Palladium Charcoal-Catalyzed Suzuki-Miyaura Coupling and Iridium-Catalyzed Aromatic C-H Borylation

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We report here on the "Palladium Charcoal-Catalyzed Suzuki-Miyaura Coupling and Iridium-Catalyzed Aromatic C-H Borylation." In the Pd/C-catalyzed Suzuki-Miyaura coupling, we found that the combination of non-prereduced Pd/C and a phosphine ligand, such as PPh_3, was essential for the reaction of halopyridines and haloquinolines. In the catalytic C-H borylation of arenes, we found that 2,6-diisopropyl-*N*-(2-pyridylmethylene) aniline acted as a good ligand. The bulkiness around the imine moiety was important for obtaining the products in high yields.

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Introduction

Suzuki-Miyaura coupling[1)], which involves the cross-coupling of organic halides and organic boron compounds, is a powerful synthetic tool for carbon-carbon bond formation. This reaction has often been used to obtain biaryl compounds, which are widely used in various industries (**Fig. 1**).

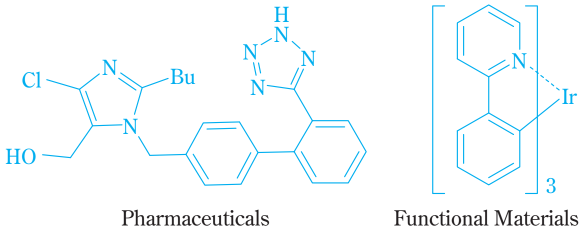


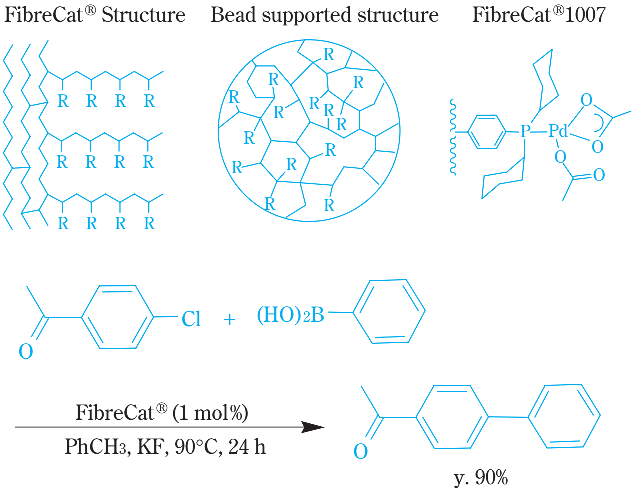
Fig. 1 Compounds Including a Biaryl Skeleton

Palladium Charcoal-Catalyzed Suzuki-Miyaura Coupling

1. Suzuki-Miyaura Coupling Using a Heterogeneous Catalyst

Several examples of Suzuki-Miyaura coupling using homogeneous catalysts have been reported. However, many recent studies have focused on heterogeneous catalysts because of the ease of recovering the catalyst.[2)]

The heterogeneous catalysts shown in **Scheme 1** are fiber-supported palladium catalysts that are available commercially from Johnson Matthey. Compared with conventional polymer bead-supported catalysts, these catalysts can be easily removed by filtration. In addition, a substrate can easily approach the reaction site (R). In particular, FibreCat 1007® promotes the reaction of low-reactive arylchlorides to give the desired products in high yields.



Scheme 1

Scheme 2 shows the hydroxyapatite-supported palladium catalyst developed by Kaneda et al.[3)] Hydroxyapatite is a main component of hard tissues in the body,

