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# An organic cation as a silver(I) analogue for the arylation of $sp^2$ and $sp^3$ C–H bonds with iodoarenes†

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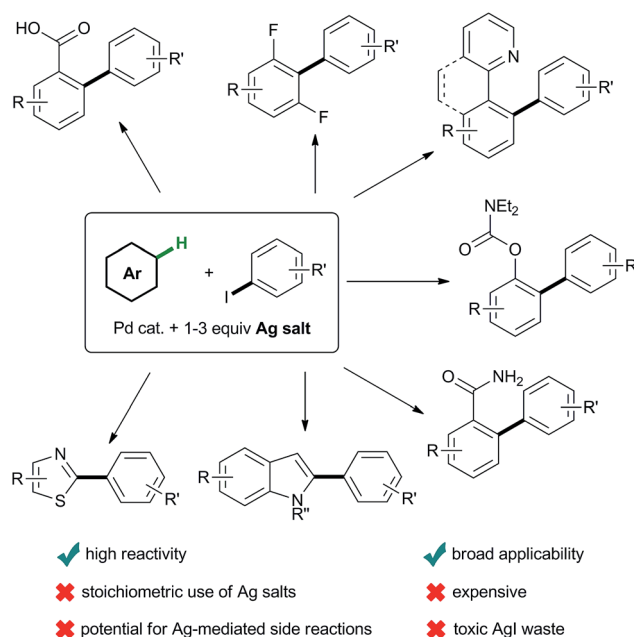
Reactions promoted by stoichiometric amounts of silver salts suffer from high cost, limited availability and raise environmental concerns. This manuscript describes studies leading to the discovery of a general replacement for silver with an inexpensive and convenient organic salt in palladium catalyzed direct  $C(sp^2)$ –H and  $C(sp^3)$ –H arylation reactions.

One of the fundamental goals in chemical research is the development of broadly applicable, cost-effective, practical and sustainable synthetic methods. In this context, the development of C–H bond arylation processes has attracted significant interest as more environmentally-friendly alternatives to traditional cross-couplings. These new transformations use readily available starting materials, thus avoiding the preparation and use of organometallic reagents as coupling partners and the associated generation of stoichiometric amounts of metallic waste.<sup>1</sup>

In 2005, Daugulis and Zaitsev developed a method for the direct arylation of anilides with iodoarenes using a catalytic system involving  $Pd(OAc)_2$  in combination with stoichiometric  $AgOAc$ .<sup>2</sup> This powerful system and its various modifications have since been successfully applied to a great variety of C–H arylation processes involving iodoarene coupling partners (Scheme 1).<sup>3,4</sup> However, to date one of the major drawbacks of these methodologies is the requirement for stoichiometric silver additives.<sup>5</sup> Silver(I) salts are a uniquely appropriate partner for Pd, Au, Cu, Rh, Ru and Pt catalysts, particularly when halide abstraction is required in the catalytic process.<sup>6</sup> However, due to the ability of silver salts to also act as oxidants and Lewis acids, sometimes undesired side reactions are observed.<sup>7</sup> Furthermore, when used as stoichiometric reagents, these expensive silver salts considerably increase the overall cost of the process and generate significant amounts of metal

waste. Therefore those transformations are prohibitively expensive for industry. Importantly, whereas there are alternatives to Ag salts in their role of oxidants, the only other well-known halide scavengers (Pb, Tl and Hg salts) are highly toxic and rarely used for this purpose.

Recent studies on the use of Ag salts as additives in Au-catalyzed reactions have shown that, in addition to abstracting a halogen, Ag may play additional roles essential to the catalytic process and form mixed Au–Ag active species.<sup>8</sup> In the case of C–H arylation reactions, it is possible that Ag salts may also be



**Scheme 1** Selected examples of the general scope of current protocols for C–H arylation using iodoarenes and stoichiometric silver salts.

