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# Direct intermolecular C–H arylation of unactivated arenes with aryl bromides catalysed by 2-pyridyl carbinol<sup>†</sup>

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Direct intermolecular C-H arylation employing aryl bromide as the arene source has been developed. This process proceeds *via* a simple transition-metal-free pathway. With the aid of inexpensive and commercially available 2-pyridyl carbinol and potassium *tert*-butoxide, various unactivated arene C-H bonds can be directly arylated by aryl bromides through homolytic aromatic substitution.

Biaryl motifs are essential sub-units of a number of synthetically valuable intermediates. They are often found in many natural products, biologically active and pharmaceutically useful compounds.<sup>1</sup> In addition, biaryl scaffolds also have high relevance in graphene materials science.<sup>2</sup> Transition metal-catalysed/mediated aromatic carbon–carbon bond construction processes have been successful since 1970s.<sup>3</sup> However, organohalide (Ar–X) and organometallic (Ar'–M) reagents are necessary to be employed in these cross-coupling reactions. The pre-activation of coupling partners (organometallic reagents), as well as the need for transition metal catalysts, would lead to problematic metal waste disposal.

A greener and more economical synthetic approach which circumvents transition metal catalysts is highly attractive.<sup>4</sup> Thus, a transition metal-free biaryl synthesis is highly desirable.<sup>5</sup> In 2008, Itami initially reported the C–H arylation of activated heterocycles under transition metal-free conditions.<sup>6</sup> In 2010, Lei and Kwong,<sup>7</sup> Hayashi and Shirakawa,<sup>8</sup> and Shi<sup>9</sup> independently disclosed further advancements of this process for non-activated arenes. The catalyst of *N*,*N*'-dimethylethylene-diamine (DMEDA), 1,10-phenanthroline (Phen) and its derivatives are necessary to be employed under these sodium/ potassium *tert*-butoxide-mediated conditions. It is believed

that this coupling process goes through a homolytic aromatic substitution (HAS) pathway.<sup>10</sup> After these recent breakthroughs, numerous reports have emerged demonstrating other applicable catalysts for the successful transition metalfree C-H arylation.<sup>11</sup> In 2013, Liu even showed a simple alcohol which could facilitate the direct C-H arylation of nonactivated arenes with aryl iodides.<sup>12</sup> Apart from the added catalysts, the photoirradiation-stimulated biaryl synthesis was also recently established.<sup>13</sup> In early 2014, Wilden showed that the catalyst is not even essential while potassium tert-butoxide alone could promote the coupling reaction.<sup>14</sup> However, a relatively high reaction temperature (160 °C) is required. In fact, previous literature reports were mainly focused on aryl iodide coupling. Thus a catalyst system, which allows general aryl bromides to serve as the coupling partner, is still in demand. In continuing our former work on DMEDA-catalyzed C-H arylation of benzene and intramolecular C-H arylation by ethylene glycol,<sup>15</sup> herein, we report our efforts of using aryl bromides as the coupling partners for direct intermolecular C-H arylation of non-activated arenes.

We started to embark the C-H bond cross-coupling of 4-bromotoluene with benzene using previously successful proprietary organo-promoters (e.g. DMEDA and Phen).<sup>16</sup> Yet, inferior results were obtained. Only less than 5% conversion of aryl bromides was observed by GC-FID analysis. Inspired from our previous work on ethylene glycol-catalysed phenanthridine synthesis,<sup>15</sup> we became interested in evaluating simple alcohols associated with amines, for the C-H arylation of non-activated arenes with aryl bromides. 2-Pyridyl carbinol was initially chosen as the catalyst for examining the coupling between 4-bromotoluene and benzene (Table 1). To our delight, the result showed that this coupling was feasible and excellent product yield was obtained (entry 1). Upon lowering the reaction temperature, the desired product yields decreased (entries 1-4). The reaction proceeded well even at room temperature with extended reaction time (entry 5). This example represents the first direct C-H arylation of a non-activated arene with non-activated aryl bromide at ambient temperature under transition metal-free conditions. 10 mol% of the catalyst

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#### Table 1 Initial optimization of reaction conditions<sup>a</sup>



Entry	Catalyst loading	Base	Temp./°C	% yield <sup>b</sup>
L	40 mol%	KOt-Bu	80	96
2	40 mol%	KOt-Bu	60	75
3	40 mol%	KOt-Bu	40	58
1	40 mol%	KOt-Bu	r.t.	35
5 <sup>c</sup>	40 mol%	KOt-Bu	r.t.	68
5	30 mol%	KOt-Bu	80	95
7	20 mol%	KOt-Bu	80	95
3	10 mol%	KOt-Bu	80	95
)	5 mol%	KOt-Bu	80	65
10	40 mol%	_	80	n.r.
1	_	KOt-Bu	80	n.r.
12	40 mol%	$K_2CO_3$	80	n.r.
13	40 mol%	NaOt-Bu	100	Trace
$14^d$	40 mol%	KOt-Bu	120	8
$15^e$	40 mol%	KOt-Bu	80	n.r.
$16^{f}$	40 mol%	KOt-Bu	80	n.r.
17 <sup>g</sup>	40 mol%	KOt-Bu	80	n.r.
$18^h$	40 mol%	KOt-Bu	80	n.r.