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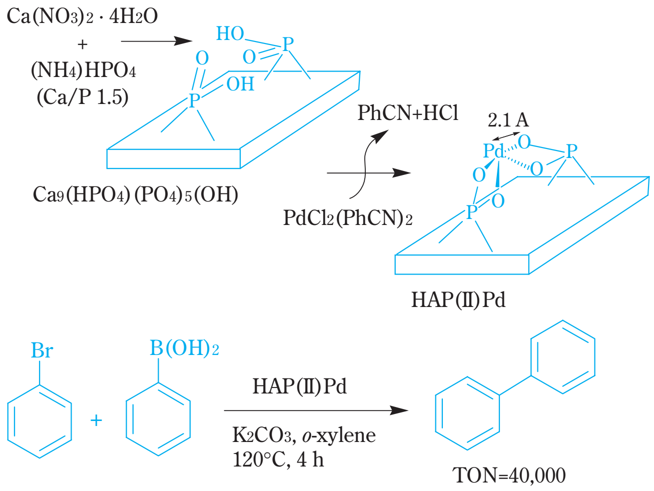
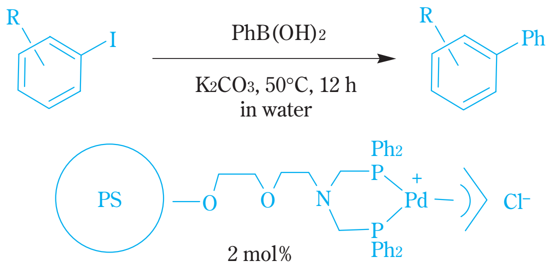
such as bones and teeth, and has ion-exchange and ion-absorption capabilities. When calcium nitrate and ammonium hydrogenphosphate were mixed in the ratio of 1:1.5, hydroxyapatite with the composition $Ca_9(HPO_4)(PO_4)_5(OH)$ was produced. This hydroxyapatite reacts with bis (benzonitrile) dichloro palladium to produce a catalyst with palladium phosphate as a partial structure. This catalyst is effective for the Heck reaction and Suzuki-Miyaura coupling. When bromobenzene was used as a substrate in Suzuki-Miyaura coupling, TON reached 40,000. The catalyst could be reused without being deactivated.



Scheme 2

Uozumi et al. have developed an amphiphilic polystyrene-supported Pd catalyst[4] (**Scheme 3**). The coupling reaction of iodobenzene takes place quantitatively with this catalyst in an aqueous solution. The catalyst can be recovered by filtration and reused three times without any loss of activity.



Scheme 3

2. Industrial Advantages of Palladium Charcoal-Catalyzed Suzuki-Miyaura Coupling

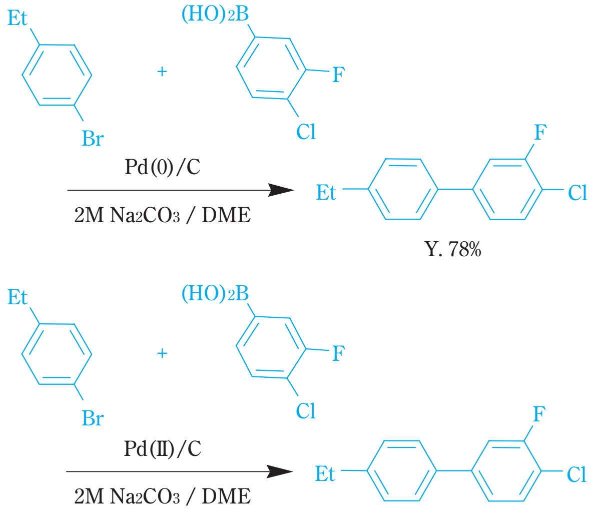
Among these heterogeneous catalysts, Pd/C was the most attractive catalyst for the industrial application of Suzuki-Miyaura coupling. These are the main industrial advantages of Pd/C. (1) Pd/C-containing water is commercially available and can be handled safely. (2) Pd/C can be easily removed from the reaction mixture by simple filtration. (3) There is an established method for recycling the recovered Pd/C as palladium metal. (4) The processing costs are lower than with homogeneous systems.

There are two types of Pd/C, which differ with regard to the degree of the reduction of palladium. The first type, Pd(0)/C, has a high degree of palladium reduction [mainly Pd(0)]. The second type, Pd(II)/C, has a low degree of palladium reduction [mainly Pd(II)].

3. Example of Palladium (0) Charcoal-Catalyzed Suzuki-Miyaura Coupling

In 1994, Buchecker first reported the synthesis of biaryl compounds using Suzuki-Miyaura coupling catalyzed by Pd(0)/C[5]. A solution of a phenylhalide and a phenylboronic acid in aqueous DME (dimethoxyethane) was heated in the presence of Pd(0)/C (4.5 mol%) with PPh_3 (18 mol%) and sodium carbonate (3 eq.). Under these conditions, aryl triflate coupled in good yield. Furthermore, when arylbromides were used as the substrate, the reaction took place even without the addition of PPh_3, using either Pd(0)/C or Pd(II)/C as the catalyst (**Scheme 4**).

