



## Palladium-catalyzed desulfinitative arylation of 3-haloquinolines with arylsulfonates

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### ABSTRACT

3-Haloquinolines can be functionalized via a palladium-catalyzed desulfinitative coupling of arylsulfonates. This method tolerates substitution upon the aromatic ring and shows good selectivity toward variously substituted aromatic rings.

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Throughout our investigations into the design of serotonin ligands, arylation of the 3 position of 8-chloro-quinolines was a necessary step. Palladium-catalyzed Suzuki reactions using arylboron reagents could provide an efficient route to such functionalization.<sup>1–3</sup> However, during the past few years, alternatives to transition-metal-catalyzed cross-coupling, without the use of organometallic reagents, have also been investigated. Decarboxylative cross-couplings of aryl carboxylic acids have emerged as an interesting strategy.<sup>4,5</sup> Nevertheless, a high reaction temperature or microwave heating is required for the decarboxylation step. More recently, desulfinitative coupling reactions have been described in C–H activation<sup>6–9</sup> or Heck reaction<sup>10–12</sup> allowing the construction of C–C bonds under relatively mild conditions.

Such a coupling with halo-aromatic substrates has been described to a lesser extent. To our knowledge, since the pioneering works of Garbes,<sup>13</sup> only the work of Sato and Okoshi has so far reported an efficient palladium-catalyzed desulfinitative synthesis of biaryls with sodium arylsulfonates and aromatic bromides.<sup>14</sup> In this patent, 3-bromo-pyridine is the only described heterocyclic substrate. To our knowledge, no quinolines have been implied in such reactions. Very recently, similar reactions starting from aryltriflates have been reported, once again, lacking heteroaromatic examples.<sup>15</sup> On the other hand, Cacchi et al. have described the palladium mediated reaction of 2-triflyl-quinoline with *p*-toluenesulf-

inate mediated by palladium, however, a sulfonylation reaction (without SO<sub>2</sub> extrusion) was observed.<sup>16</sup>

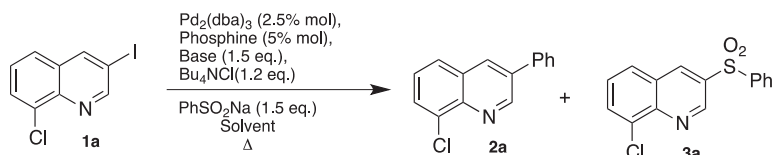
Consequently, we focused our interest on the desulfinitative arylation of 3-iodo-quinolines with arylsulfonates. This desulfinitative cross-coupling reaction was, initially, studied on 8-chloro-3-iodo-quinolines (**1a**) with sodium phenylsulfinate as a model reaction to screen several experimental parameters (Table 1).

Firstly, the presence of an ammonium salt appears to be crucial (entries 1 and 2) because of the low solubility of sulfinate which must be transferred into the organic phase. Concerning the phosphine ligand, apart from XantPhos (entry 1), all other tested phosphines furnish similar or better results with toluene as the reaction solvent. Furthermore, this allows recycling of starting material **1** (entries 3–9). From this screening, DavePhos appears to be the best ligand within the scope of the reaction. An increase in temperature induces the C–C coupling (entries 11–14), with an optimal temperature of 150 °C (entry 12). This effect can be explained by favoring a better extrusion of gaseous SO<sub>2</sub>. When the reaction is carried out in toluene, the nature of base used appears to have little influence on the reaction outcome (entries 1, 3, and 4) however, in NMP, K<sub>2</sub>CO<sub>3</sub> furnishes a markedly improved yield and selectivity for C–C coupling over Cs<sub>2</sub>CO<sub>3</sub> (entries 10 and 11). Such observations are difficult to explain but could be connected to the low dissociation of bases in toluene and of K<sub>2</sub>CO<sub>3</sub> in NMP compared to the high dissociation of Cs<sub>2</sub>CO<sub>3</sub> in NMP. This increased dissociation should modify the basicity and nucleophilicity of intermediate species and consequently have an impact onto the mechanism. Finally, an assay to reduce the loadings of palladium catalyst has been

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**Table 1**  
Arylation of 3-iodo-8-chloro-quinoline (**1**) with sodium phenylsulfinate



No	Phosphine	Base	Solvent	T (°C)	<b>1</b> (%)	<b>2</b> (%)	<b>3</b> (%)
1	XantPhos	$\text{Cs}_2\text{CO}_3$	Toluene	110	0	31	12
2 <sup>a</sup>	XantPhos	$\text{Cs}_2\text{CO}_3$	Toluene	110	0 <sup>a</sup>	<5 <sup>a</sup>	0 <sup>a</sup>
3	XantPhos	$\text{K}_2\text{CO}_3$	Toluene	110	0	28	11
4	XantPhos	$\text{K}_3\text{PO}_4$	Toluene	110	0	28	9
5	XPhos	$\text{Cs}_2\text{CO}_3$	Toluene	110	55	38	7
6	DPPF	$\text{Cs}_2\text{CO}_3$	Toluene	110	15	35	16
7	BINAP	$\text{Cs}_2\text{CO}_3$	Toluene	110	41	34	5
8	DavePhos	$\text{Cs}_2\text{CO}_3$	Toluene	110	49	41	10
9	DavePhos	—	Toluene	110	12	47	10
10	DavePhos	$\text{Cs}_2\text{CO}_3$	NMP	150	0	30	30
11	DavePhos	$\text{K}_2\text{CO}_3$	NMP	150	0	81	10
12	DavePhos	$\text{K}_2\text{CO}_3$	NMP	130	10	71	6
13	DavePhos	—	NMP	150	0	83	10
14	DavePhos	$\text{Cs}_2\text{CO}_3$	Mesitylene	150	6	70	15

<sup>a</sup> Without  $\text{Bu}_4\text{NCl}$ .

**Table 2**  
Desulfative arylation of 3-iodo-quinolines<sup>a,17</sup>

Entry	<b>1</b>	<b>2</b>	Yield <sup>b</sup> (%)
1			81
2			71
3			60
4			61
5			84
6			63
7			91
8			89

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