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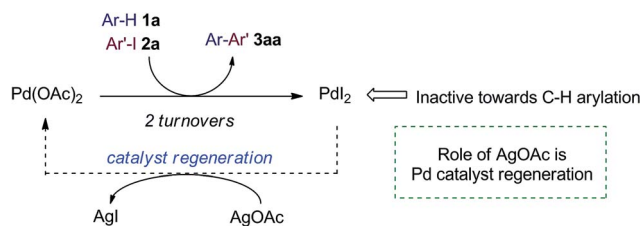
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acting as terminal oxidants, assisting in the oxidative addition step or facilitating the C–H activation. A recent mechanistic study on the role of additives in palladium acetate-catalyzed *ortho*-C–H bond functionalizations suggested that Ag interacts with Pd in a cooperative manner for an enhanced hetero-bimetallic C–H activation.<sup>9</sup> We now report studies that demonstrate that the role of silver salts in several C–H arylation processes with iodoarenes is exclusively that of iodide capture. Furthermore, we have identified that in these processes silver salts can be conveniently replaced with a more redox stable and inexpensive quaternary ammonium salt while maintaining the high reactivity and broad substrate class scope displayed by the previous Pd/Ag systems. To the best of our knowledge, this is the first example of a silver replacement of general applicability to a wide range of C–H arylation processes.

Our initial efforts were directed at assessing the role of Ag salts in a common C–H arylation methodology: the *ortho*-arylation of benzoic acid **1a** with iodoarene **2a** (Table 1). Reaction under standard, Ag salt-mediated, conditions led to formation of biaryl product **3aa** in 87% yield (entry 1).<sup>4ac</sup> Replacement of AgOAc with KOAc led to a reduction in yield to 9%, roughly consistent with two turnovers of the Pd catalyst (entry 2). A qualitative colorimetric test suggested the presence of PdI<sub>2</sub> in the reaction mixture.<sup>10</sup> Replacing Pd(OAc)<sub>2</sub> with PdI<sub>2</sub> led to no reaction (entry 3). Finally, using PdI<sub>2</sub> in combination with AgOAc fully restored the high reactivity of the system (entry 4). These results suggest that in these reactions Pd(OAc)<sub>2</sub> is a competent catalyst for the C–H arylation process, but is poisoned by iodide after two turnovers (Scheme 2). Thus, the silver salt is required for regenerating catalytically active Pd(OAc)<sub>2</sub> from inactive PdI<sub>2</sub> *via* the formation and precipitation of the highly insoluble AgI salts, and not for the C–H arylation itself.

Having established that Ag salts are not intrinsically required for the C–H arylation process, we hypothesised that a more benign acetate salt could equally facilitate regeneration of the Pd catalyst if the acetate counter-cation produced a highly insoluble iodide salt within the reaction medium. To examine



Scheme 2 Poisoning and regeneration of Pd catalyst in C–H arylation.

the validity of this hypothesis we investigated the replacement of AgOAc with a variety of acetate salts (Table 2). The addition of NaOAc, CsOAc or Cu(OAc)<sub>2</sub> proved to be ineffective for the regeneration of the catalyst (entries 1–3).<sup>11</sup> To our delight, a survey of quaternary ammonium salts (entries 4–7) revealed that tetramethylammonium acetate could be used to regenerate the catalyst (entry 5), leading to the product in 45% yield (*ca.* 9 catalyst turnovers). Further, NMe<sub>4</sub>OAc could be formed *in situ* by the equimolar combination of the more readily available and inexpensive NMe<sub>4</sub>Cl and KOAc (entry 8). An experiment using unreactive PdI<sub>2</sub> demonstrated that, like AgOAc, NMe<sub>4</sub>OAc salts are able to regenerate catalytically active Pd species *in situ* (entry 9). Increasing the equivalents of base and iodide abstractor gave an improved yield (entries 10 and 11), with 2.05 equiv. of NMe<sub>4</sub>Cl affording similar yields of product to those obtained using AgOAc (compare entry 11 with entry 1 in Table 1).<sup>12</sup>

The effect of NMe<sub>4</sub> salts on the catalytic activity is remarkable, in particular when compared with the ineffective ammonium salts bearing much larger (NBu<sub>4</sub> and NEt<sub>4</sub>) or smaller (NH<sub>4</sub>) cations. This may be due to a more favourable cation/anion radii ratio, leading to a more effective crystal packing of

Table 1 Mechanistic studies on the role of Ag salt additives<sup>a</sup>

Entry	Pd cat.	Additive (equiv.)	3aa <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub>	AgOAc (1)	87
2	Pd(OAc) <sub>2</sub>	KOAc (1)	9
3	PdI <sub>2</sub>	KOAc (1)	0
4	PdI <sub>2</sub>	AgOAc (1)	84

<sup>a</sup> Reactions were carried out using 0.5 mmol of **1a** and 3 equiv. of **2a**.  
<sup>b</sup> Yields were determined by <sup>1</sup>H NMR analysis using an internal standard.