In 1997, Gala et al. produced 4'-fluorobiphenylacetic acid in a batch reaction on a kilogram-scale using Pd(0)/C-catalyzed Suzuki-Miyaura coupling[6] (**Scheme 5**).



Scheme 4

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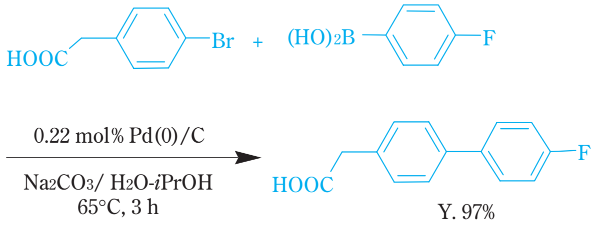
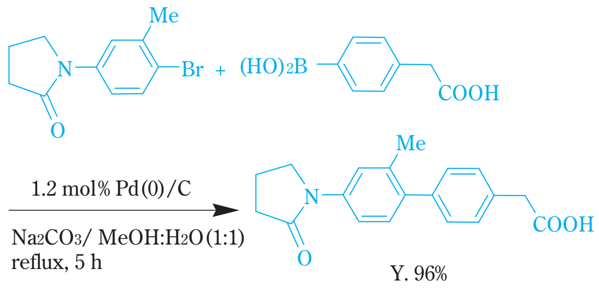


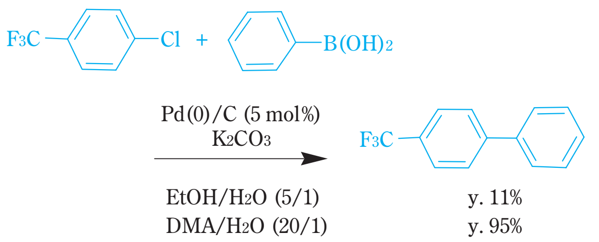
Scheme 5

In addition, Ennis et al. also used these conditions to produce a drug used for the treatment of depression in a batch reaction on a kilogram-scale in 1999[7] (**Scheme 6**). Type 58 [Pd(0)/C] from Johnson Matthey was used as a catalyst. It was reported that selection of the solvent was important in this reaction. Although the reaction was accomplished in five hours in methanol-water (1:1), it started, but did not go to completion in ethanol-water, regardless of the solvent ratio. In addition, the reaction does not proceed in DME-water (1:1).



Scheme 6

Another example of the solvent effect in the coupling of 4-trifluoromethylphenyl chloride and phenyl boronic acid was reported by Sun et al. in 2001[8] (**Scheme 7**). When the reaction was carried out in aqueous ethanol, the yield was only 11%. However, when it was carried out in aqueous dimethylacetamide (DMA), the yield was improved to 95%. In this reaction, the reaction was restarted by the addition of PPh_3.

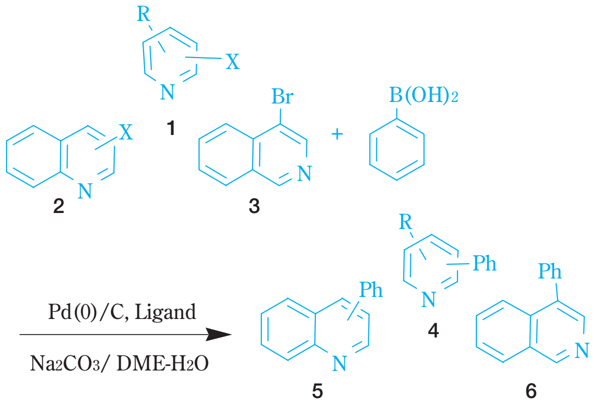


Scheme 7

4. Work at Koei Chemical Co., Ltd.

Based on the Buchecker's conditions, halopyridines and haloquinolines were reacted with phenyl boronic acid (1.5 eq.). Under these conditions, the reaction either did not start or did not go to completion (**Table 1**). However, when PPh_3 was added, the reaction took place with good yield even with the substrates described above (Table 1). In contrast to the reactions of phenylhalides reported previously, phosphine ligands are essential for the reactions of halopyridines and haloquinolines.

