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Continuous-Flow C-H Borylation of Arene Derivatives

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Abstract: A new continuous-flow system for C–H borylation has been developed. An insoluble catalyst prepared from chloro(1,5-cyclooctadien)iridium(I) dimer and 2,2'-bipyridine-4,4'-dicarboxylic acid in the presence of bis(pinacolato)diboron exhibited high reactivity under continuous-flow processing without the loss of expensive iridium metal.

Keywords: 2,2'-bipyridine-4,4'-dicarboxylic acid; C– H borylation; continuous-flow system; iridium

Flow chemistry is a well-established technology for industrial processes as well as laboratory experiments.^[1] Compared with reactions under standard batch conditions, flow chemistry has been reported to offer many advantages, such as 1) operational simplicity, 2) rapid and efficient heat dispersion, 3) ability to handle a multi-step reaction in a continuous sequence,^[2] and 4) rapid scale-up with little or no process development by either changing the reactor volume or by running several reactors in parallel.

Arylboronates are synthetic intermediates that are used in the synthesis of drugs^[3–5] and functional materials.^[6–8] Therefore, arylboronates are synthesized in quantities ranging from bulk chemicals to fine chemicals. Among the methods used for their preparation, C–H borylation is one of the most promising because it has high atom efficiency and can be conducted under milder reaction conditions compared with traditional halogen-metal exchange reactions.^[9,10]

Recently, we reported the preparation of a recyclable iridium catalyst for the C-H borylation reaction.^[11] The iridium catalyst, which can be prepared from an iridium precursor, 2,2'-bipyridine-4,4'-dicarboxylic acid (BPDCA) and bis(pinacolato)diboron $(Pin_2B_2, 1)$, could be reused at least ten times in the borvlation of benzene. This iridium catalyst has low solubility in organic media, but does not have support materials, such as resins, silica gels or charcoals. Furthermore, this non-supported catalyst also offers the further advantages of robustness and solvent-independent behaviour, such as swelling. We next studied the application of this iridium catalyst to continuousflow processes. In this paper, we report the first continuous-flow C-H borylation system using our new recyclable catalyst.

First, we synthesized a recyclable iridium catalyst according to our procedure (Scheme 1).^[11] A mixture of iridium precursor [IrCl(COD)]₂ (1.2 mmol) with 2,2'-bipyridine-4,4'-dicarboxylic acid (2.4 mmol) in benzene (21.4 mL, 240 mmol) was heated at 80 °C for 4 h in the presence of Pin₂B₂ **1** (8.0 mmol). During the reaction, the reaction mixture turned black with the evolution of hydrogen gas. After the reaction, the reaction mixture was filtered off in a glove-box and the iridium complex (**BPDCA-cat**) was obtained in quantitive yield (1.58 g) based on iridium metal.^[12] The cat-



Scheme 1. Preparation of BPDCA-cat.

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alyst had to be handled in a glove-box, because it is ignitable under air.

We checked the activity of **BPDCA-cat** in C–H borylation using various arenes and **1** in the presence of 3 mol% of isolated catalyst under batch conditions. The results are shown in Table 1. After the reaction, the catalyst could be separated by filtering through a disk filter (0.45 μ m mesh). In the case of benzene, the catalyst had sufficient activity and gave the product in excellent yields as checked by both GC and isolation. In the case of benzofuran, a 17 mol% of catalyst loading was necessary to obtain the borylated product in good yield.

Next, C-H borylation under continuous-flow conditions using **BPDCA-cat** was studied, and the flow system used is shown in Figure 1. A stainless steel reactor was constructed using Swagelock components, a sintered metal filter, and a stainless tube, which were commercially available for columns in liquid chromatography. No special equipment is necessary. This reactor has a bed size of $30 \text{ mm} \times 4 \text{ mm}$ and is packed with 145 mg of **BPDCA-cat** in a glove-box. The reactor was heated by an aluminum block heating system. The results of C–H borylation under continuous-flow conditions are shown in Table 2. In the first run, a benzene solution of **1** (0.18M) was passed through the column packed with catalyst at $80 \,^{\circ}$ C at different flow rates: 0.1 mmol/h, 0.2 mmol/h, and 0.3 mmol/h. As the substrate solution flowed, hydrogen gas was evolved. The reactions proceeded smoothly, and the



	$R \xrightarrow{f_{1}} X$ or $+ \xrightarrow{f_{0}} B \xrightarrow{f_{0}} C$ I 2.0 mmol (0.72 M) $(0.36 M)$	BPDCA-Cat (3 mol%) methylcyclohexane 80 °C, 12 h	^p in BPin
Entry ^[a]	Substrate	Product	Yield ^[b,c]
1 ^[d]	\bigcirc	BPin	93% (88%)
2		CI BPin CI	82% (78%)
3		CI BPin CI	87% (83%)
4	F ₃ C CF ₃	F_3C $BPin$ CF_3	87% (83%)
5		PinB Cl N Cl	77% (71%)
6	$\langle \rangle_{s}$	BPin	87% (83%)
7	$\langle \rangle$	BPin	59% ^[e] (43% ^[f])

^[a] Reactions were carried out in a methylcyclohexane solution of the substrates (0.72 M) and 1 (0.36 M) unless otherwise noted.

