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Direct C−H Arylations of Unactivated Arenes Catalyzed by Amido-Functionalized Imidazolium Salts

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Abstract: The synthesis of biaryls from unactivated arenes and a broad range of aryl bromides and chlorides *via* the direct C−H functionalization can be efficiently performed with the aid of amido-functionalized imidazolium salts as organocatalysts. This method avoids the use of toxic transition metal catalysts and organometallic reagents.

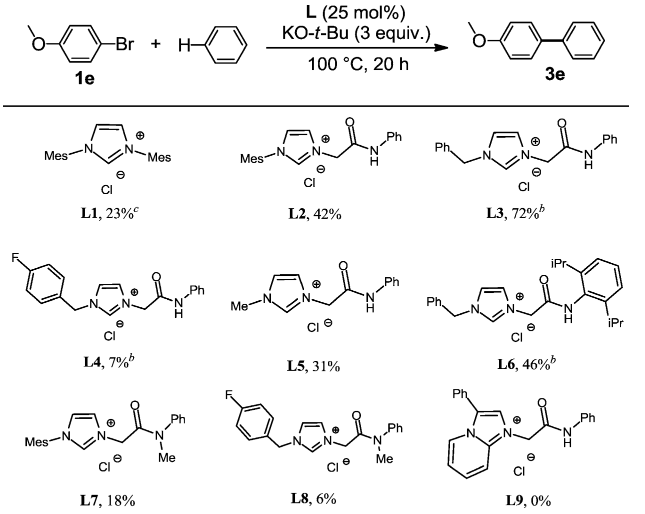
Keywords: C−H activation; imidazolium salts; organocatalysis; transition metal-free conditions; unactivated arenes

Biaryls are privileged structural units employed in a wide diversity of applications in pharmaceuticals, drug candidates, and functional materials.[1] Palladium-catalyzed cross-coupling reactions have been widely used for the construction of these important building blocks.[2] Recently, transition metal-catalyzed direct C−H arylation reactions have attracted considerable attention for the preparation of these scaffolds.[3] Such methodologies for biaryl construction without the need of pre-formed organometallic reagents are environmentally benign because of the reduced waste and fewer reaction steps required. So far, a wide range of homo- and heteroaromatic biaryls has been prepared *via* these methods.[3] Lately, transition metal-free direct C−H arylation reactions of unactivated arenes without the involvement of organometallic reagents as well as transition metal catalysts have been successfully demonstrated.[4,5] Various organocatalysts such as DMEDA,[4a] 1,10-phenanthroline,[4b,c] simple alcohols,[5h] and carbenes[5c] in the presence of *tert*-butoxide as base are known to effectively promote the direct C−H arylation of unactivated arenes with aryl iodides and bromides.

During the course of our investigations on Pd-carbene complexes and their applications in cross-coupling reactions[6] and direct C−H arylations,[7] we have accumulated a library of effective catalyst systems based on amido-functionalized carbene ligand precursors, most of which are imidazolium salt derivatives. Recently, Ong has reported the successful application of free carbenes in catalyzing the direct C−H functionalization of arenes using aryl iodides as coupling partners.[5c] Thus far, although some effective organocatalysts for direct C−H arylation have been developed, coupling partners have been generally limited to aryl bromides and iodides.[4,5] Thus the development of alternative organocatalysts that can effectively utilize aryl bromides as well as chlorides would be a useful addition to the field. Herein, we report the use of the above-mentioned inexpensive amido-functionalized imidazolium salts as organocatalysts in the direct C−H arylation of unactivated arenes. To our delight, the catalysts were effective in promoting reactions with a range of aryl bromides and even chlorides.

Initially, a model reaction between 4-bromoanisole and benzene was performed employing 20 mol% of commercially available IMes·HCl (**L1**) in the presence of 3 equiv. of KO-*t*-Bu at 100 °C. The desired product, 4-methoxybiphenyl (**3e**), was obtained in 23% yield. The coupling activities did not occur in the absence of the organocatalyst. Encouraged by this result, we examined the catalytic performances of a series of imidazolium salts with amide functionalities (Table 1). When **L2** was employed, yield of the desired product increased to 36%, indicating that an imidazolium salt with a free N−H moiety can effectively catalyze the coupling reaction. Reaction optimization by an increase in catalyst loading to 25 mol% of **L2** resulted in the complete conversion of the starting material with 42% yield of the desired product. Under the optimized conditions (**L**, 25 mol%; KO-*t*-Bu, 1.5 mmol; 4-bromoanisole, 0.5 mmol; benzene, 2.25 mL; reaction temperature, 100 °C; reaction time, 20 h), a series of imidazolium salts was screened; the

