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An Annulative Approach to Highly Substituted Indoles: Unusual Effect of Phenolic Additives on the Success of the Arylation of Ketone Enolates

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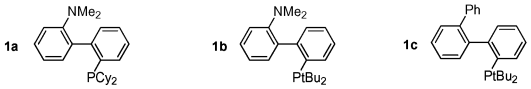
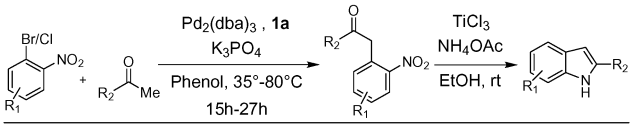
The synthesis of indoles has occupied organic chemists for well over a century.[1] The combination of traditional and modern methods has provided accessibility to a wide variety of structural variations of this important class of heterocycles.[2−9] Still, a general, mild, and efficient method to access 4-, 5-, 6- as well as 5,6- and other polysubstituted indoles from simple and readily accessible (non-aryl iodide) precursors has proved elusive. Herein we disclose a method, based on the Pd-catalyzed arylation of ketone enolates, that concatenates simple ketones with widely available chloro- and bromoaromatics,[10] to provide a wide range of polysubstituted indole derivatives. The success of the method is due to an unexpected effect of an additive in the ketone arylation process: the inclusion of a catalytic quantity of a phenol in the enolate arylation of *o*-halonitroarenes effects a remarkable increase in the efficiency of the transformation.

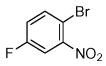
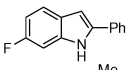
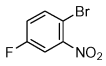
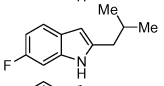
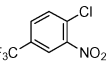
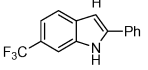
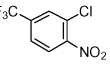
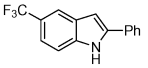
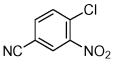
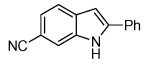
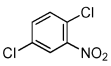
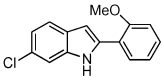
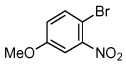
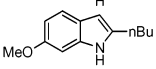
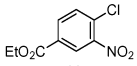
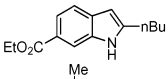
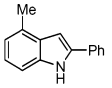
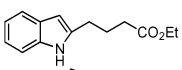
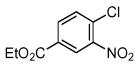
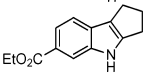
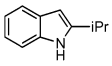
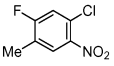
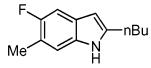
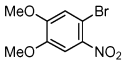
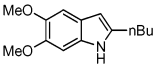
The Pd-catalyzed arylation of ketone enolates has recently emerged as a useful method in organic synthesis.[11] However, to our knowledge, *o*-halonitroarenes have never appeared as coupling partners in this reaction. In our preliminary studies toward this goal, we found that along with trace product, we observed the persistent formation of 2-nitrophenol. Any attempts to lessen the quantity of this phenolic impurity also resulted in suppression of product formation, indicating that the phenol might be performing a beneficial role. In fact, we found that addition of 20 mol % phenol, in combination with phosphine **1a**, led to the development of a highly efficient process. With the ability to couple ketones with



o-halonitroarenes, we were then able to synthesize substituted indoles in a straightforward manner following previously described reductive cyclization procedures.[9,12] The substrate scope of this reaction was found to be quite broad, as is depicted in Table 1. Both electron-rich and -deficient *o*-bromo or *o*-chloro nitroarenes were effective coupling partners under mild reaction conditions. The reactions were carried out at 35−50 °C (save entry 9) in toluene using K_3PO_4 as the base in the presence of 20 mol % of a phenol (4-methoxyphenol was found to be optimum in most cases). Acetophenone derivatives, as well as alkyl methyl ketones, including acetone, were viable substrates in this process. However, the current reaction conditions are successful only when arylating either methyl or cyclic ketones. Mitigating this limitation was that the arylated ketones **I** could be deprotonated and efficiently alkylated with several electrophiles, and subsequently reductively cyclized to give 2,3-substituted indoles in moderate to excellent yields (Table 2). In our first alkylation protocol, the ketone arylation process was carried out followed by aqueous workup and isolation of the crude product. Without purification, this was alkylated with the electrophile (1.1 equiv) using NaH (1.2 equiv) as the base in THF.

Table 1. Synthesis of 2,*n*-Substituted Indoles[a]



Entry	Aryl Halide	Indole	T (°C) / t (h)	Yield (%)
1			50/15	78
2			50/24	63
3			50/18	75
4			50/25	79
5			35/24	44
6			50/24	64[b]
7			50/24	67
8			35/27	65
9			80/25	71[c,f]
10			50/23	65
11			35/26	55[d]
12			50/21	64[e]
13			50/23	71
14			50/23	75

[a] Reaction conditions: 1.0 equiv of ArX, 2.2 equiv of ketone, 0.2 equiv of phenol (see Supporting Information for exact phenol used), 2.5 equiv of K_3PO_4, 1 mol % $Pd_2(dba)_3$, 4 mol % **1a**, toluene. Isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and GC or combustion analysis. [b] 4 mol % Pd, 8 mol % **1a**. [c] 2.0 equiv of ketone. [d] 6 equiv of ketone. [e] 1.2 equiv of ketone. [f] **1c** used as ligand.

