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Direct arylation of aromatic C–H bonds catalyzed by Cp*Ir complexes†

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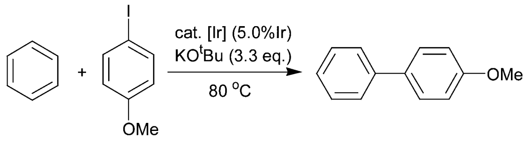
The C–H bond of benzene was directly arylated by reaction with aryl iodides in the presence of a catalytic amount of a pentamethylcyclopentadienyliridium complex and potassium *tert*-butoxide.

Biaryls are one of the most important classes of organic compounds because they are found in natural products, advanced materials and ligands for metal catalysts *etc*. For the past several decades, much effort has been devoted to the synthesis of biaryls *via* coupling of aromatic compounds.[1,2] In recent years, a number of transition metal-catalyzed cross-coupling reactions have been developed. Reactions of arylated metal reagents, such as Mg, Zn, Sn, B and Si with haloarenes catalyzed by Ni or Pd complexes are frequently utilized for the synthesis of biaryls.[2] All these reactions have the common feature that both reactants should have a reacting substituent, such as a metal or a halogen group. In the past few years, some transition metal-catalyzed arylations involving the activation of unreactive aromatic C–H bond have been reported by Oi,[3] Miura,[4] Kakiuchi,[5] and Bedford.[6] However, these reactions require an appropriate directing group adjacent to the activated C–H bond, and arylation of unsubstituted aromatics has not been accomplished. On the other hand, direct arylation of unreactive aromatic C–H bonds has been achieved *via* radical pathways requiring stoichiometric or excess radical sources.[7] Because of this disadvantage, this type of reaction has rarely been applied to the synthesis of biaryls. In this study, we report direct arylation of aromatic C–H bonds with aryl iodides catalyzed by iridium complexes, which require no directing group.[8]

First, iridium-catalyzed arylation of benzene with 4-iodoanisole under various conditions was investigated. The results are summarized in Table 1.[9] When the reaction was carried out in the presence of $[Cp^*IrHCl]_2$ (5.0% Ir) ($Cp^* = \eta^5$-pentamethylcyclopentadienyl) catalyst and 3.3 equivalents of KO^tBu at 80 °C, 4-methoxybiphenyl was obtained in a yield of 66% *via* cross-coupling of 4-iodoanisole and C–H bond of benzene (entry 1). Reaction at 60 °C resulted in a lower yield (entry 2). When the amount of base was reduced to 2.0 eq., the yield decreased to 31% (entry 3). Other bases, such as K_2CO_3, CH_3COOK, or NaO^tBu were ineffective for the reaction. The catalyst $[(Cp^*Ir)_2(\mu\text{-}H)_3]Cl$ showed catalytic activity comparable to $[Cp^*IrHCl]_2$, however, $[Cp^*IrCl_2]_2$ showed lower activity (entries 4 and 5). Other catalysts Cp*Ir(cod) or $[IrCl(cod)]_2$ showed almost no activity in this reaction (entries 6 and 7).

Under the optimized conditions, the arylation of benzene with variety of aryl iodides was examined.[10] The results are summarized in Table 2. The reaction of benzene with 4- and 3-iodoanisoles proceeded in good yield (66 and 59%) to give corresponding

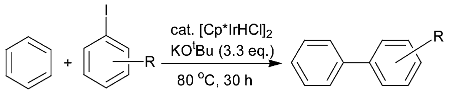
Table 1 Arylation of benzene with 4-iodoanisole catalyzed by several iridium complexes[a]

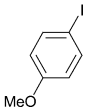
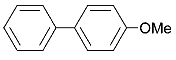
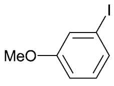
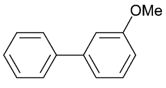
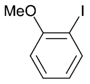
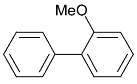
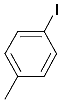
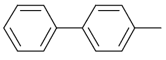
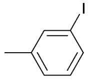
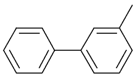
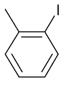
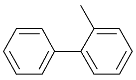
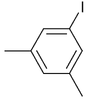
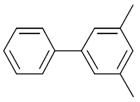
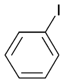
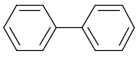
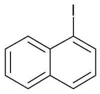
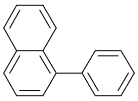


Entry	Catalyst	Time/h	Yield (%)[b]
1	$[Cp^*IrHCl]_2$	30	66
2[c]	$[Cp^*IrHCl]_2$	30	26
3[d]	$[Cp^*IrHCl]_2$	17	31
4	$[(Cp^*Ir)_2(\mu\text{-}H)_3]Cl$	30	58
5	$[Cp^*IrCl_2]_2$	30	44
6	Cp*Ir(cod)	17	0
7	$[IrCl(cod)]_2$	17	3

[a] The reaction was carried out with iodoanisole (0.50 mmol), catalyst (5.0% Ir), and KO^tBu (1.65 mmol) in benzene (20 mmol) at 80 °C. [b] Determined by GC. [c] Reaction temperature was 60 °C. [d] $[Cp^*IrHCl]_2$ (3.0% Ir) and KO^tBu (1.0 mmol) were used.

