves the use of a directing group to direct a transition metal into a C−H bond.[5] The resulting metallocycle then reacts with an aryl halide via oxidative addition, affording the desired biaryl product following reductive elimination. However, the reverse, or *umpolung*, version of this reaction involving the application of a directing group to facilitate transition metal oxidative addition and the reaction of such a metallocycle with an unactivated arene has received little or no attention. In addition, although there have been few reports on the arylation of benzene[6] and other electron-poor arenes,[7] they often require several reagents, increasing the cost of the reaction and decreasing their atom economy. The advantage of using such an *umpolung* technique includes that the aryl halide can be readily prepared using efficient directed orthometalation reactions from inexpensive starting materials,[8] and the arene can be not only used as a reaction feedstock, but also separated and reused for further reaction. Herein we report a facile, high-yielding, Pd-catalyzed direct arylation reaction involving aryl halides containing an α-directing group with an unactivated arene. The protocol is conducted under phosphine-free conditions, requiring only 0.51 equiv of silver carbonate.

Scheme 1. Scope of the Directing Group with Isolated Yields



The optimized conditions require only 5 mol % of $Pd(OAc)_2$ and 0.51 equiv of Ag_2CO_3 to execute the desired arylation of 2-bromoethylbenzoate by benzene (Scheme 1).[9] With these conditions in hand, we proceeded to explore the scope of the directing group for the reaction. Indeed, the presence of a directing group *ortho* to the halide was needed. While aryl bromides and iodides were tolerated, aryl chlorides did not react. A range of directing

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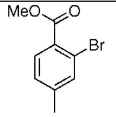
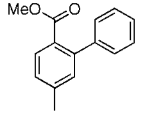
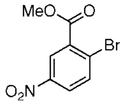
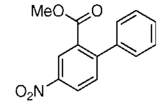
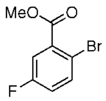
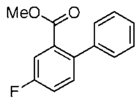
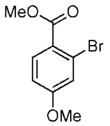
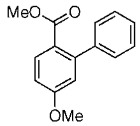
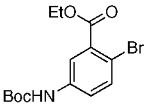
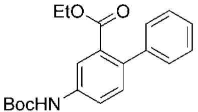
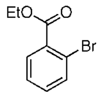
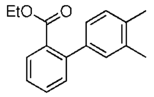
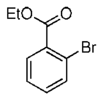
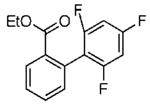
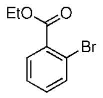
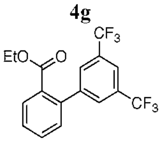
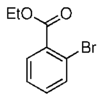
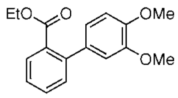
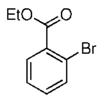
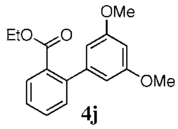
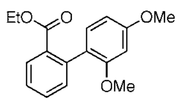
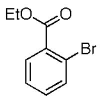
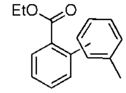
groups could be employed. A trend of note includes improved yields as the Lewis basicity of the group is increased. As a result, phenyl ketones (**1e**) are more efficient that esters (**1a**, **1c**) and amides are also quite effective (**1d**). 2′-Bromoacetophenone (**1f**) is viable in moderate yield despite the presence of an enolizable center. Full conversion is observed with 2-bromobenzoic acid, though the desired biphenyl product **2g** was only isolated in 42% yield. This is thought to be due to the decarboxylation of the product with the resulting biphenyl being removed upon purification.[10] The potentially sensitive 2-bromobenzaldehyde **1h** gives the product in good yields. Compounds **1i** and **1j** were less efficient, giving the products in 25% and 33% yields respectively. This is believed to be the result of the formation of a six-membered palladacycle intermediate rather than the five-membered cycle, as the Lewis basicity of the *O*- and *N*-Piv carbonyl groups are comparable to those of the ester and aldehyde respectively.[11]