Table 1. Organocatalyst screening for direct C–H functionalization.[a]



L1, 23%[c] **L2**, 42% **L3**, 72%[b]

L4, 7%[b] **L5**, 31% **L6**, 46%[b]

L7, 18% **L8**, 6% **L9**, 0%

[a] *Reaction conditions* (unless otherwise specified): 4-bromoanisole (0.5 mmol), KO-*t*-Bu (1.5 mmol), benzene (2.25 mL), **L** (25 mol%), 100 °C, 20 h, isolated yields.

[b] Yields were determined by GC.

[c] Isolated yield using 20 mol% **L**.

results indicated that the structures of the imidazolium salts play a crucial role in the reaction outcome.

Compound **L3** featuring a more flexible benzyl instead of a rigid mesityl group afforded the desired product in 72% yield. A drastic decline in efficiency was observed with **L4** bearing an electron-withdrawing 4-fluorobenzyl group. In this case, the homocoupling product from 4-bromoanisole was observed. The transformation was also attenuated using **L5** with a smaller methyl group. A comparison of activities between **L3** and **L6** (72 *vs.* 46%) indicated that the sterically encumbered group attached to the NH moiety was also detrimental to the coupling activities. The NH proton on the catalyst was proven to be crucial, as its replacement with a methyl group led to a drastic decrease in product yield (42% for **L2** *vs.* 18% for **L7**). Cross-coupling failed to proceed when **L9**, an abnormal carbene precursor was employed. Intriguingly, the Pd(II) complex comprising **L3** and PCy_3[6a] (2.5 mol%) was less efficient in mediating the formation of **3e** (48% yield), firmly establishing the essence of the transition metal-free conditions.

To better understand the reaction profile, the progress of the coupling reactions catalyzed by **L3**, **L4**, and **L6** was monitored by GC chromatography (Figure 1). The superiority of **L3** over the other catalysts was confirmed and its reaction rate slowed down drastically after 10 h. Bases other than KO-*t*-Bu were found to be ineffective. It is also noteworthy that, contrasting to most reports in the literature,[4,5] aryl iodides appeared to be less compatible under the present reaction conditions and can be recovered after the typical reaction time for the aryl bromides. In fact, longer reaction times (*ca.* 36 h) were required for the full conversion of aryl iodides to the coupled products (see the Supporting Information).

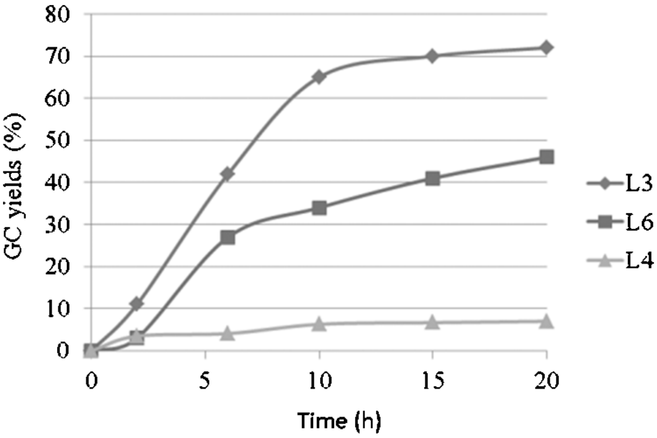
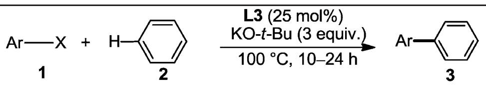


Figure 1. Comparison of imidazolium salts for direct C–H functionalization of benzene with 4-bromoanisole.