Table 2 Arylation of benzene with various aryl iodides catalyzed by $[Cp^*IrHCl]_2$[a]



Entry	Ar–I	Amount of catalyst (% Ir)	Product	Yield (%)[b]
1		5.0		66
2		10		59(53)
3		10		32(29)
4		5.0		56(50)
5		10		70(52)
6		10		43(30)
7		10		(51)
8		5.0		72(66)
9		10		(20)

[a] The reaction was carried out with aryl iodides (0.50 mmol), $[Cp^*IrHCl]_2$ (5.0 or 10% Ir), and KO^tBu (1.65 mmol) in benzene (20 mmol) at 80 °C for 30 h. [b] Determined by GC. The values in parentheses are isolated yields.

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b4/b407116f/

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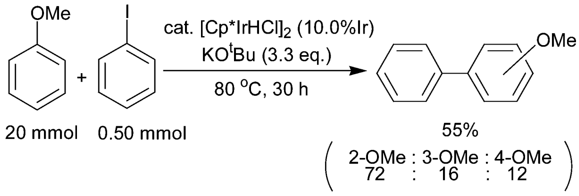
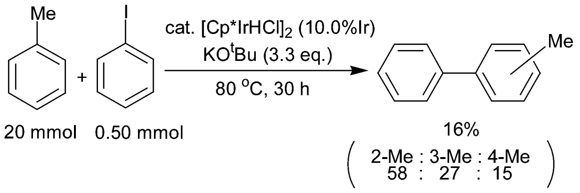
methoxybiphenyls, while 2-iodoanisole showed lower reactivity (32%) probably because of a steric effect (entries 1–3). The reaction of benzene with 4-, 3-, and 2-iodotoluenes gave the corresponding methylbiphenyls in yields of 56, 70, and 43%, respectively (entries 4–6). 3,5-Dimethyliodobenzene and simple iodobenzene could be also applicable to the present catalytic system (entries 7 and 8). The reaction of benzene with 1-iodonaphthalene was also examined, however, the yield of 1-phenylnaphthalene was lower than other reactions (entry 9).

We next examined the phenylation of C–H bonds in anisole or toluene by reaction with iodobenzene. The results are shown in eqn. (1) and (2). The reaction of anisole with iodobenzene gave three products (2-, 3-, and 4-methoxylbiphenyls) in a total yield of 55% with a ratio of 72 : 16 : 12 (eqn. (1)). The reaction of toluene with iodobenzene also gave three products (2-, 3-, and 4-methylbiphenyls) in a total yield of 16% with a ratio of 58 : 27 : 15 (eqn. (2)). The regioselectivities observed for these reactions are very similar to those for the radical aromatic substitution reactions reported by Davies,[7c,d] suggesting that radical intermediates would be involved in the pathway for the present arylation reactions.[11]



(1)



(2)

Although the mechanism for the present reaction is not completely clear yet, it is highly probable that the phenyl radical would participate as an intermediate. Thus, the first step of the reaction would be reduction of a trivalent catalyst precursor Cp*Ir^{III} to a divalent Cp*Ir^{II} species by reaction with base. Reduction of Cp*Ir^{III} complex, $[(Cp^*Ir)_2(\mu\text{-}H)_3]^+$, to Cp*Ir^{II} complex by treatment with base (KO^{t}Bu) has been reported by Wakatsuki.[12] Then an electron transfer from Cp*Ir^{II} species to aryl iodide would occur to give an aryl iodide radical anion accompanied by regeneration of Cp*Ir^{III} catalyst. Subsequent elimination of I$^-$ from the radical anion would afford aryl radical, which is subject to the reaction with benzene to give the biaryl product.

In summary, we have developed a new system for arylation of aromatic C–H bonds catalyzed by Cp*Ir complexes. To the best of our knowledge, the present reaction is the first example of transition metal-catalyzed arylation of unreactive aromatic C–H bonds requiring no directing groups. This system provides a novel method for generating aryl radicals catalytically under mild conditions. Further applications of this system to new catalytic reactions for organic synthesis are promising.

Notes and references

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9 In the reaction in Tables 1 and 2, a small amount (10 to 15%) of hydrodehalogenated product was also detected in the GC analyses.

10 Other than those shown in Table 2, reactions of benzene with 4-iodoaniline, 4-iodonitrobenzene and 4-iodotrifluoromethylbenzene were examined. However, the desired biphenyl products were not obtained in these reactions.

11 When the reaction was performed in the presence of a radical scavenger, the yield of biaryl product considerably decreased. For example, when 0.20 mmol of 2,6-di-*tert*-butylphenol was added to the reaction of benzene with 3-iodotoluene (entry 5 in Table 2), the yield of 3-methylbiphenyl was 10%. This result also supports the radical mechanism.

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