Table 1 Pd/C-Catalyzed Suzuki-Miyaura Coupling of Halopyridines or Haloquinolines



Run	Substrate	Ligand	Product	Yield (%)[a]
1	**1a**: X=2–Br, R=H	none	**4a**: Y=2–Ph, R=H	21
		PPh_3		85
2	**1b**: X=3–Br, R=H	none	**4b**: Y=3–Ph, R=H	54
		PPh_3		90
3	**1c**: X=4–Br, R=H[b]	none	**4c**: Y=4–Ph, R=H	55
		PPh_3		60
4	**1d**: X=2–Cl, R=3–NO_2	none	**4d**: Y=2–Ph, R=3–NO_2	49
		PPh_3		94
5	**1e**: X=2–Cl, R=5–CN	none	**4e**: Y=2–Ph, R=5–CN	34
		PPh_3		90
6	**1f** : X=2–Cl, R=5–NO_2	none	**4f** : Y=2–Ph, R=5–NO_2	24
		PPh_3		85
7	**1g**: X=2–Cl, R=H	none	**4a**: Y=2–Ph, R=H	No reaction
		PPh_3		82
8	**1h**: X=2–Cl, R=3–CN	none	**4g**: Y=2–Ph, R=3–CN	16
		PPh_3		quant.
9	**1i** : X=2–Cl, R=5–CF_3	none	**4h**: Y=2–Ph, R=3–CF_3	30
		PPh_3		85
10	**2a**: X=2–Cl	None	**5a**: Y=2–Ph	No reaction
		PPh_3		91
11	**2b**: X=3–Br	none	**5b**: Y=3–Ph	No reaction
		PPh_3		82
12	**3**	none	**6**	36
		PPh_3		72

a) Isolated yield.
b) 4-Bromopyridinium hydrochloride was used as a starting material.

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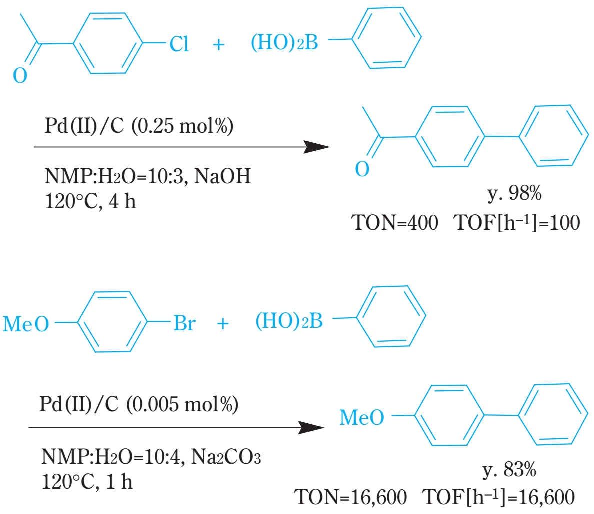
5. Examples of Reactions in the Presence of Palladium (II)-Charcoal

In 2002, Köhler reported that the reactive palladium charcoal for Suzuki-Miyaura coupling was characterized by a high Pd dispersion (for example greater than 50%), a low degree of Pd reduction [mainly Pd(II)], and a high water content (greater than 50%). This describes Pd(II)/C (**Scheme 8**).



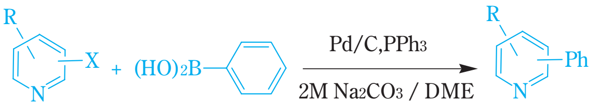
Scheme 8

In fact, with Pd(II)/C, 4-acetylphenylchlorides, which are commonly less reactive than phenylbromides successfully coupled with phenylboronic acid without PPh_3. The reaction was carried out in NMP (*N*-methyl-2-pyrrolidone)-water in the presence of sodium hydroxide at 120°C in four hours to give the biaryl product in a yield of 98% . Only 0.25 mol% of the catalyst was needed. In the case of bromoanisole, sodium carbonate was used as a base, to prevent dehalogenation. After one hour, the coupling product was obtained in an 83% conversion with a yield of 83%, and TOF $[h^{-1}]$ reached 16,600.

6. Work at Koei Chemical Co., Ltd.

With Pd (II)/C (Degussa), 2-chloropyridines with an electron-donating group were used in this reaction in the presence of PPh_3. As described above, when Pd(0)/C was used in the reaction of 2-chloro-6-methoxypyridine and 3-amino-2-chloropyridine, the yields were 25% and 19%, respectively. When Pd (II)/C was used in these reactions, the yield was significantly increased to 90% and 97%, respectively[9] (**Table 2**). Based on these results, it is clear that even in halopyridine reactions, the reactivity of Pd(II)/C is greater than that of Pd (0)/C, as in halobenzene reactions.

