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Direct Intermolecular C-H Arylation of Unactivated Arenes with Aryl Bromides Catalysed by 2-Pyridyl Carbinol

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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 bond can be directly arylated by aryl bromides through homolytic aromatic substitution.

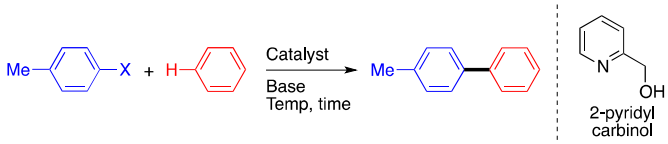
Biaryl motifs are essential sub-units of a number of synthetically valuable intermediates. They are often found in many natural products, biologically active and pharmaceutically useful compounds.[1] In addition, biaryl scaffolds also have high relevance in graphene material sciences.[2] Transition metal-catalysed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

A greener and more economical synthetic approach which circumvented transition metal catalysts is of high attractiveness.[4] Thus, a transition metal-free biaryl synthesis is highly desirable.[5] In 2008, Itami initially reported the C-H arylation of activated heterocycles under transition metal-free conditions.[6] In 2010, Lei/Kwong,[7] Hayashi/Shirakawa,[8] and Shi[9] independently disclosed further advancements of this process for non-activated arenes. The catalyst of *N,N'*-dimethylethylenediamine (DMEDA), 1,10-phenanthroline (Phen) and its derivatives are necessary to be employed under this sodium/potassium *tert*-butoxide-mediated conditions. It is believed that this coupling process goes through a homolytic aromatic substitution (HAS) pathway.[10] After these recent breakthroughs, numerous reports have emerged demonstrating other applicable catalysts for the successful transition metal-free C-H arylation.[11] In 2013, Liu even showed a simple alcohol which could facilitate the direct C-H arylation of non-activated arenes with aryl iodides.[12] Apart from the added catalysts, the photoirradiation-stimulated biaryl synthesis was also recently established.[13] In early 2014, Wilden showed that the catalyst was not even essential while potassium *tert*-butoxide alone could promote the coupling reaction.[14] However, a relatively high reaction temperature (160 °C) was required. In fact, previous literature reports were mainly focused on aryl iodide coupling. Thus a catalyst system, which allows general aryl bromide to serve as the coupling partner, is still in demand. In continuing our former works on DMEDA-catalyzed C-H arylation of benzene[7] and intramolecular C-H arylation by ethylene glycol,[15] 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 succeeded proprietary organo-promoters (e.g. DMEDA and Phen).[16] Yet, inferior results were obtained. Only less than 5% conversion of aryl bromides were observed from GC-FID analysis. Inspired from our previous work of ethylene glycol-catalyzed phenanthridine synthesis,[15] we are attracted to evaluate simple alcohol associated with amine, 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 afforded (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 of reaction time (entry 5). This example represents the first direct C-H arylation of non-activated arene with non-activated aryl bromide at ambient temperature under transition metal-free conditions. 10 mol% of catalyst were sufficient to promote this reaction (entries 6-9). In the absence of either 2-

pyridyl carbinol or potassium *tert*-butoxide, no reaction was resulted (entries 10-11). A survey of other bases indicated that KO*t*-Bu was crucial to this biaryl synthesis (entries 1 & 12-13). Nevertheless, aryl chloride was found inapplicable (entry 14). To our surprise, when the 4-pyridyl carbinol (the regioisomer of 2-pyridyl carbinol), 3-aminno-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.

Table 1. Initial optimization of reaction conditions[a]

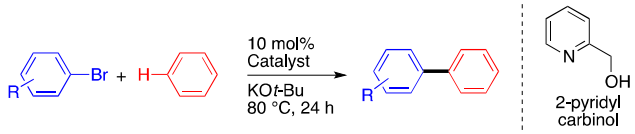


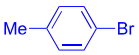
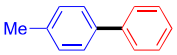
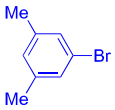
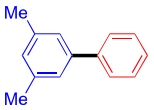
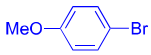
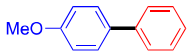
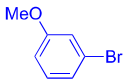
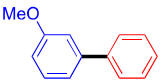
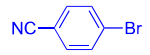
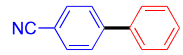
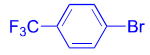
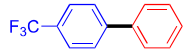
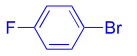
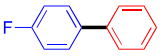
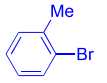
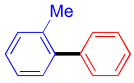
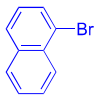
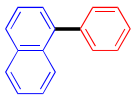
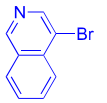
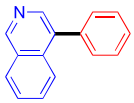
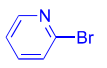
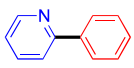
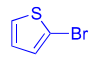
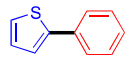
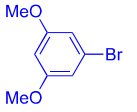
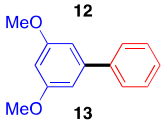
entry	catalyst loading	base	temp./ °C	% yield[b]
1	40 mol%	KO*t*-Bu	80	96
2	40 mol%	KO*t*-Bu	60	75
3	40 mol%	KO*t*-Bu	40	58
4	40 mol%	KO*t*-Bu	r.t.	35
5[c]	40 mol%	KO*t*-Bu	r.t.	68
6	30 mol%	KO*t*-Bu	80	95
7	20 mol%	KO*t*-Bu	80	95
8	**10 mol%**	**KO*t*-Bu**	**80**	**95**
9	5 mol%	KO*t*-Bu	80	65
10	40 mol%	--	80	n.r.
11	--	KO*t*-Bu	80	n.r.
12	40 mol%	K_2CO_3	80	n.r.
13	40 mol%	NaO*t*-Bu	100	trace
14[d]	40 mol%	KO*t*-Bu	120	8
15[e]	40 mol%	KO*t*-Bu	80	n.r.
16[f]	40 mol%	KO*t*-Bu	80	n.r.
17[g]	40 mol%	KO*t*-Bu	80	n.r.
18[h]	40 mol%	KO*t*-Bu	80	n.r.

