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Free porphyrin catalyzed direct C-H arylation of benzene with aryl halides

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ABSTRACT

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Keywords: C-H arylation Free porphyrin Biaryls Organocatalyst A general procedure for free porphyrin catalyzed direct C–H arylation of benzene was demonstrated. This air tolerant, transition-metal-free process provides a promising system for cheap and efficient synthesis of biaryls in a user-friendly approach.

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Biaryl motifs are widely present in a variety of natural products and drugs,¹ such as Diovan[®] and Micardis[®] as hypertension medicine (Fig. 1). Their sales are up to billion and possess large values.^{2,3} A cheap and efficient way to prepare such fine chemicals with biaryl motif is of great interest.

The aryl-aryl bond formation was first reported by Ullmann in 1901 using aryl halides and a stoichiometric amount of elemental copper.⁴ Since then, various transition metal catalyzed systems were developed for the synthesis of both symmetrical and unsymmetrical biaryls from aryl halides and activated arenes.⁵ Though with mild conditions, these reactions often require expensive late transition metal catalysts such as palladium,^{5c,6} ruthenium,⁷ or gold⁸ for maximal efficiency. Moreover, the need of preactivation also made the reaction less convenient.

The direct C–H arylation of arenes with aryl halides using cheaper first row transition metal catalysts was developed rapidly in recent years.⁹ Yet, metal contamination in products requires an additional purification step especially in drug industry.¹⁰

The transition metal free, organocatalytic C–H arylation of arenes with aryl halides has been reported recently. Itami first reported the potassium *tert*-butoxide mediated cross coupling of nitrogen-based heterocycles with haloarenes.¹¹ Shortly after, Lei–Kwong,¹² Shi,¹³ and Shirakawa–Hayashi¹⁴ have reported the direct C–H arylation of unactivated arenes with aryl halides using DMEDA, 1,10-phenan-throline, and 1,10-bathophenanthroline catalysts, respectively. Lately, further improvements in organocatalysts such as the use of quinoline-1-amino-2-carboxylic acid,¹⁵ 2,3'-biimidazo[1,2-*a*]pyridin-2'-one radical,¹⁶ and Al(OH)(bpydc) metal-organic framework¹⁷



Figure 1. Structures of Diovan® and Micardis®.



Figure 2. Structures of free base porphyrins.

were also reported. These findings provide a very promising approach for clean, efficient, and cheap synthesis of biaryl motif. Herein, we describe the free base porphyrin $H_2(por)$ catalyzed direct C–H arylation of benzene with aryl halides in air.

Previously, our group has reported the cobalt(II) porphyrin catalyzed C–H arylation,¹⁸ we adopt the same reaction conditions





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Table 1

Free porphyrin catalyzed direct C-H arylation of benzene with 4-iodotoluene



^a GC yield.

^b 26% 1a recovered.

Table 2

Base effect on direct C-H arylation of benzene with 4-iodotoluene



^a GC yield.

^b Trace amounts **3a** and **3b**.

^c 33% **3a** and 31% **3b**.

Table 3

Free porphyrin catalyzed direct C-H arylation of benzene with various aryl halides

while switching $Co^{II}(por)$ to $H_2(por)$ only. 4-Iodotoluene **1a** in the presence of 5 mol % tetratolylporphyrin $H_2(ttp)$ (Fig. 2), 10 equiv of KOH, and 10 equiv of 'BuOH successfully coupled with benzene at 200 °C to produce 4-methylbiphenyl **2a** in 73% yield in 10 h under N₂ (Table 1, entry 1). To our delight, there was no significant difference when the reaction was carried out in air (Table 1, entry 3). Thus the reaction can be carried out conveniently without purging off oxygen with nitrogen. However, the product yield dropped significantly in an O₂ atmosphere (Table 1, entry 2).

The catalytic activity of various electronically different porphyrins was examined by employing $H_2(tpp)$, $H_2(tap)$, and $H_2(t_{4-Cl}pp)$ (Fig. 2). Among all porphyrins tested (Table 1, entries 3–6), $H_2(tp)$ was found to be the most effective with the shortest reaction time, while $H_2(tpp)$, $H_2(tap)$, and $H_2(t_{4-Cl}pp)$ gave similar yields but in longer times.

We screened both group I and II metal hydroxides and alkoxide for study of base effect (Table 2). Only group I metal hydroxides promoted the formation of **2a** (Table 2, entries 1–3), with the performance increased down the group, CsOH/^tBuOH was the most effective base system to give 76% of **2a** in 2 h (Table 2, entry 3). Group II metal hydroxides, Ba(OH)₂ and Ca(OH)₂, were all ineffective (Table 2, entries 4 and 5). The strongest base ^tBuOK was not effective as well (Table 2, entry 6).

Trace amounts of *meta-* and *para-tert*-butoxytoluene **3a** and **3b** (<5%) were detected in 1:1 ratio by GC/MS (Table 2, entries 2 and 3), suggesting the elimination–addition of **1a** with ¹BuO[–] via aryne intermediate is operating. This side reaction became dominant when ¹BuOK was used with **3a** and **3b** formed in 33% and 31% yields, respectively (Table 2, entry 6).

The coupling protocol is general to aryl iodides (Table 3). Both electron rich and moderate electron poor aryl iodides reacted smoothly to give the corresponding biaryl products in good yields (Table 3, entries 1–6). The decreased reactivity with 2-iodotoluene suggests that the steric effect of an *ortho*-methyl group is important (Table 3, entry 3).

The coupling of 1-chloro-4-iodobenzene with benzene yielded terphenyl **2f** as the major product together with **2g** (Table 3, entry 6). The couplings of aryl bromide and chloride with benzene are less efficient. The coupling with 4-bromotoluene afforded a moderate yield of **2a** in 48% (Table 3, entry 7). 4-Chlorotoluene was unre-



Table 3 (continued)



b





Figure 3. Proposed reaction mechanism.

active, with only a trace amount of product formed (Table 3, entry 8).

To gain more insight into the reaction mechanism, a competition experiment was performed to study the kinetic isotopic effect (Eq. 1). A small KIE value of 1.0 ± 0.1 (by ¹H NMR) was measured. Therefore, the C–H bond cleavage is not the rate determining step.

To test the radical nature of any intermediate formed, a radical scavenger, TEMPO was added to the reaction (Eq. 2). Both the yield and rate of the reaction decreased significantly. Therefore, the aryl radical generated from an aryl halide is an intermediate.

Based on the above data, a radical chain mechanism was proposed for the coupling of aryl iodides with benzene (Fig. 3).¹⁹ The reaction is initiated by a one electron reduction of aryl iodide with base, mediated by a free porphyrin. The aryl iodide radical anion then undergoes C-I bond dissociation to give an aryl radical and an iodide. The aryl radical then adds to a benzene molecule to give an aryl-substituted cyclohexadienyl radical intermediate. It is then deprotonated by base to give a biaryl radical anion. Finally, this radical anion undergoes a single electron transfer to another aryl iodide to complete the catalytic cycle and give the biaryl product. Termination in the middle of the radical chain occurs when the aryl-substituted cyclohexadienyl radical intermediate reacts with an oxygen molecule to give the biaryl product and a hydroperoxy radical.²⁰

In summary, the air tolerant free base porphyrin catalyzed C-H arylation of benzene with aryl halides to yield biaryls is demonstrated. A radical chain mechanism was proposed according to preliminary mechanistic study. Further studies are ongoing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05. 073.

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