Table 2 Coupling with Pd(II)/C



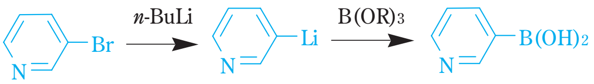
1 **4**

Run	Substrate	Product	Pd/C	Yield(%)[a]
1	**1j** : X=2–Cl, R=6–OMe	**4i** : X=2–Ph, R=6–OMe	Pd(0)/C	25
2	**1j** : X=2–Cl, R=6–OMe	**4i** : X=2–Ph, R=6–OMe	Pd(II)/C	90
3	**1k**: X=2–Cl, R=3–NH_2	**4j** : X=2–Ph, R=3–NH_2	Pd(0)/C	19
4	**1k**: X=2–Cl, R=3–NH_2	**4j** : X=2–Ph, R=3–NH_2	Pd(II)/C	97

a) Isolated yield.

Ir-Catalyzed Aromatic C-H Borylation

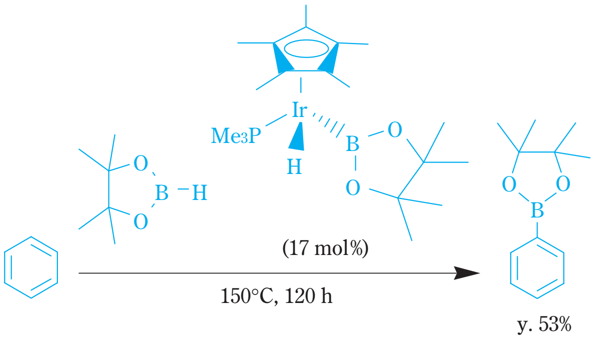
Aryl and heteroarylborons are versatile synthons in Suzuki-Miyaura coupling.Usually, they are synthesized by the borylation of magnesium or lithium intermediates, which are produced from arylhalides[11] (**Scheme 9**). In addition to these traditional methods, the direct borylation of aromatic compounds has also been reported recently.



Scheme 9

In 1999, Smith[12] reported the C-H borylation of benzene with pinacol borane in the presence of the Ir catalyst shown in **Scheme 10**. The reaction required prolonged heating and the product was obtained with only a 53% yield.

In the same year, Hartwig[13] developed the Re-catalyzed reaction using bis (pinacolato) diboron (pin_2B_2) (**Scheme 11**).



Scheme 10

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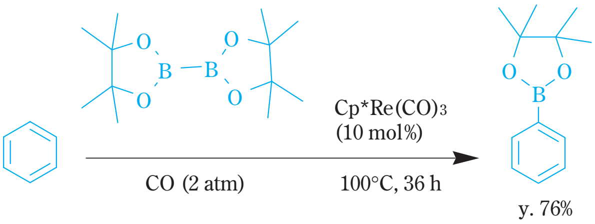
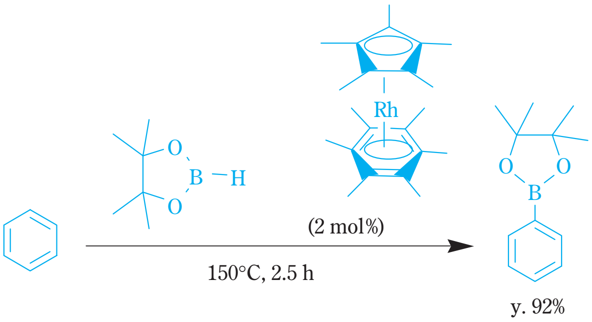
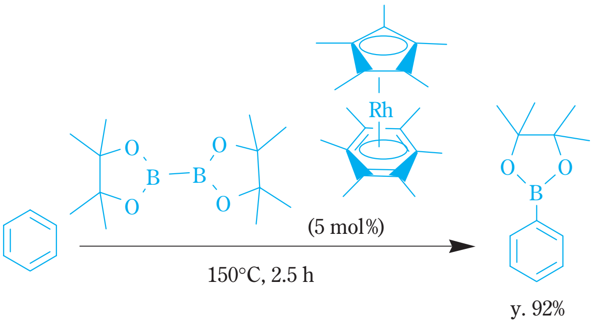


Scheme 11

In 2000, Smith reported the Rh complex-catalyzed reaction with pinacol borane (**Scheme 12**). The borylation was complete in 2.5 hours to give the product with a yield of 92%. In the same year, Hartwig used the same Rh catalyst in the reaction of benzene with bis (pinacolato) diboron (**Scheme 13**).