^[b] Yields were determined by GC using 4-ethylbiphenyl as an internal standard, except that tetralin was used as an internal standard in entry 3.

^[c] Yields in parentheses are the isolated yield.

^[d] Reaction was carried out in a benzene solution of 1 (0.18M).

^[e] Reaction was carried out using 0.36M of **1** (0.18 mmol) and 0.72M of benzofuran (0.36 mmol) in the presence of 17 mol% of catalyst.

^[f] Product contained *ca.* 5% of 3-borylated isomer as observed by ¹H NMR.

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Figure 1. Continuous-flow system.

 Table 2. C-H borylation under continuous-flow conditions.

Entry	Substrate ^[a]	Concentration Substrate	(mol/L) 1	Flow rate [mmol/h]	Yield ^[b,c] [%]	Ir leaching ^[d] [ppm]
1 2 3	\bigcirc	_	0.18	0.1 0.2 0.3	85 (80) 83 (79) 85	<0.1 <0.1 <0.1
4 5 6		0.36	0.18	0.3 0.1 0.2 0.3	53 (49) 43 36	<0.1 <0.1 N.A. ^[e] N.A. ^[e]
7 8 9		0.72	0.36	0.1 0.2 0.3	89 83 70	0.4 0.2 0.1
10 11 12		0.72	0.36	0.1 0.2 0.3	88 (82) 73 63	<0.1 N.A. ^[e] N.A. ^[e]
13 14 15	F ₃ C	0.72	0.36	0.1 0.2 0.3	93 (87) 80 76	0.4 0.6 0.6
16 17 18		0.72	0.36	$\begin{array}{c} 0.1^{[f]} \\ 0.2^{[f]} \\ 0.3^{[f]} \end{array}$	75 (71) 65 54	17 7.9 6.7
19 20	S	0.72	0.36	$0.1 \\ 0.1^{[f]}$	78 (75) 85 (78)	1.5 2.7
21	$\langle \rangle$	0.72	0.36	0.1	67 (62) ^[g]	0.6

^[a] In the case of benzene (entries 1–3), benzene was used as a substrate as well as a solvent.

^[b] Yields based on boron atoms of **1** were determined by GC analysis using 4-ethylbiphenyl as an internal standard, except that in the reaction of 1,3-dichlorobenzene the yield was determined by GC analysis using tetralin as an internal standard.

^[c] Yields in parentheses are isolated yields.

^[d] The contents of iridium in the reaction mixture were analyzed by ICP.

^[f] Cyclopentyl methyl ether was used as a solvent.

^[g] Product contained *ca*. 5% of 3-borylated isomer as observed by ¹H NMR. The structures of the products are shown in Table 1.

^[e] Not analyzed.

desired borylated product 2 was obtained in respective yields of 85%, 83%, and 85%. Between reactions with different substrates, the catalyst was washed with methylcyclohexane (10 mL, flow rate 0.2 mL/min) to avoid contamination of the products. Indeed, the previous substrate and product could be removed by washing to less than 0.1% as detected by GC analysis.

For substrates other than benzene, methylcyclohexane or cyclopentyl methyl ether (CPME) was used as an inert solvent. Compared with the reaction of benzene, the reaction of 1,2-dichlorobenzene proceeded slowly with 1 at a concentration of 0.18M. On the other hand, the reaction rate increased at a higher concentration. Furthermore, as the flow rate increased, the yield of product decreased. In the case of 2,6-dichloropyridine, CPME was used as a solvent because of its low solubility in methylcyclohexane to make a 0.72 M solution. Notably, benzofuran was borylated under these flow conditions (entry 21), the same as in the batch condition using 17 mol% of catalyst, although the reaction was slower than with other substrates. The best result was achieved using a flow rate of 0.1 mmol/h with substrates other than benzene. Less than 10 ppm of iridium leaching was observed in the reaction mixture. All reactions (Table 2) were carried out using a single column under heating at 80°C for more than one month. No significant deactivation of the catalyst was observed. Furthermore, this flow system can be readily performed even outside of a glove box because the catalyst is hardly exposed to air and moisture in a column reactor. This is the most important advantage of this flow system.

In conclusion, we have developed a continuousflow C–H borylation system using an insoluble iridium catalyst which we developed. This catalyst exhibited high reactivity and also high stability toward heating. Although this catalyst is sensitive to air and moisture, it could be easily handled as a packed stainless steel column. This continuous-flow system, which has many advantages, such as easy separation of the catalyst from the reaction mixture, simple operation, and application to a variety of substrates, can be applied to the industrial-scale production of aromatic borates without the loss of expensive iridium metal. Further studies to apply this flow system to other substrates are now in progress.