<sup>a</sup> Reaction conditions: 4-bromotoluene (1.0 mmol), benzene (8.0 mL), catalyst (as indicated in table), and KOt-Bu (2.0 mmol) were stirred under nitrogen at indicated temperatures for 24 hours. <sup>b</sup>Calibrated GC yields were reported, using dodecane as the internal standard. <sup>7</sup>72 hours was applied. <sup>d</sup>4-Chlorotoluene was used instead of 4-bromotoluene. <sup>e</sup> 4-Pyridyl carbinol was used instead of 2-pyridyl carbinol. <sup>*J*</sup> 3-Amino-1-propanol was used the catalyst. as <sup>g</sup> 2-Aminobenzyl alcohol was used as the catalyst. <sup>h</sup> 2-Amino-4-hydroxy-6-methylpyrimidine was used as the catalyst.

were sufficient to promote this reaction (entries 6-9). In the absence of either 2-pyridyl carbinol or potassium tert-butoxide, no reaction occurred (entries 10 and 11). A survey of other bases indicated that KOt-Bu was crucial to this biaryl synthesis (entries 1, 12 and 13). Nevertheless, aryl chlorides were found inapplicable (entry 14). To our surprise, when 4-pyridyl carbinol (the regioisomer of 2-pyridyl carbinol), 3-amino-1-propanol, 2-aminobenzyl alcohol and 2-amino-4-hydroxy-6-methylpyrimidine were evaluated as the promoter, no observable substrate conversion was detected (entries 15-18). Thus, 10 mol% of 2-pyridyl carbinol was the best catalyst loading for catalyzing the reaction with potassium tert-butoxide at 80 °C for 24 hours.

With the preliminary optimized reaction conditions in hand, we next examined the generality of the catalyst system for direct arylation of benzene with various aryl bromides (Table 2). In general, 10 mol% of 2-pyridyl carbinol was sufficient to catalyse the reaction. Notably, the direct arylation could be performed at room temperature with extended reaction time with specific substrates (entries 2 and 14). Electron-donating aryl bromides afforded the corresponding desired product in good-to-excellent yields. Cyano and fluoro groups were compatible under these reaction conditions (entries 4-8). Sterically hindered ortho-substituted aryl bromides furnished the desired product in moderate yields (entries 9 and 10). Heteroaryl bro-

Table 2 Transition metal-free direct C-H arylation of benzene with ArBr<sup>a</sup>



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<sup>a</sup> Reaction conditions: aryl bromides (1.0 mmol), benzene (8.0 mL), 2-pyridyl carbinol (10 mol%), KOt-Bu (2.0 mmol) were stirred at 80 °C under nitrogen for 24 hours (reaction times for each substrate were not optimized). <sup>b</sup> Isolated yields. <sup>c</sup> The reaction was performed with 40 mol % 2-pyridyl carbinol under room temperature for 72 hours. <sup>d</sup> GC yield was obtained.

Table 3 Transition metal-free direct arylation of unactivated arenes with  $\mbox{ArBr}^a$ 



<sup>*a*</sup> Reaction conditions: aryl bromides (1.0 mmol), unactivated arenes (8.0 mL), 2-pyridyl carbinol (10 mol%), KO*t*-Bu (2.0 mmol) were stirred at 80 °C under nitrogen for 24 hours (reaction times for each substrate were not optimized). <sup>*b*</sup> Isolated yields.



Scheme 1 Kinetic isotope effect studies (reaction conditions are the same as in Table 2, entry 1 except that 80 equiv. of either benzene or d-benzene was used).

mides such as thienyl-, pyridyl-, and isoquinolinyl bromides were feasible coupling partners for this transformation to give moderate-to-good product yields (entries 11–13).

Apart from benzene, other unactivated arenes were also examined for the direct arylation (Table 3). Mesitylene, p-xylene could be directly arylated with corresponding aryl bromides to give good yields (entries 1–4). A mixture of regioisomers was observed when toluene was used as the coupling substrate, which indirectly showed that an aryl radical was involved in the reaction mechanism.

Further investigations were carried out to gain some insight into the dependence of the C–H bond cleavage (Scheme 1). A kinetic isotope effect (KIE) experiment was performed and consistent KIE values were observed from aryl bromides ( $k_{\rm H}/k_{\rm D}$ = 1.21). This result indicated that the C–H bond cleavage step might not be involved in the rate-determining step of this transformation.

## Conclusions

In summary, we have reported a general C–H arylation of unactivated arenes with a wide range of aryl/heteroaryl bromides in the presence of 2-pyridyl carbinol and potassium *tert*-butoxide. Various aryl bromides were coupled well with unactivated arenes under mild reaction conditions. Particularly noteworthy is that only 10 mol% of the catalyst is enough to promote the arylation. The use of 2-pyridyl carbinol provides a simple and inexpensive protocol to tackle the challenging C–H arylation under transition-metal-free conditions. Further investigations are currently underway.

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