Table 2 Selected optimization results<sup>a</sup>

Entry	Pd cat.	Additive (equiv.)	3aa <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub>	NaOAc (1)	9
2	Pd(OAc) <sub>2</sub>	Cu(OAc) <sub>2</sub> (1)	9
3	Pd(OAc) <sub>2</sub>	CsOAc (1)	10
4	Pd(OAc) <sub>2</sub>	NH <sub>4</sub> OAc (1)	4
5	Pd(OAc) <sub>2</sub>	NMe <sub>4</sub> OAc (1)	45
6	Pd(OAc) <sub>2</sub>	NEt <sub>4</sub> OAc (1)	9
7	Pd(OAc) <sub>2</sub>	NBu <sub>4</sub> OAc (1)	12
8	Pd(OAc) <sub>2</sub>	NMe <sub>4</sub> Cl (1) + KOAc (1)	44
9	PdI <sub>2</sub>	NMe <sub>4</sub> Cl (1) + KOAc (1)	42
10	Pd(OAc) <sub>2</sub>	NMe <sub>4</sub> Cl (1.25) + KOAc (1.25)	62
11 <sup>c</sup>	Pd(OAc) <sub>2</sub>	NMe <sub>4</sub> Cl (2.05) + KOAc (1.8)	85

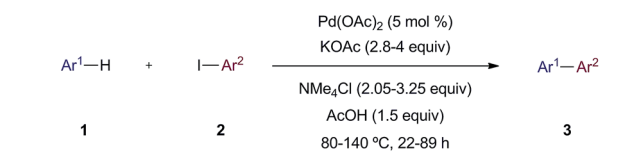
<sup>a</sup> Unless otherwise noted, all reactions were carried out using 0.5 mmol of **1a** and 3 equiv. of **2a**.  
<sup>b</sup> Yields were determined by <sup>1</sup>H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.  
<sup>c</sup> Reaction run for 48 h. NMe<sub>4</sub>Cl and KOAc added in two portions.



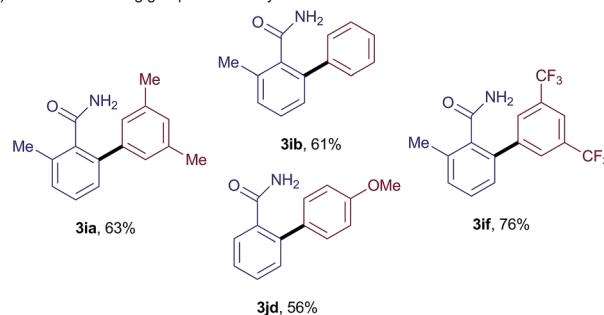
the corresponding iodide salt.<sup>13</sup> The solubility of  $\text{NMe}_4\text{I}$  in  $\text{AcOH}$  was determined to be lower than  $0.3 \text{ mg mL}^{-1}$ , which compares favourably to the higher solubilities of  $\text{NH}_4\text{I}$  ( $4.7 \text{ mg mL}^{-1}$ ),  $\text{NEt}_4\text{I}$  ( $6.5 \text{ mg mL}^{-1}$ ) and  $\text{NBu}_4\text{I}$  ( $647 \text{ mg mL}^{-1}$ ).

Having found a suitable cheap and benign replacement for  $\text{Ag(I)}$  salts, we explored the effects of substitution in both the benzoic acid and the iodoarene coupling partners (Scheme 3). Gratifyingly, both electron-poor and electron-rich iodoarenes led to the corresponding biaryl products in yields similar to, or higher than, those reported for the same  $\text{AgOAc}$  mediated process (**3ab–ae**).<sup>4ac</sup> Varied substitution was also possible on the benzoic acid coupling partner, with high yields observed for *ortho*, *meta* and/or *para* substituted benzoic acids (**3ba–ha**).

