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C–H arylation of unactivated arenes with aryl halides catalyzed by cobalt porphyrin

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ABSTRACT

A general procedure for cobalt-catalyzed direct C–H arylation of unactivated arenes has been discovered. This method employs aryl halides as the direct coupling partners with arenes without using any Grignard-type reagents. This catalysis opens a new methodology for the preparation of symmetrical as well as unsymmetrical biaryls in a user-friendly approach.

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Carbon–carbon bond forming reaction is a backbone in organic synthesis. Transition metal complexes have been used to catalyze homo- and cross-coupling of carbon–carbon bonds. Among the catalytic carbon–carbon bond formations, aryl–aryl bond formation to construct biaryls is important as biaryls are widely present in ligands, natural products, drugs, and materials.¹

Since the discovery of Ullmann reaction in 1901 for the synthesis of symmetrical biaryls from aryl halides,² more efficient catalytic systems have been developed in the past few decades to obtain symmetrical and unsymmetrical biaryls from aryl halides and aryl organometallics, such as the Kumada,³ Negishi,⁴ Stille,⁵ Suzuki,⁶ and Hiyama⁷ coupling reactions. These established methods however require expensive palladium catalysts, preparation and handling of air and moisture sensitive Grignard type or related reagents, making the reaction less user-friendly. Therefore, an alternative convenient method is desired. Recently, there are increasing reports employing 1st row transition metal catalysts, for example, Fe,⁸ Co,^{8c,9} Ni¹⁰ and Cu,¹¹ for cross-coupling reactions to obtain biaryl compounds. These complexes are much cheaper in price and less toxic, making them much more attractive.

Furthermore, direct C–H arylation of arenes with aryl halides partners is an attractive approach for aryl–aryl bond formation as Grignard type reagents are avoided. Examples using palladium as catalysts have been reported.¹² 1st row transition metal catalysts have also appeared very recently.⁸ To the best of our knowledge, cobalt catalyzed arylation is scarce and direct arylation of unactivated arenes is unprecedented. Herein, we report a novel cobalt(II) porphyrin catalyzed cross-coupling reactions between Ar-X (X = I, Br) and unactivated Ar'-H to synthesize biaryls (Tables 1 and 2).

To our delight, 4-iodotoluene (1 equiv) in the presence of 5 mol % $Co(t_{4-OMe}pp)$ $(t_{4-OMe}pp = tetrakis-4-methoxyphenylpor$ phyrinato dianion), KOH (10 equiv) and ^tBuOH (10 equiv) reacted with benzene (100 equiv) at 200 °C under N₂ to yield the 4-methylbiphenyl in 63% isolated yield (Table 1, entry 2). Trace amounts of biphenyl (<5%) and 4,4'-dimethylbiphenyl (<1%) were also detected by GCMS. The coupling protocol is general for aryl iodides. Iodobenzene reacted well to give biphenyl in 70% yield (Table 1, entry 1). Both electron rich and electron poor aryl iodides were compatible under the reaction conditions and the desired biaryls were obtained in good yields (Table 1, entries 3–6). To our delight, aryl bromides also reacted successfully to afford biaryls in moderate yields (Table 1, entries 7-11). The longer reaction times were consistent with the stronger C-Br bond. Sterically hindered 2-bromotoluene and 2-bromoanisole also produced the corresponding biaryls though in 36% and 15% yields, respectively (Table 1, entries 9 and 11).

We further examined the coupling reactions of 4-iodotoluene with substituted arene derivatives (Table 2). Toluene and anisole were arylated to afford a mixture of *ortho-*, *meta-*, and *para-*substituted isomers in 43% and 53% total yields, respectively (Table 2, entries 1 and 2). The regioisomeric ratios (o/m/p = 1.6:1.0:2.0 for toluene and o/m/p = 3.3:1.0:2.3 for anisole) imply that the electronic effect of substituent does not affect the regioselectivity of arylation much. However, steric hindrance was again proved to be important. *p*-Xylene required 6 h for completion of the reaction to give the coupling product in 24% yield





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Table 1

Cobalt-catalyzed arylation of benzene with various aryl halides





^a GC yield. Isolated yield is in parentheses.



(1)

only (Table 2, entry 3). In comparison, the less hindered *o*-xylene and *m*-xylene reacted faster (Table 2, entries 4 and 5). Besides, dibenzyl and diarylmethane derivatives were detected when toluene and xylenes were employed as coupling partners. Arylation at the methoxy carbon of anisole was also observed. The detection of these products provides mechanistic insight of the reaction. As the benzylic C-H bond (89.7 kcal mol⁻¹) and the anisyl C-H bond (92.0 kcal mol⁻¹) are weaker than the aromatic C-H bond (112.9 kcal mol⁻¹),¹³ competitive arylations through a radical process are very likely.

In order to gain further understanding of the reaction mechanism, a competition experiment using an equimolar mixture of benzene and benzene- d_6 with 4-iodotoluene was carried out and yielded the KIE of 1.03 ± 0.01 (by GCMS) (Eq. 1). This indicates that the C–H bond cleavage is not rate-determining.

Based on the above data, we propose the reaction mechanism as shown in Figure 1. The Ar–X bond is first activated by $Co^{II}(t_{4-OMe}pp)$ via a formal halogen atom abstraction to give $Co^{III}(t_{4-OMe}pp)X$ and generate an Ar radical.¹⁴ The Ar radical intermediate then adds onto the arene. Biaryl is released by abstraction of a hydrogen atom from

Table 2

Cobalt-catalyzed arylation of unactivated arenes with 4-iodotoluene





^a GC yield of desired biaryl only. Total isolated yield with other arylation products is in parentheses.



Figure 1. Proposed reaction mechanism.

 $Co^{II}(t_{4-OMe}pp)$. The resultant $Co^{III}(t_{4-OMe}pp)H$ generated quickly undergoes dehydrogenation to give back the active catalyst $Co^{II}(t_{4-OMe}pp)$ with release of H_2 .¹⁵ Meanwhile, $Co^{III}(t_{4-OMe}pp)X$ undergoes fast ligand substitution reaction with KOH to give a transient intermediate $Co^{III}(t_{4-OMe}pp)OH$, which rapidly produces the

 $\rm Co^{II}(t_{4-OMe}pp)$ and $\rm H_2O_2.^{16}~H_2O_2$ then decomposes to give water and oxygen by base.^{17}~\rm Co^{II}(t_{4-OMe}pp) is regenerated to complete the catalytic cycle.

In summary, we have successfully demonstrated a cheap and user-friendly Co(II) porphyrin catalyzed cross-coupling between aryl halides with unactivated arenes to prepare biaryls. Preliminary mechanistic study suggests that the reaction operates by a radical mechanism. Further studies are ongoing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.092.

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