With the **L3**/KO-*t*-Bu catalyst system identified, the substrate scope of the coupling reaction between benzene and a wide range of aryl halides was investigated (Table 2). Reaction progress was monitored by TLC, and the reactions were stopped after complete consumption of the starting materials. Bromoarenes with electron-donating substituents were found to be excellent substrates, affording the corresponding biaryl scaffolds in good yields (70–78% yields, entries 1, 2, 4, 7). Pleasingly, the coupling reactions provided acceptable yields (58–71%, entries 3, 5, 6) even with sterically hindered *ortho*-substituted aryl bromides after prolonged reaction times (36 h). Although electron-deficient aryl bromides led to the rapid consumption of starting bromides (10–18 h), moderate yields of products were obtained (61–63%, entries 10–13). It is worth noting that the reported reaction conditions are compatible with bromoarenes substrates with potentially sensitive nitrile, ketone, and esters groups. Heterocyclic haloarenes such as 2-bromothiophene and 2-bromopyridine were also found to be suitable substrates, providing yields of 82 and 63%, respectively (entries 8 and 9). In general, aryl chlorides followed the same reactivity pattern as that of bromides, affording slightly lower yields (50–56%, entries 14–18). Electron-rich 4- and 3-chloroanisoles could be utilized as coupling partners, giving the desired coupled products in reasonable yields (54 and 56%, entries 14 and 15). To the best of our knowledge, this is the first report on the use of chloroanisoles for the preparation of biaryls *via* transition metal-free intermolecular direct C–H arylation of unactivated arenes.[8] Sterically congested aryl chlorides such as 2-chloroanisole and 2-chloro-1,3-dimethylbenzene, however, were unreactive under the identical conditions.

Table 2. Imidazolium salt-catalyzed direct arylation of benzene with aryl halides.[a]



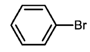
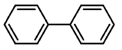
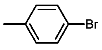
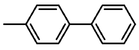
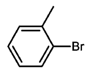
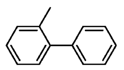
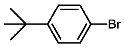
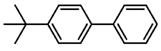
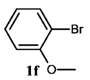
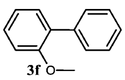
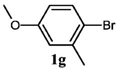
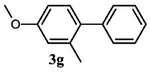
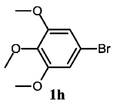
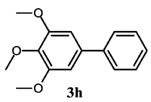
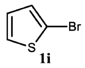
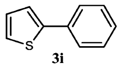
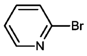
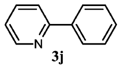
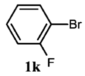
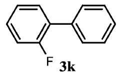
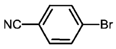
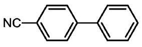
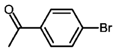
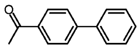
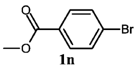
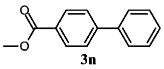
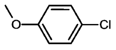
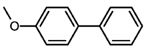
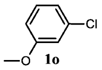
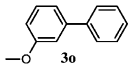
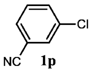
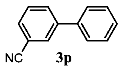
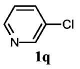
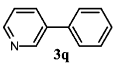
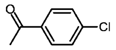
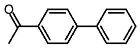
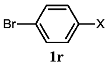
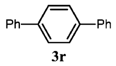
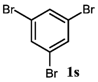
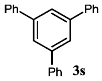
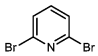
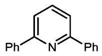
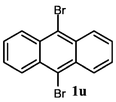
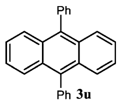
Entry	Arene	Aryl Bromide	Yield [%]
1	 **1a**	 **3a**	75
2	 **1b**	 **3b**	72
3[c]	 **1c**	 **3c**	62
4	 **1d**	 **3d**	78
5[c]	 **1f**	 **3f**	58
6[c]	 **1g**	 **3g**	71
7	 **1h**	 **3h**	70
8	 **1i**	 **3i**	82
9	 **1j**	 **3j**	63
10	 **1k**	 **3k**	61
11	 **1l**	 **3l**	61
12	 **1m**	 **3m**	63
13	 **1n**	 **3n**	63
14[b]	 **1e-Cl**	 **1e**	54
15[b]	 **1o**	 **3o**	56
16[b]	 **1p**	 **3p**	50
17[b]	 **1q**	 **3q**	52
18[b]	 **1m-Cl**	 **3m**	52
19[d] 20[d]	 **1r**	 **3r**	65 (X = Br) 56 (X = Cl)

Table 2. (Continued)

Entry	Arene	Aryl Bromide	Yield [%]
21[e]	 **1s**	 **3s**	58
22[d]	 **1t**	 **3t**	53
23[d,f]	 **1u**	 **3u**	32

[a] *Reaction conditions* (unless otherwise specified): ArBr (0.5 mmol), KO-*t*-Bu (1.5 mmol), benzene (2.25 mL), **L3** (25 mol%), 100 °C, 10–24 h.

[b] ArCl (1.0 mmol), KO-*t*-Bu (3.0 mmol), benzene (4.5 mL).

[c] Time was prolonged to 36 h.