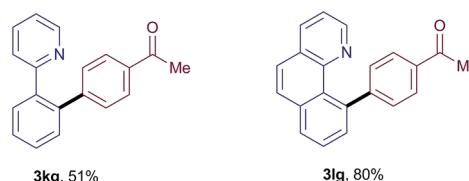
We envisaged that formation of unreactive  $\text{PdI}_2$  may be a common intermediate in the majority of  $\text{Pd(II)}$ -catalysed C–H arylation reactions with iodoarene coupling partners. Therefore, we explored the general applicability of  $\text{NMe}_4\text{OAc}$  as an organic analogue for  $\text{Ag(I)}$ -salts to a wide variety of C–H arylation reactions (Scheme 4). It is noteworthy that simply by adjusting a few reaction parameters the system could be applied to other classes of substrates. Using free amides instead of carboxylic acids as the directing group, the  $\text{NMe}_4$ -mediated protocol furnished the biaryl products in good yield (**3ia–jd**). Other common directing groups for C–H arylation, pyridine and



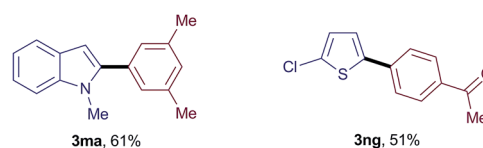
a) Amides as directing groups for C–H arylation:



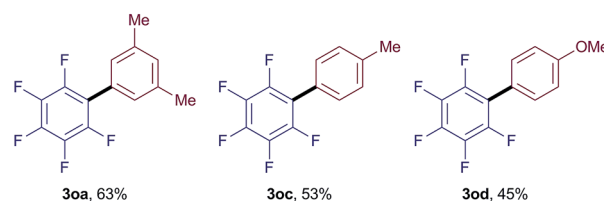
b) Pyridines as directing groups for C–H arylation:



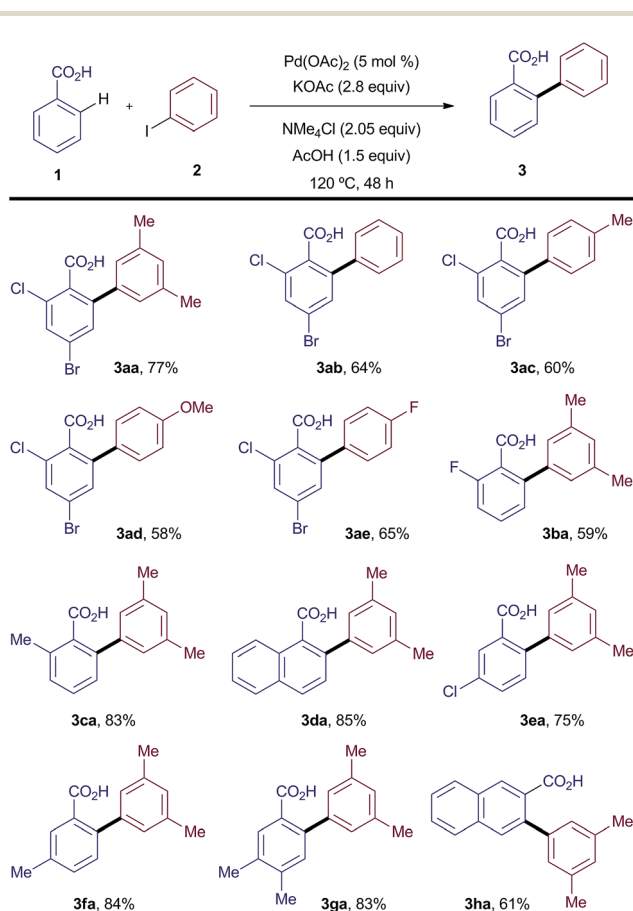
c) Use of electron-rich heteroarenes:



d) Use of electron-poor arenes:



**Scheme 4** Generality of the silver-free C–H arylation of arenes with iodoarenes. All reactions were carried out on 0.5 mmol scale. Yields are of the isolated pure material.

