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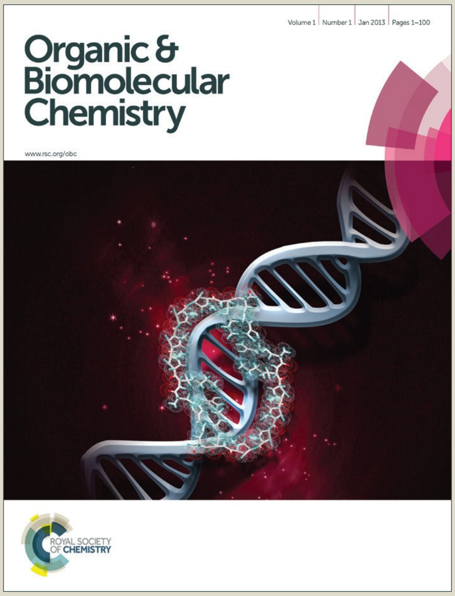

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Palladium-Catalyzed Direct Arylation of Phenols with Aryl Iodides

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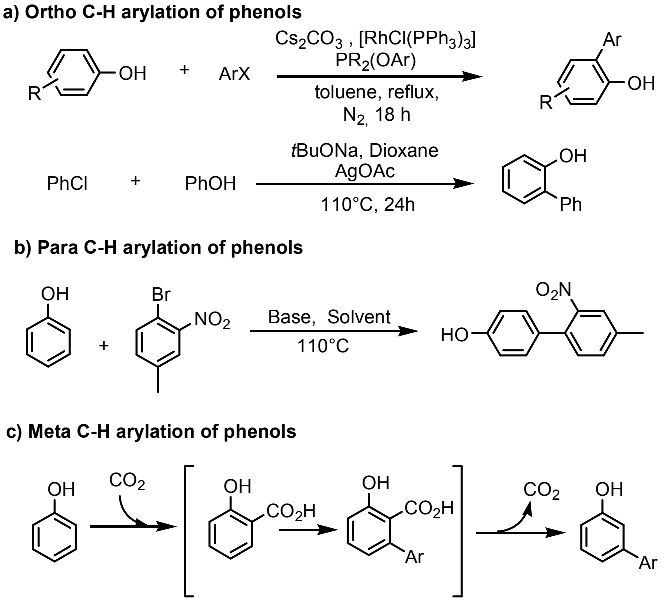
An efficient protocol of palladium-catalyzed direct *para*-arylation of unfunctionalized phenols with aryl iodides under mild conditions was reported. A variety of substrates were applied in this reaction in yields up to 87%.

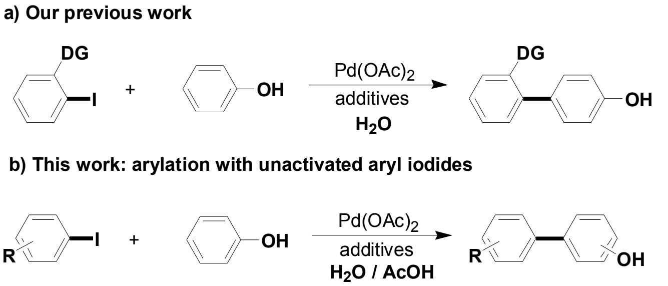
The transition-metal-catalyzed cross-coupling reaction of aryl halide or pseudohalide with aryl organometallic reagent has been regarded as one of the most useful methods for the construction of biaryl compounds.[1] However, these reactions are usually accompanied by a substantial amount of undesired side products, and several synthetic steps might be required to obtain the coupling partners from readily available starting materials. Over the past decade, extensive efforts have been devoted to the development of new strategy towards the direct arylation of C−H bonds as an ecologically and economically friendly alternative.[2,3]