Scheme 12

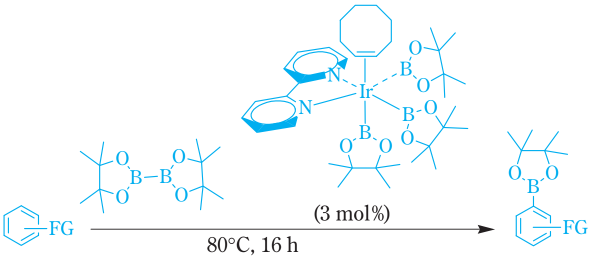


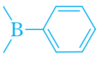
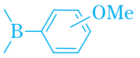
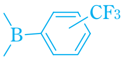
Scheme 13

1. Aromatic C-H Borylation Using Bipyridyl Ligands

In 2002, Miyaura$^{14)}$ and Hartwig et al. developed an Ir complex with a bipyridyl ligand. The borylation of benzene with bis (pinacolato) diboron was conducted using this Ir complex with excess benzene, which was used as the solvent and substrate. The Ir complex [IrCl (COD)]$_2$ was used in an amount of 3 mol% of bis (pinacolato) diboron. The bipyridyl ligand required one equivalent of Ir. With regard to the regioselectivity of the borylation of monosubstituted aromatic series, the para:meta ratio is 1:2 using substrates with either an electron-withdrawing group or an electron-donating group. Ortho substitutions did not take place. This means that the reaction is influenced by steric factors and not by electronic factors (**Table 3**).

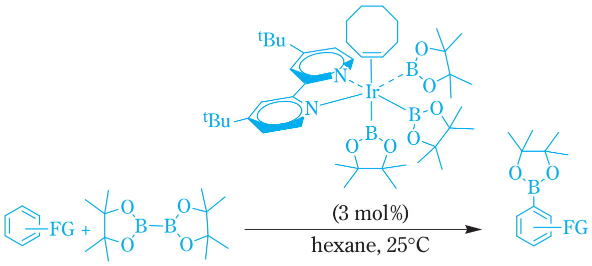
Table 3 Aromatic C–H Borylation of Arenes by 1/2[IrCl(COD)]$_2$-bpy

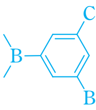
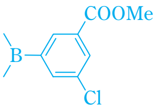
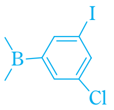


Product			
Yield(%)	95	95	80
(o:m:p)		(0:74:25)	(0:70:30)

The borylation reactions with 1/2[IrCl (COD)]$_2$-bpy require an excess amount of the substrate and prolonged heating. However, with the Ir complex prepared from {Ir (OMe)(COD)}$_2$ and 4,4'-tert-butyl-2,2'-bipyridine, a stoichiometric amount of the substrate successfully reacted with pin$_2$B$_2$ or pinBH in an inert solvent at room temperature. As shown in **Table 4**, boron compounds with functional groups, such as esters and halogens, were synthesized by this method because they were difficult to synthesize using metal-halogen exchange as a key process.

Table 4 Aromatic C–H Borylation of Arenes by 1/2[Ir(OMe)(COD)]$_2$-dtbpy



Product			
Yield(%)	83	80	84
Time(h)	2	8	4

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2. Work at Koei Chemical Co., Ltd.

The diimine structures of bipyridyl ligands drew our attention, and the feasibility of three types of diimine ligands (Types I–III) was studied. Cyclohexyl, phenyl and 2,6-dimethylphenyl groups were introduced as an R group in each type of ligand, as shown in **Fig. 2**. As a result, Type II was found to be the most promising ligand[15] (**Table 5**).