[d] ArBr (0.5 mmol), KO-*t*-Bu (3.0 mmol), benzene (4.5 mL), 36 h.

[e] ArBr (0.5 mmol), KO-*t*-Bu (4.5 mmol), benzene (7.0 mL), 36 h.

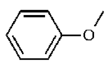
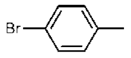
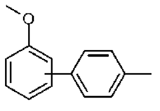
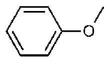
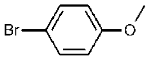
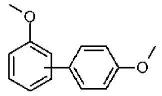
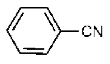
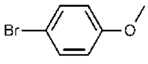
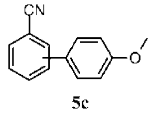
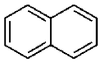
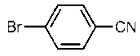
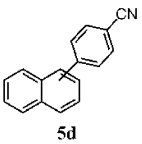
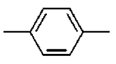
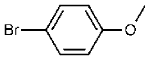
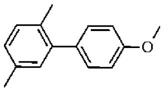
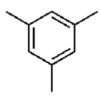
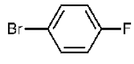
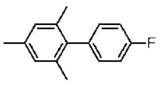
[f] 35% of 10-bromo-9-phenylanthracene was isolated.

When 1,4-dibromobenzene was employed, double coupling took place, providing *para*-terphenyl in 65% yield (entry 19). The more challenging substrate 1-bromo-4-chlorobenzene underwent double arylation as well to furnish the desired product in comparable 56% yield (entry 20). More interestingly, three-fold arylation of 1,3,5-tribromobenzene occurred smoothly, affording a respectable yield of 1,3,5-triphenylbenzene as a single product (58%, entry 21). The reactions of 2,6-dibromopyridine and 9,10-dibromoanthracene were also investigated (entries 22 and 23), with the corresponding heteroaromatic arylated products being obtained in 53 and 32% yields, respectively.

Next we investigated the coupling reactions of different unactivated arenes under our new catalytic conditions. Monosubstituted arenes such as anisole and benzonitrile afforded mixtures of regioisomers favoring *ortho*-substitution over the *meta*- and *para*-positions with moderate yields in all cases (Table 3, entries 1–3). When naphthalene was employed as the coupling partner, α-arylated **5d** predominated (74% regioselectivity, entry 4). *para*-Xylene and mesitylene afforded the desired biaryls in relatively longer times with moderate yields of 58 and 42%, respectively (entries 5 and 6).

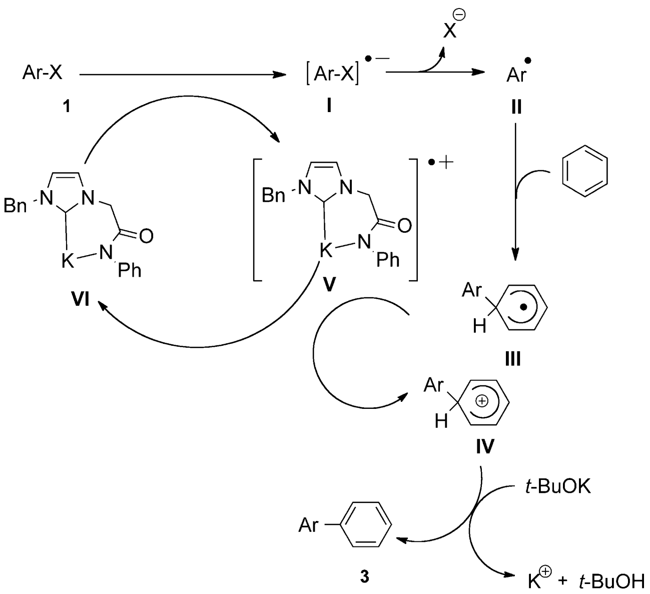
Most notable throughout the entire study was the absence of side products due to dehalogenation from the corresponding aryl halides. Also, in all of the above reactions, regioisomers with respect to the aryl halides were not detected, ruling out the possibility of a benzyne mechanism.[9] In fact, the aforementioned *ortho*-selectivity with respect to the monosubstituted

Table 3. Imidazolium salts-catalyzed direct arylation of arene with aryl bromides.[a]