Arylphenols are common and important structural units found in nature products, pharmaceuticals, organocatalysts, and other organic materials.[4] There have been increased interests in catalytic functionalization of free phenols to provide the valuable arylated derivatives. For example, in 2003, Bedford and coworkers described rhodium-catalyzed *ortho* C−H arylation of substituted phenols with aryl halides, in which phosphinite ligand was required as a co-catalyst (Scheme 1a).[5] Subsequently, *ortho* arylation of phenols by aryl chlorides *via* benzyne mechanism was disclosed by Daugulis and coworkers (Scheme 1a).[6] Very recently, Kumar and coworkers demonstrated that bromoarenes bearing strong electron-withdrawing nitro group could be utilized as efficient arylation reagents to produce *para*-arylphenol derivatives in the presence of KO^{t}Bu (Scheme 1b).[7] One-pot direct *meta*-selective arylation of phenols based on a “traceless” directing group strategy was also reported by Larrosa and coworkers (Scheme 1c).[8]



Scheme 1. Recent reported protocols of arylation of unprotected phenols.

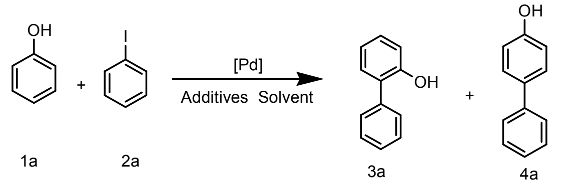
Recently, we reported a new method that enabled highly *para*-selective direct arylation of phenols with aryl iodides by palladium catalyst in water (Scheme 2a).[9a] However, an *ortho* coordination group was necessary for aryl iodide substrates in order to increase their activities, which would limit the appeal of the methodology in synthetic applications. The development of new straightforward methods of widespread applications for C−H arylation of phenols is still highly desirable. In a continuation of our work in the metal-catalyzed C−H functionalization,[9] herein is described an efficient protocol for the direct arylation of unfunctionalized phenols with aryl iodides without *ortho* coordination group under mild conditions (Scheme 2b).



Scheme 2. Palladium-catalyzed C−H arylation of phenols.

At the outset of our study, phenol (1a) and iodobenzene (2a) were chosen as model substrates for the optimization of the reaction conditions. As shown in Table 1, a variety of organic solvents were tested, and no arylated phenol was found by using $Pd(OAc)_2$ as catalyst in the presence of AgOAc (Table 1, entries 1-4). Next, we revisited our previous palladium-catalyzed aqueous system.[9a] Unfortunately, only 5% yield of the desired product was detected when the reaction was performed at 60 °C for 48 hours in water (Table 1, entry 5). Then, a series of silver salts were examined, however the reactions did not lead to better results (Table 1, entries 6-9). After many attempts, it was observed that the mixed solvent was crucial for this reaction. By using mixed solvent ($V_{H_2O}/V_{AcOH}=1:1$), we were delighted to find that phenol could be transformed into the corresponding arylated product in the presence of AgOAc, $AgOCOCF_3$ or AgOTs in yields of 42%, 38% and 40% respectively (Table 1, entries 10-12). Both of ortho and *para*–arylated products were found, and *para*-arylated phenol was the major product. The proportion of the mixed solvent also played an important role in this reaction, and 1:1 was the best choice (see the details in supporting information). Further investigation revealed that the addition of protonic acid was necessary for the promotion of higher product yield.[9a,10] TsOH was found to be beneficial to the reaction, and 59% yield was obtained by combination of AgOAc and TsOH as additives (Table 1, entry 13). Moreover, elevating the reaction temperature from 60 °C to 70 °C improved the yield to 68% as well as increment of *para*/ortho selectivity to 10:1 (Entry 14). However, higher temperature seemed not to be beneficial to the reaction (Table 1, entries 15). The followed palladium source screening showed that $Pd(OH)_2$, $Pd(PPh_3)_4$ and $PdCl_2$ resulted in much lower yields (Table 1, entries 16-18). Also, control reaction indicated that the reaction did not work in the absence of the palladium catalyst (Table 1, entry 19). More importantly, the replacement of air environment by N_2 resulted in higher ratio of *ortho*/*para*–arylated products as 1:17 as well better yield 72% (Table 1, entry 20).