[a]Reaction conditions: 4-bromotoluene (1.0 mmol), benzene (8.0 mL), catalyst (as indicated in table), and KO*t*-Bu (2.0 mmol) were stirred under nitrogen at indicated temperature for 24 hours. [b]Calibrated GC yields were reported, using dodecane as the internal standard. [c]72 hours was applied. [d]4-Chlorotoluene was used instead of 4-bromotoluene. [e]4-Pyridyl carbinol was used instead of 2-pyridyl carbinol. [f]3-amino-1-propanol was used as the catalyst. [g]2-aminobenzyl alcohol was used as the catalyst. [h]2-amino-4-hydroxy-6-methylpyrimidine was used as the catalyst.

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 of reaction time with specific substrates (entry 2 and 14). Electron-donating aryl bromides afforded the corresponding desired product in good-to-excellent yield. 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 9-10). Heteroaryl bromides such as thienyl-, pyridyl-, and isoquinolinyl bromides were feasible coupling partners for this transformation to give moderate-to-good product yields (entries 11-13).

Table 2. Transition metal-free direct C-H arylation of benzene with ArBr[a]

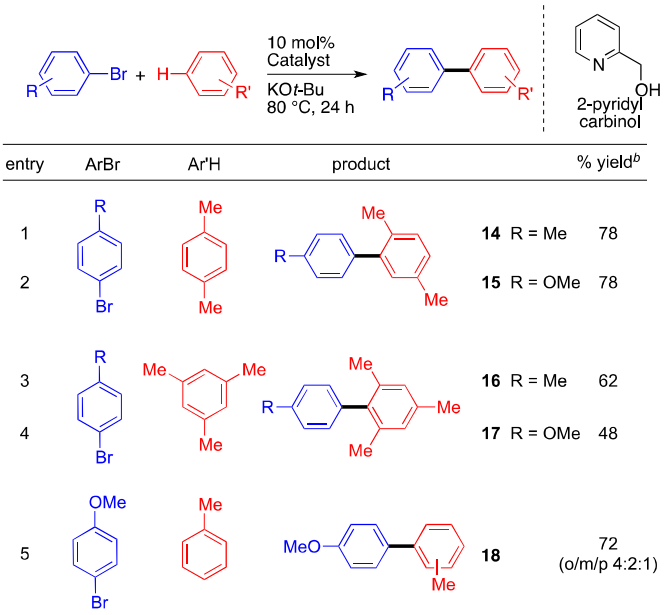


entry	ArBr	product	% yield[b]
1			88
2[c]			60
3			69
4			81
5			80
6			76
7			60
8			46
9			50
10			43
11			70
12			72
13		 **12**	55
14[c,d]		 **13**	20

[a]Reaction conditions: Aryl bromides (1.0 mmol), benzene (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). [b]Isolated yields. [c]The reaction was performed with 40 mol% 2-pyridyl carbinol under room temperature for 72 hours. [d]GC yield was obtained.

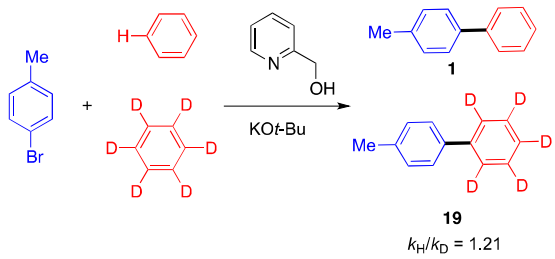
Apart from benzene, other unactivated arenes were also examined for the direct arylation (Table 3). Mesitylene, *p*-xylene could be directly arylated with corresponding aryl bromides to give good yields (entries 1-4). A mixture of regioisomers was observed when toluene was used as the coupling substrate,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

Table 3. Transition metal-free direct arylation of unactivated arenes with ArBr[a]



[a]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). [b]Isolated yields.

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_H/k_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.



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

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 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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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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(16) Reaction conditions: 4-bromotoluene (1.0 mmol), benzene (8.0 mL), DMEDA or Phen (10 mol%), KO*t*-Bu (2.0 mmol) were stirred at 80 °C under nitrogen for 24 hours.