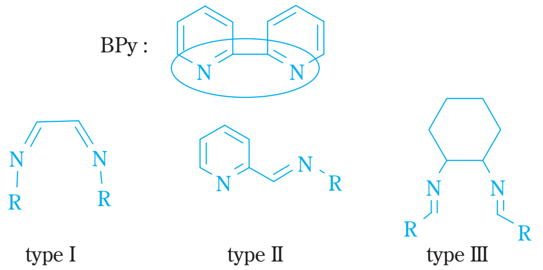
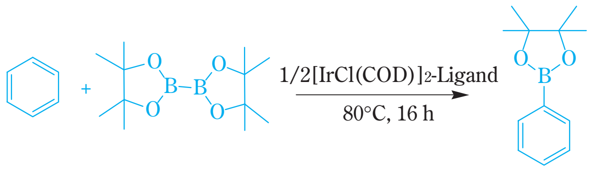


Fig. 2 Diimine Ligands

Table 5 Influence of Ligands Type I–Ⅲ on the C–H Borylation of Benzene



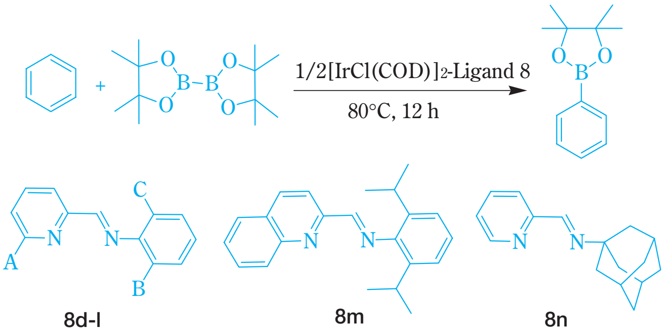
Run	Ligand	Type	R	Yield (%)[a]
1	**7a**	Type I	Cy	9
2	**7b**	Type I	Ph	5
3	**7c**	Type I	2,6-dimethylphenyl	5
4	**8a**	Type Ⅱ	Cy	27
5	**8b**	Type Ⅱ	Ph	17
6	**8c**	Type Ⅱ	2,6-dimethylphenyl	50
7	**9a**	Type Ⅲ	Cy	5
8	**9b**	Type Ⅲ	Ph	6
9	**9c**	Type Ⅲ	2,6-dimethylphenyl	5

a) Yield was determined by GC using 4,4'-dimethylbiphenyl as an internal standard.

(1) Modification of Diimine Ligand Type II

The Type II ligand was modified to improve the reaction yields. When the substituent effects at the ortho position of the aniline ring were investigated, absolutely no effect was seen with a monoalkyl substituent (**Table 6**, runs 1–5). However, the introduction of two alkyl groups and especially large alkyl groups improved the yield. When two isopropyl groups were introduced to the phenyl ring, the yield was as high as 74% (Table 6, run 7). It seems that the steric bulkiness around the imine moiety was important for obtaining a high product yield.

Table 6 Influence of Ligands Type I–Ⅲ on the C–H Borylation of Benzene



8d-l **8m** **8n**

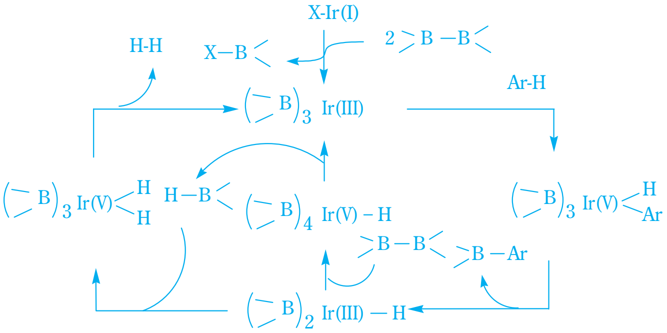
Run	Ligand	A	B	C	Yield (%)[a]
1	**8d**	H	Me	H	21
2	**8e**	H	Et	H	19
3	**8f**	H	^{i}Pr	H	20
4	**8g**	H	^{t}Bu	H	16
5	**8h**	H	Ph	H	19
6	**8i**	H	Et	Et	32
7	**8j**	H	^{i}Pr	^{i}Pr	74
8	**8k**	Me	^{i}Pr	^{i}Pr	78
9	**8l**	Br	^{i}Pr	^{i}Pr	11
10	**8m**				14
11	**8n**				60

a) Yield was determined by GC. using 4,4'-dimethylbiphenyl as an internal standard.

The same trend was observed in the case of aliphatic amines. Although the yield was only 27% in the reaction of cyclohexylamine (Table 5, run 4), it improved to 60% with adamantylamine (Table 6, run 11). Furthermore, if A on the pyridine ring was replaced by bromine or the pyridine ring itself was replaced with quinoline, the yield dropped dramatically, due to the coordination ability of the ligands (Table 6, runs 9 and 10). When a methyl group was introduced at A, no great effect was observed (Table 6, run 8). Based on these results, we chose the sterically bulky diimine 8j as a ligand to continue the investigation.