Table 1 Optimization of the reaction conditions[a]



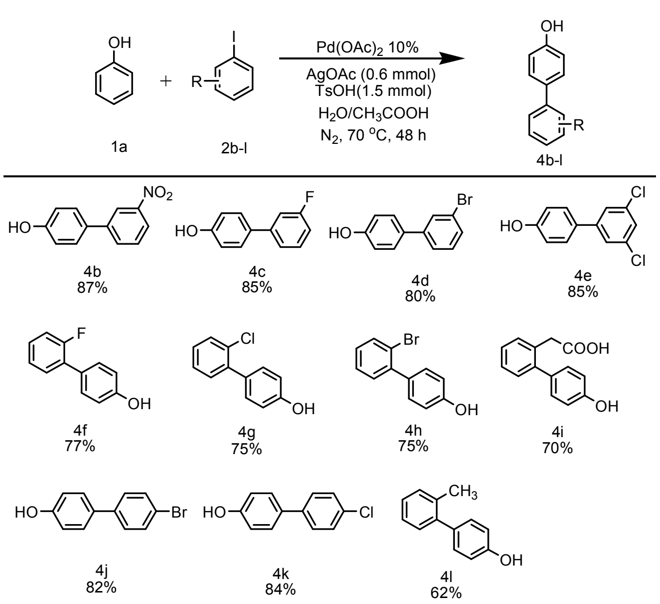
Entry	[Pd]	Additive	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	AgOAc	t-BuOH	0
2	$Pd(OAc)_2$	AgOAc	toluene	0
3	$Pd(OAc)_2$	AgOAc	DMF	0
4	$Pd(OAc)_2$	AgOAc	AcOH	0
5	$Pd(OAc)_2$	$AgOCOCF_3$	H_2O	5
6	$Pd(OAc)_2$	Ag_2CO_3	H_2O	0
7	$Pd(OAc)_2$	Ag_2O	H_2O	0
8	$Pd(OAc)_2$	AgOAc	H_2O	0
9	$Pd(OAc)_2$	o-NO_2PhCOOAg	H_2O	0
10	$Pd(OAc)_2$	AgOAc	H_2O/AcOH	42(1:5)
11	$Pd(OAc)_2$	$AgOCOCF_3$	H_2O/AcOH	38(1:5)
12	$Pd(OAc)_2$	AgOTs	H_2O/AcOH	40(1:4)
13	$Pd(OAc)_2$	AgOAc/TsOH	H_2O/AcOH	59(1:4)
14[c]	$Pd(OAc)_2$	AgOAc/TsOH	H_2O/AcOH	68(1:10)
15[d]	$Pd(OAc)_2$	AgOAc/TsOH	H_2O/AcOH	66(1:10)
16[c]	$Pd(OH)_2$	AgOAc/TsOH	H_2O/AcOH	6
17[c]	$Pd(PPh_3)_4$	AgOAc/TsOH	H_2O/AcOH	10
18[c]	$PdCl_2$	AgOAc/TsOH	H_2O/AcOH	8
19[c]	-	AgOAc/TsOH	H_2O/AcOH	0
20 [c,e]	**$Pd(OAc)_2$**	**AgOAc/TsOH**	**H_2O/AcOH**	**72(1:17)**

[a] Reactions conditions:1a (0.5 mmol), 2a (1 mmol), $Pd(OAc)_2$ (0.05 mmol), AgOAc (0.6 mmol), TsOH(1.5 mmol), HOAc (0.3 mL), H_2O (0.3 mL), 60 °C, 48 h. [b] GC yields, regioselectivity (*ortho*/*para*) is shown in parentheses. [c] 70 °C. [d] 80 °C. [e] Under N_2.

With the optimized reaction conditions in hand, we then explored the scope of aryl iodides for this reaction. To our delight, different aryl iodides bearing NO_2 or other halogen substituents were well tolerated, leading to the desired *para*-products as major products while only trace of *ortho*-products was obtained as shown in Table 2. Moreover, iodobenzenes with electron-withdrawing substituents were found to be beneficial to the reaction than those with electron-donating substituents. For example, 2-chloro and 2-methyl iodobenzene resulted in yields 75% or 62% respectively (Table 2, 4g and 4l). Meanwhile, the steric hindrance of the *ortho* groups also exhibited obvious effects on the results. For instance, 2-fluoro and 3-fluoro iodobenzene gave 77% and 85% yields (Table 2, 4f and 4c).