We next considered the functional group tolerance of the halide coupling component. Although 2-bromobenzophenone was determined to be the optimal directing group, we elected to pursue the reaction scope with the methyl and ethyl esters, due to the plethora of chemistry that can be performed on these functional groups. A methyl group *meta* to the bromide is well tolerated (Table 1, entry 1), although, when the methyl is *ortho* to the halide, the arylation only proceeds with 25% conversion, indicating some sensitivity to steric hindrance. Electron-poor substrates bearing even a potentially problematic nitro group perform very well,[2a] presumably due to their increased reactivity toward oxidative addition (entries 2, 3). Coincidentally, electron-rich substrates provide the biaryl products in moderate, though synthetically useful, yields (entries 4, 5).[12]

Cognizant of the interest in arenes other than benzene, we considered the scope of the C−H coupling partner. Whereas the reaction had been performed with 100 equiv of the benzene for a cleaner process, it was found that 50 equiv of arene for high-boiling reagents were sufficient to provide the desired product in acceptable yields. Generally speaking, the reaction products are obtained in moderate to very good yields. There was a noticeable difference between 1,3,5-trifluorobenzene and 1,3-bis(trifluoromethyl)benzene (entries 7, 8). The former provided the arylated product in good yield while the latter in low yield.[12] The phenomenon of Pd inserting *ortho* to fluorine has been well documented, owing to a combination of the increased Brønsted acidity of the C−H bond and interactions between the transition metal and the halogen lone pairs directing metalation.[7,13] In the case of 1,3-bis(trifluoromethyl)benzene, the low yield may be the result of poor π-complexation with the metal catalyst. A striking feature of the reaction is the high regioselectivity of the process, as, in many examples, only one regioisomer was observed (entries 6, 8, 9).

Given the lack of need for a phosphine ligand, and the requirement of only a substoichiometric amount of Ag_2CO_3, we explored the possible mechanistic pathway of the reaction. A Pd^{II} source seems to be vital for the reaction to proceed, as Pd_2dba_3 was ineffective both with and without the presence of a phosphine ligand (Table 2, entries 2, 3). Curiously, Pd_2dba_3 is operative when a catalytic amount of KOAc is present (2:1 with respect to Pd), with most of the activity being restored, clearly demonstrating the importance of acetate in the reaction (entry 4). It has been demonstrated by Fagnou and Echavarren that acetate and carbonate motifs are vital proton shuttles in metalation/deprotonation sequences.[11] As a result, we attempted the reaction in the presence of $Pd(TFA)_2$, as the TFA moiety should be a less effective shuttle due to its increased acidity. Indeed a 51% yield was obtained, demonstrating a decrease in activity (entry 5). Furthermore, reactivity could be restored with the addition of KOAc (entry 6).

Table 1. Pd-Catalyzed Direct Arylation of Benzene with Aryl Bromides[a]

entry	aryl halide	product	yield (%)[d]
1[a]	 **3a**	 **4a**	82
2[a]	 **3b**	 **4b**	94
3[a]	 **3c**	 **4c**	89
4[a]	 **3d**	 **4d**	48
5[a]	 **3e**	 **4e**	47
6[b]	 **1a**	 **4f**	77
7[c]	 **1a**	 **4g**	80
8[b]	 **1a**	 **4h**	27
9[b]	 **1a**	 **4i**	43
10[b]	 **1a**	 **4j**  **4k**	48[e] **4j** = 18% **4k** = 30%
11[b]	 **1a**	 **0:1:1 *o:m:p*** **4l**	88

[a] Reaction conditions: **1** (1 equiv), arene (100 equiv), $Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (0.51 equiv), 125 °C, 16−20 h. [b] Same conditions as those for (a) except that 50 equiv of the arene were applied. [c] Same conditions as those for (b) except that 1 equiv of Ag_2CO_3 was applied. [d] Yield of isolated product. [e] Combined yield of products.

Silver acetate was applied as a base, with the product being observed in 50% yield (entry 7). This yield could be increased to 65% through the inclusion of K_2CO_3 (entry 8), suggesting that the carbonate may play a role in regulating the pH of the reaction mixture and ensuring the presence of $^-$OAc and not necessarily be involved in the deprotonation. Lastly, a KIE of 5.4 was observed, indicating that the C−H breaking event is rate-limiting.