Experimental Section

Synthesis of BPDCA-cat

A 100-mL flask equipped with a magnetic stirring bar and a three-way cock with a septum inlet was charged with [IrCl-(COD)]₂ (806 mg, 1.2 mmol), 2,2'-bipyridine-4,4'-dicarboxylic acid (586 mg, 2.4 mmol) and bis(pinacolato)diboron (2.03 g, 8.0 mmol). After the flask had been flushed with nitrogen, benzene (21.4 mL) was added and the mixture was stirred at 80 °C for 4 h. In a glove-box, the reaction mixture was filtered through a filter paper (Kiriyama No. 5C) and the black solid obtained was washed twice with 10 mL benzene. The black solid was dried under vacuum. The combined filtrate and washings were analyzed by GC to determine the yield of 2 (33% yield based on boron atom of 1) using 4-ethylbiphenyl as an internal standard. Iridium and boron contents in the catalyst were calculated to be 31% (w/w) for iridium and 3.7% (w/w) for boron by ICP analysis. BPDCA-cat (1.58 g) was obtained in quantitive yield based on iridium metal. *Caution:* The catalyst is ignitable under air.

C-H Borylation of Benzene using BPDCA-cat under Batch Conditions

A 20-mL test tube equipped with a magnetic stirring bar and a three-way cock with a septum inlet was charged with BPDCA-cat (19 mg) in a glove-box. A benzene solution (0.18M) of 1 (5.56 mL, 1.0 mmol) was added and the mixture was stirred at 80°C for 12 h. The reaction mixture was filtered through a disc filter (0.45 µm mesh) and the black solid obtained was washed twice with 5 mL benzene. The combined filtrate and washings (11.68 g) were divided into two portions. One portion was used for GC and ICP analysis. The GC yield was determined using 4-ethylbiphenyl as an internal standard (93%). The remaining portion (3.613 g)was evaporated and distilled using a Kügelrohr apparatus (oven temperature; 80-100 °C, pressure; 1-2 mmHg) to give analytically pure (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)benzene as a colorless oil; yield: 111 mg (88%). ¹H NMR: $\delta = 1.35$ (s, 12H), 7.37 (t, 2H, J = 7.4 Hz), 7.46 (t, 1 H, J=7.3 Hz), 7.81 (d, 2H, J=7.3 Hz); ¹³C NMR: $\delta =$ 24.86, 83.74, 127.69, 131.24, 134.74.

C-H Borylation of Benzene using BPDCA-cat under Continuous-Flow Conditions

A benzene solution (0.18 M) of **1** was passed through the reactor packed with catalyst at 80 °C at 0.1 mmol/h for *ca.* 18 h (8.7 mL) using a syringe pump. The reaction mixture was transferred to another bottle from a product stock bottle. The product stock bottle was washed with 10 mL benzene. The combined filtrate and washings (15.35 g) were divided into two potions. One portion was used for GC and ICP analysis. The GC yield was determined using 4-ethylbiphenyl as an internal standard (85%). The remaining portion (4.832 g) was evaporated and distilled using a Kügelrohr apparatus (oven temperature; 80–100 °C, pressure; 1–2 mmHg) to give analytically pure (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene as a colorless oil; yield: 161 mg (80%).

C-H Borylation of 1,3-bis[trifluoromethyl]benzene using BPDCA-cat under Continuous-Flow Conditions

A methylcyclohexane solution of 1 (0.36 M) and 1,3-ditrifluoromethylbenzene (0.72 M) was passed through the reactor packed with catalyst at 80 °C at 0.1 mmol/h for *ca*. 13 h (4.0 mL) using a syringe pump. The reaction mixture was transferred to another bottle from a product stock bottle. The product stock bottle was washed with 10 mL methylcyclohexane. The combined filtrate and washings (10.29 g) were divided into two portions. One portion was used for

GC and ICP analysis. The GC yield was determined using 4ethylbiphenyl as an internal standard (93%). The remaining portion (3.112 g) was evaporated and distilled using a Kügelrohr apparatus (oven temperature; 80–100°C, pressure; 2– 3 mmHg) to give analytically pure 1,3-ditrifluoromethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene as a white solid; yield: 258 mg (87%). ¹H NMR: δ =1.37 (s, 12H), 7.95 (s, 1H), 8.24 (s, 2H); ¹³C NMR: δ =24.83, 84.84, 123.49 (q, J_{CF} =273 Hz), 124.72 (q, J_{CF} =3.3 Hz), 130.88 (q, J_{CF} =33 Hz), 134.65 (d, J_{CF} =3.3 Hz).

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- [12] Note: borylated product 2 was generated in 33% yield based on the boron atoms of 1. BPDCA-cat contains 31% (w/w) of iridium and 3.7% (w/w) of boron by ICP analysis. The molar ratio of iridium and boron is 1:2.1.

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