And the highest yield 87% was obtained in the case of reaction between 3-nitro iodobenzene and phenol (4b).

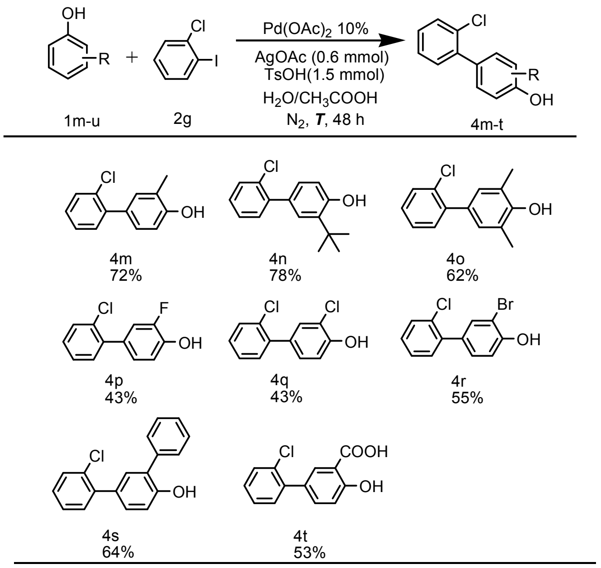
Table 2 Scope of aryl iodides[a]



[a]1a (0.5 mmol), 2 (1 mmol), $Pd(OAc)_2$ (0.05 mmol), AgOAc (0.6 mmol), TsOH (1.5 mmol), HOAc (0.3 mL), H_2O (0.3 mL), 70 °C, 48 h, isolated yields of *para*-products.

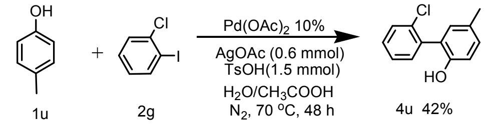
Next, the scope of phenols bearing diverse substituents was examined by the reactions with 2-chloro iodobenzene. As shown in Table 3, a variety of substituents were also tolerated, affording the corresponding *para*-arylated phenols in good yields from 42% to 78% (4m−u). In contrast with Table 2, phenols bearing electron-donating groups seemed to be beneficial to the reactions. For example, arylation of the 2-methyl or 2-fluoro phenol occurred, formation of the desired 4m or 4p in 72% or 43% yield.

Table 3 Substrate Scope of Phenols[a]



[a]1 (0.5 mmol), 2g (1 mmol), $Pd(OAc)_2$ (0.05 mmol), AgOAc (0.6 mmol), TsOH (1.5 mmol), HOAc (0.3 mL), H_2O (0.3 mL), 70 °C, 48 h Isolated yields.

Furthermore, 4-methylphenol was also used as substrate and was found to provide the mono-*ortho* arylated product 4u in yield of 42%.



Scheme 3. Arylation of 4-methylphenol with aryl iodide[a]

[a]1u (0.5 mmol), 2g (1 mmol), $Pd(OAc)_2$ (0.05 mmol), AgOAc (0.6 mmol), TsOH (1.5 mmol), HOAc (0.3 mL), H_2O (0.3 mL), 70 °C, 48 h Isolated yields.

The exact mechanism of this reaction is not clear at this stage. Based on the previous reports[9,10] of C−H arylation with aryl iodides and the observed *ortho*/*para* selectivity, we reasoned that this reaction system might obey the Friedel-Crafts-type arylation reaction mechanism.[7] Meanwhile, the role of the Ag(I) salt would be as an iodide scavenger.[11] The reported Friedel-Crafts reactions afford mixtures due to the minor difference in electron density between *ortho* and *para* positions. In this work, the use of Pd-catalytic system played a key role in recognizing different reactivity to achieve highly selective *para*-arylated products.

Conclusions

we have described an efficient method for the palladium-catalyzed direct arylation of unprotected phenol derivatives with aryl iodides under mild conditions. From an operational perspective, these arylation reactions are compatible with functional groups, tolerant of water[12]. We are currently engaged in more detailed mechanistic studies as well as the application of this methodology for the synthesis of complex molecules.

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