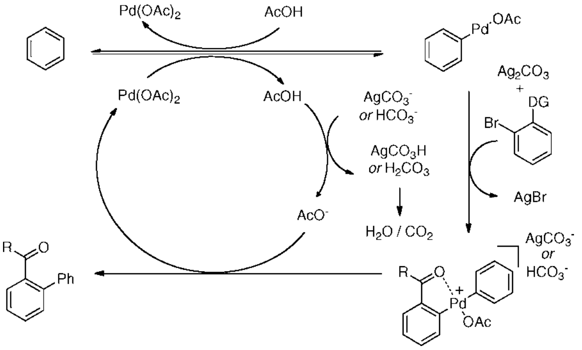
Table 2. Determination of the Role of the Reagents[a]

entry	Pd source	Ag	additive	yield[b]
1	$Pd(OAc)_2$[c]	Ag_2CO_3[e]	none	90
2	Pd_2dba_3[d]	Ag_2CO_3[e]	none	<5
3	Pd_2dba_3[d]	Ag_2CO_3[e]	PCy_3 (7.5 mol %)	<5
4	Pd_2dba_3[d]	Ag_2CO_3[e]	KOAc (10 mol %)	76
5	$Pd(TFA)_2$[c]	Ag_2CO_3[e]	none	51
6	$Pd(TFA)_2$[c]	Ag_2CO_3[e]	KOAc (10 mol %)	73
7	$Pd(OAc)_2$[c]	AgOAc[f]	none	50
8	$Pd(OAc)_2$[c]	AgOAc[f]	K_2CO_3 (0.51 equiv)	65

[a] Reaction conditions: **1a** (1 equiv), benzene (100 equiv), 125 °C, 20 h. [b] Yield (%) determined by ^{1}H NMR analysis using an internal standard. [c] 5 mol % of catalyst. [d] 2.5 mol % of catalyst. [e] 0.51 equiv. [f] 1 equiv.

Based on these results, we believe that the reaction proceeds as follows. First, the palladium inserts into the benzene ring (Scheme 2). This reversible process was first reported in 1965 by Van Helden and later again by Sasson.[14] However, given the importance of acetate not only in their disclosures but also in our results, in addition to known work in the area, we propose that this happens through a concerted metalation deprotonation sequence over the previously suggested Wheland intermediate.[7c,15] The resulting phenylated Pd then undergoes Ag-assisted oxidative addition to obtain the corresponding Pd^{IV} species that is directed and stabilized by the presence of a Lewis basic group.[16] This intermediate reductively eliminates to give the observed product. Simultaneously, the AcOH generated in the carbopalladation step is deprotonated by the carbonate and ligates to the Pd, regenerating the active catalyst. This pathway also accounts for the trace amount of biphenyl observed in the reaction mixture, as a result of homocoupling of two benzene molecules.[10] Indeed, the phenylated Pd is known to disproportionate to provide $Pd(OAc)_2$ and $PdPh_2$, the latter of which reductively eliminates to give biphenyl and Pd^0.[10]

Scheme 2. Proposed Catalytic Cycle



In conclusion, we have disclosed an efficient Pd-catalyzed direct arylation process that can be performed in the absence of an external ligand and that requires only substoichiometric amounts of Ag_2CO_3. The reaction displays inverse reactivity to what has been previously reported, where the reactant is also the solvent that can be recycled for future transformations. Work is currently underway to gain further insights into the reaction's mechanism, and results will be disclosed in due course.

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Note Added after ASAP Publication. Structure **4e** was corrected in Table 1 on September 29, 2010.

Supporting Information Available: Experimental procedures, sample spectra, and compound characterization data for each reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Though full conversions were reported with 0.50 equiv of Ag_2CO_3, more reproducible results were obtained with slightly more reagent.
(10) Bipenyl is always generated in the reaction in a non-reproducible manner. In the case where additional biphenyl would be formed due to decarboxylation, differentiating it from naturally forming byproducts would not be possible.
(11) In all cases the halide was consummed. The balance of material provided a complex mixture.
(12) Entries resulting in lower yields are the result of incomplete consumption of the bromide starting material. Efforts to drive the consumption to completion were unsuccessful.
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