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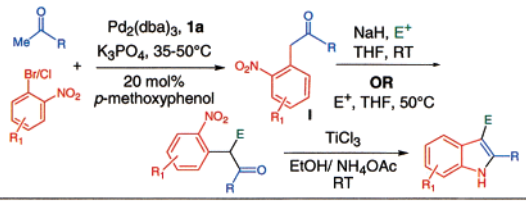
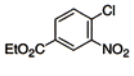
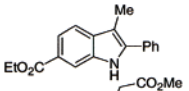
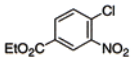
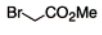
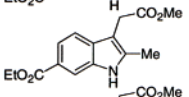
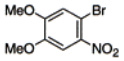
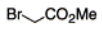
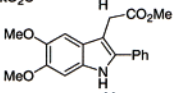
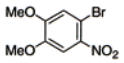
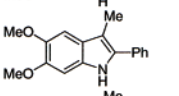
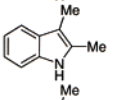
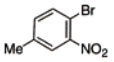
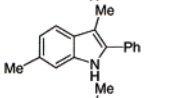
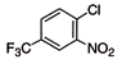
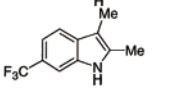
Table 2. Synthesis of 2,3,*n*-Substituted Indoles[a]

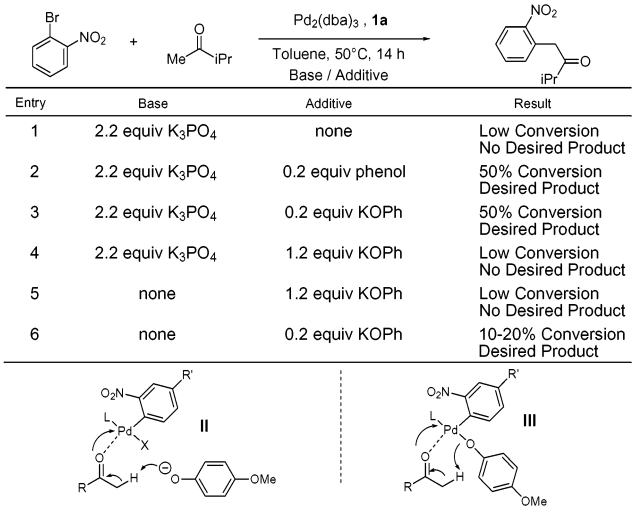


Entry	Aryl Halide	Electrophile	Indole	Yield (%)
1		MeI		61
2				71[c]
3				65
4		MeI		84[d]
5		MeI		76[c]
6		MeI		90[b]
7		MeI		54[c,d]

[a] Reaction conditions: 1.0 equiv of ArX, 2.0 equiv of ketone, 2.5 equiv of K_3PO_4, 0.2 equiv of 4-methoxyphenol, 1 mol % $Pd_2(dba)_3$, 4 mol % **1a**, 1 mL of toluene, 22 h. Isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and GC or combustion analysis. [b] 1.1 equiv of ketone, 2.0 equiv of K_3PO_4. [c] 6.0 equiv of ketone. [d] 1.5 equiv of iodomethane, 1 mL of THF added upon completion of ketone arylation.

Alternatively, we found that upon completion of the ketone arylation, addition of iodomethane and THF (as a cosolvent) to the crude reaction mixture and then heating at 50 °C provided the same intermediate as obtained above. In both cases, the alkylated material was carried on crude to the reductive cyclization step. This method allows for the independent variation of the three substrate components, providing a route to numerous indoles not previously readily available.

To date, we have only seen such a remarkable effect of the added phenol in the case of electron-deficient aryl halide substrates. Moreover, its magnitude is significantly larger for *o*-halonitrobenzene derivatives than for other substrates. To delineate the reason for the effect of the added phenol, a series of experiments were performed as outlined in Figure 1. From these, we found that no desired product was formed in the presence of an excess of the phenolic addititive or in its absence. However, good results were obtained when the reaction was performed in the presence of a catalytic quantity of a phenol. Several explanations are plausible. The simplest of these is that the formation of an intermediate palladium phenoxide (e.g., **III**) stabilizes an otherwise unstable intermediate preventing catalyst decomposition.[13] A second is that intermediate **II** serves as a Lewis acid, while the phenoxide serves as a base to deprotonate the coordinated ketone. A third explanation is that **III** can coordinate to the ketone, facilitating deprotonation with concomitant formation of a Pd−O bond. At present, we have been unable to differentiate between the possibilities discussed above. However, we favor the third, intermediacy of a complex of



Entry	Base	Additive	Result
1	2.2 equiv K_3PO_4	none	Low Conversion No Desired Product
2	2.2 equiv K_3PO_4	0.2 equiv phenol	50% Conversion Desired Product
3	2.2 equiv K_3PO_4	0.2 equiv KOPh	50% Conversion Desired Product
4	2.2 equiv K_3PO_4	1.2 equiv KOPh	Low Conversion No Desired Product
5	none	1.2 equiv KOPh	Low Conversion No Desired Product
6	none	0.2 equiv KOPh	10-20% Conversion Desired Product

Figure 1. Role of the phenol additive.

type **III**, as a dramatic decrease in efficiency is seen as more hindered phenols are used with the same substrate combination. In summary, we have described a procedure for the arylation of methyl and cyclic ketone enolates with *o*-halonitroarenes. This process has provided for the regioselective synthesis of a wide variety of substituted indoles from commercially available materials.

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Supporting Information Available: Preparation and characterization of all substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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