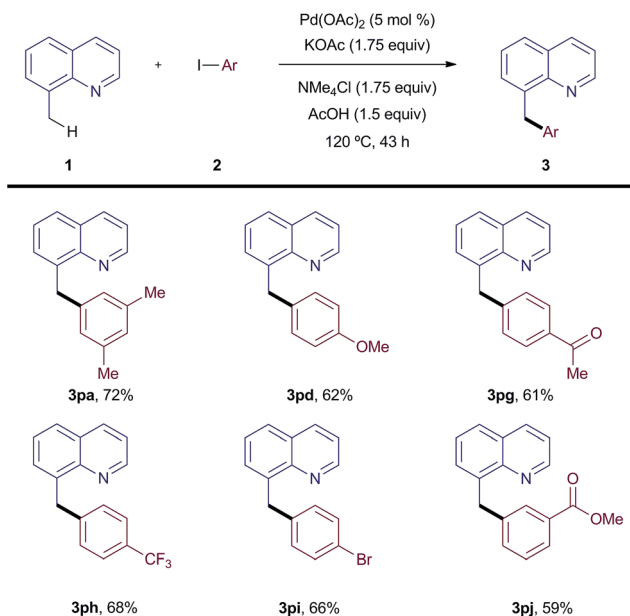


**Scheme 3** Scope of the silver-free C–H arylation of benzoic acids with iodoarenes. All reactions were carried out on 0.5 mmol scale. Yields are of the isolated pure material.

benzoquinoline, were also successfully used under silver-free conditions (**3kg–lg**). We then explored the application of our arylation protocol to other heteroarenes in the absence of a directing group. Remarkably, this protocol also allowed the arylation of *N*-methylindole and 2-chlorothiophene in good yields (**3ma–ng**). These reactions proceeded with high C2 and C5 regioselectivity, respectively (>95 : 5 by  $^1\text{H}$  NMR). Finally, the C–H arylation of electron-poor arenes was also tested and, to our delight, silver-free couplings with pentafluorobenzene could be successfully achieved (**3oa–od**).

To further highlight the applicability and significance of the new catalytic system, we then examined  $\text{C(sp}^3\text{)}\text{–H}$  bond arylation reactions (Scheme 5). Importantly, functionalization at the benzylic position of 8-methylquinoline proceeded well under



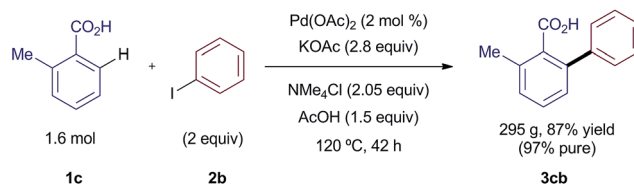


Scheme 5 Scope of the C(sp<sup>3</sup>)-C(sp<sup>2</sup>) coupling. All reactions were carried out on 0.5 mmol scale. Yields are of the isolated pure material.

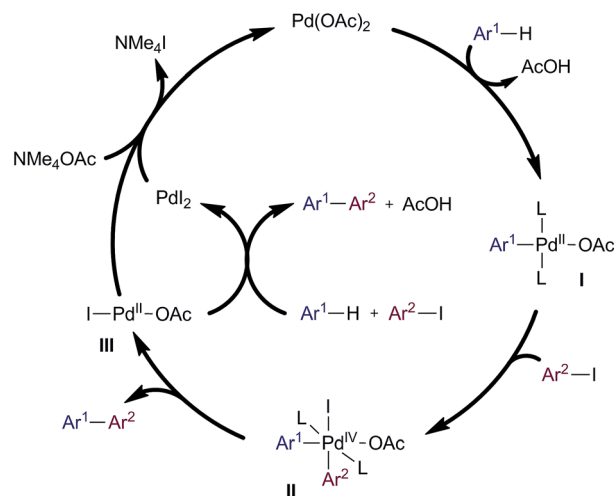
silver-free conditions for iodoarenes containing both electron-donating and electron-withdrawing groups (**3pa-pj**).

The development of NMe<sub>4</sub>-promoted reactions offers major economical and practical advantages over existing Ag-mediated methods. Firstly, the method provides a new avenue to reduce the cost of a number of chemical processes; NMe<sub>4</sub>Cl is *ca.* 50 times cheaper than AgOAc,<sup>14</sup> and is produced in large scale (>5000 tons per year). Secondly, the synthetic advancement is also favourable from an environmental point of view; while AgOAc and AgI are both classed as very toxic to the aquatic environment, NMe<sub>4</sub>OAc and its by-product NMe<sub>4</sub>I<sup>15</sup> are only classed as irritants. Moreover, the tolerance of the system covers a broad range of chemical motifs and the procedure is operationally trivial; the reaction proceeds smoothly under air with no special precautions needed. Overall, the methodology greatly increases the potential for C-H bond direct arylations to be exploited in pharmaceutical and agrochemical industries, where the value of a synthetic process is mainly assessed by the viability in terms of cost and environmental impact.