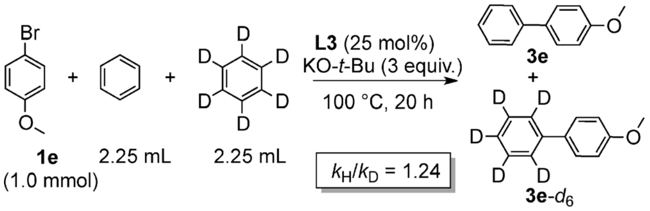
Entry	Arene	Aryl Bromide	Product	Yield (%)
1	 4a	 1b	 5a	62[b] (o/m/p = 65:27:8)
2	 4a	 1c	 5b	56[b] (o/m/p = 61:24:15)
3	 4c	 1e	 5c	65[b] (o/m/p = 58:27:15)
4[c]	 4d	 1l	 5d	71[b] (α:β = 74: 26)
5[d]	 4e	 1e	 5e	58
6[c,e]	 4f	 1w	 5f	42

[a] *Reaction conditions* (unless otherwise specified): ArBr (0.5 mmol), KO-*t*-Bu (1.5 mmol), arene (2.25 mL), **L3** (25 mol%), 100 °C, 24 h.
[b] A mixture of isomers, the yield and their ratios determined by ^{1}H NMR spectroscopy.
[c] ArBr (1.0 mmol), KO-*t*-Bu (3.0 mmol), arene (4.5 mL).
[d] Time was prolonged to 30 h.
[e] 36 h, 120 °C.

arenes is consistent with a homolytic aromatic substitution (HAS) mechanism.[4c,10] Previous studies have also established the importance of bidentate chelation with K^+ as an essential structural property for organocatalystic activity.[4] The salts selected for study including **L3** fulfill this condition; upon deprotonation of the imidazolium C-2 position and the amido NH group, a chelate carbene complex is formed. Based on the above information, we propose the involvement of an aryl radical anion intermediate in the coupling reaction, which is initiated by the chelate complex comprising an amido-functionalized carbene ligand (Scheme 1). To verify our proposal, a radical trapping experiment was carried out using TEMPO (1 equiv., see the Supporting Information), a typical radical scavenger, for the reaction between 4-bromoanisole and benzene. The reaction was completely suppressed, suggesting that the transformation indeed involved a radical pathway. A further support for the radical pathway came from the use of AIBN to initiate the coupling reaction producing the desired product, albeit in a lower yield (see the Supporting Information).



Scheme 1. A plausible mechanism.



Scheme 2. Kinetic isotopic effects experiment.

Isotopic labeling experiments were also conducted by subjecting 4-bromoanisole to the coupling reaction with equimolar amounts of benzene and benzene-d_6 (Scheme 2) and the corresponding products were obtained in a ratio of 6:5 ($k_H/k_D = 1.24$). This low kinetic isotope effect indicated that the rate-determining step is not the cleavage of the aromatic C–H bond, but a single electron-transfer process. A possible mechanism for the transformation under the new catalytic system is provided in Scheme 1. The major difference from that reported by Ong on the use of amino/NHC ligand in similar coupling reactions is the facile deprotonation of the CON*H* proton leading to a stable potassium chelate intermediate.[5c]

In conclusion, we have developed an effective organocatalyst system based on amido-functionalized imidazolium salts for the synthesis of biaryls *via* C-H functionalization of unreactive arenes with aryl bromides and even chlorides. The metal-free conditions described allowed for the preparation of biaryls in a greener, cost- effective manner in contrast to transition metal-catalyzed cross-coupling reaction and C-H arylation reactions.

Experimental Section

General Procedure for the Cross-Coupling of Aryl Halides with Arenes

An oven-dried Schlenk tube equipped with a magnetic stir bar was charged with aryl halides (0.5 mmol, if solid), **L3** (41 mg, 0.12 mmol) and KO-*t*-Bu (168 mg, 1.5 mmol) under a nitrogen atmosphere at room temperature. Anhydrous benzene/arene (2.25 mL) and aryl halides (0.5 mmol, if liquid) were then added using a syringe. The tube was then sealed and the resulting mixture was stirred at the specified temperature until complete consumption of starting material as monitored by TLC. After cooling to room temperature, the reaction mixture was quenched and extracted with ethyl acetate (10 mL × 3). The organic layers were combined, dried over Mg_2SO_4 and concentrated under reduced pressure. The crude products were purified through flash column chromatography on 230–400 mesh silica gel using hexane or hexane/ethyl acetate as eluent with a suitable ratio according to the TLC experiments. The regioisomeric distributions of isomers were determined by GC and confirmed by ^{1}H NMR spectroscopy.

Acknowledgements

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