(2) Reaction with Pinacol Borane

At the beginning of the reaction, tris (boryl) Iridium (III) complex is produced. Oxidative addition of an aromatic C-H bond to this Iridium species takes place and subsequent reductive elimination provides arylborane and bis (boryl) Iridium-hydride (III). Bis (boryl) Iridium-hydride (III) reacts with bis (pinacolato) diboron to simultaneously regenerate tris (boryl) Iridium and produce pinacolborane. This pinacolborane reacts with bis (boryl) Iridium-hydride (III) to give tris (boryl) Iridium (III) along with the generation of hydrogen gas (**Scheme 14**). Thus, both of the pinB units in bis (pinacolato) diboron were used in the reaction.



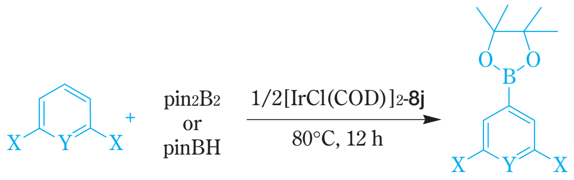
Scheme 14

When pinacolborane was used in the reaction of benzene in the presence of 8j, the product was obtained with a yield of 79%. Bis (pinacolato) diboron reacts with the substrate in a molar ratio of 1:2. Three mol% of the catalyst bis (pinacolato) diboron was used. On the other hand, pinacolborane reacts with the substrate in a molar ratio of 1:1. Therefore, in this case, we used 1.5 mol% of pinacolborane (**Table 7**).

In 2003, Miyaura et al. investigated the catalytic activity in different solvents, and reported that nonpolar solvents such as hexane were suitable for this reaction, and the catalytic activity decreased in the order mesitylene, DME and DMF[16]. Therefore, when the substrate was liquid at room temperature, excess substrate was used as both solvent and substrate (Table 7, runs 1–5). The borylation of dichloropyridine, which was solid at room temperature, was carried out with pinacolborane and bis (pinacolato) diboron in octane (Table 7, runs 6–7).

In a study of Ir-catalyzed aromatic borylation, diimine 8j was an effective ligand and the bulkiness around the diimine moiety had a large effect on the yield.

Table 7 C–H Borylation of Benzene and Pyridine Derivatives



Run	Substrate		pin_2B_2 or pinBH	Yield (%)
	X	Y		
1	H	C	pinBH	79 a)
2	Cl	C	pin_2B_2	83 b)
3	Cl	C	pinBH	85 b)
4	CF_3	C	pin_2B_2	47 a)
5	CF_3	C	pinBH	73 a)
6	Cl	N	pin_2B_2	73 b)
7	Cl	N	pinBH	93 b)

a) Yields were determined by GC using 4,4'-di-*t*-butylbipyridine as an internal standard.

b) Yields were determined by GC using 4,4'-di-*t*-butylbipyridine as an internal standard.

Conclusion

In addition to Suzuki-Miyaura coupling using boron reagents, Kumada coupling using Grignard reagents and Stille coupling using tin reagents are known methods for constructing the biaryl skelton. Among the reagents described above, boron reagents are superior with regard to safety and handling. Compared to Grignard reagents, a greater variety of phenyl boronic acids are produced industrially. Furthermore, mass production of agricultural chemicals using Suzuki-Miyaura coupling has started recently. In studies of the Pd/C-catalyzed Suzuki-Miyaura coupling of halopyridines and haloquinolines, a phosphine ligand was essential for these reactions in contrast to the reactions with halobenzenes. The most practical ligand was PPh_3. The combination of Pd(0)/C and PPh_3 was effective for the reaction of bromopyridines, 2-chloropyridine and 2-chloropyridines with an electron-withdrawing group. The combination of Pd(II)/C and PPh_3 was needed in the reaction of 2-chloropyridines with an electron-donating group and phenylbromides with an electron-donating group.

On the other hand, in Ir-catalyzed aromatic C-H borylation, 2,6-diisopropyl-*N*-(2-pyridylmethylene)aniline acted as a good ligand. Steric bulkiness around the imine moiety was important for achieving high yields.

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