In order to demonstrate the utility of the new silver-free coupling for process chemistry, we scaled-up the reaction more than 3000 times in a 5 L reactor. Further optimization of the method allowed the arylation of 1.6 mol (218 g) of *o*-toluic acid **1c** with 2 equiv. of iodobenzene (**2b**) and 2 mol % Pd(OAc)<sub>2</sub> (Scheme 6). After an acid-base work-up, the reaction afforded 295 g of product **3cb** in 87% yield with a 97% a/a purity by HPLC suitable for most applications. The purity could be upgraded to >99.9% if required by a simple re-slurry process in *n*-heptane.<sup>10</sup> The analogous reaction using AgOAc would have required 267 g of the silver salt, worth £840, and would have generated 376 g of waste in the form of AgI.<sup>16</sup> Excluding costs associated with waste streams, this new process represents savings of *ca.* 70%. We are confident that our NMe<sub>4</sub>-promoted methodology could be readily carried out on multi-kilogram scale.



Scheme 6 Scale-up of the silver-free arylation reaction. See ESI† for full details.



Scheme 7 Proposed general catalytic cycle.

Our study helps to define the mechanism of previously reported Ag-promoted systems.<sup>3,4</sup> The comparable reactivity, and required reaction times, observed between the NMe<sub>4</sub>-mediated method and those using silver salts suggests that the role of Ag(I) is purely that of a halophile in the catalyst regeneration step. Therefore, other functions attributed to Ag(I) such as terminal oxidant, activator of iodoarenes or assistant in the C-H activation step can most likely be ruled out for this type of arylation processes. Based on these results, a proposed general catalytic cycle for the reactions here reported is depicted in Scheme 7. We postulate a Pd(II/IV) cycle where the C-H activation of the arene would take place first to form an aryl Pd(II) complex **I**. This intermediate may then undergo oxidative addition to Pd(IV) species **II** which, after reductive elimination, would release the biaryl product and the catalyst in the form of PdIOAc (**III**). This intermediate could undergo ligand exchange with NMe<sub>4</sub>OAc to form Pd(OAc)<sub>2</sub>, disproportionate to PdI<sub>2</sub> and Pd(OAc)<sub>2</sub> or could also initiate a second catalytic cycle which would result in unreactive PdI<sub>2</sub>. Finally, PdI<sub>2</sub> would react with NMe<sub>4</sub>OAc, regenerating catalytically active Pd(OAc)<sub>2</sub>.

## Conclusions

In summary, we have described the discovery of an organic analogue of silver(I)-salts, and develop reaction conditions that allow the Pd-catalysed C-H coupling reaction of a variety of classes of substrates: benzoic acids, benzamides,





2-phenylpyridines, benzoquinolines, indoles, thiophenes, poly-fluorobenzenes and 8-methylquinolines with diverse substituted iodoarenes under silver-free conditions. The new method is easily scalable and benefits from the use of inexpensive and readily available reactants, an operationally simple procedure, high functional group tolerance and low-toxicity waste. We believe that this discovery will provide a pathway for facilitating application of numerous existing, and new, direct C–H bond functionalizations to industry, in addition to opening the door to other novel silver-free transition metal catalysed processes.

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- 11 Recently, Yu and co-workers have identified a viable alternative for catalyst regeneration in iodination reactions by the effective combination of a specific amide auxiliary and CsOAc as iodide scavenger, see: (a) X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 10326, Earlier studies on halogenation of C-H bonds showed that Pd(OAc)<sub>2</sub> can be obtained from PdI<sub>2</sub> with IOAc. This iodonium(I) reagent is not suitable for silver-free arylations as it has to be preformed from AgOAc or PhI(OAc)<sub>2</sub> *in situ*, see: (b) D.-H. Wang, X.-S. Hao, D.-F. Wu and J.-Q. Yu, *Org. Lett.*, 2006, **8**, 3387; (c) T.-S. Mei, R. Giri, N. Maugel and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 5215; (d) T.-S. Mei, D.-H. Wang and J.-Q. Yu, *Org. Lett.*, 2010, **12**, 3140.
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