Asymmetric 1,4-Addition Reaction of Arylboronic Acid to Eneone Catalyzed by Palladium with Ferrocene-based Phosphine Ligand

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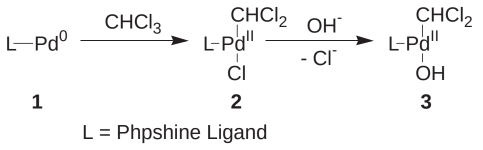
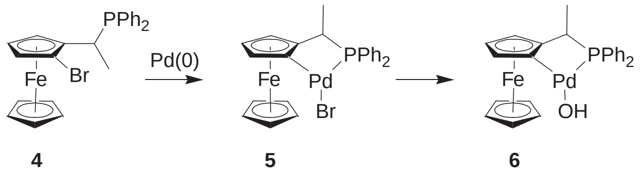
Asymmetric 1,4-addition reaction of arylboronic acid to cyclic enone was carried out in the presence of a chiral ferrocene-based phosphine ligand–palladium catalyst. The reaction of 2-cyclohexen-1-one by palladium complex with (*S*,*R*$_p$)-[1-(2-bromoferrocenyl)ethyl]diphenylphosphine afford a optically active β-arylcyclohexanone in good yield up to 71% ee.

Particularly, in various organo-main group metal compounds, organoboron compounds are non-toxic and effective for carbon–carbon bond forming reactions with various electrophiles in the presence of a transition metal.[1] Transition metal-catalyzed 1,4-conjugate addition reaction of organometallic reagents to α,β-unsaturated ketones is widely used for carbon–carbon bond formation giving β-substituted compounds.[2] Since Miyaura et al. found that rhodium(I) catalyzed 1,4-addition of aryl- and 1-alkenylboron compounds to α,β-unsaturated carbonyl compounds,[3] rhodium-catalyzed carbon–carbon coupling reaction with organoboron reagents have remarkably been developed. Addition reaction of arylboronic acid to enones,[4] aldehydes,[5] and aldimines[6] have been mainly performed with rhodium catalysts. However, only a few example of 1,4-addition of arylboronic acids to enones catalyzed by palladium have been reported.[7] Recently, it was discovered in our laboratory that catalytic amount of chloroform promotes addition reaction of arylboronic acid to enones[8] and aldehydes[9] in the presence of base, phosphine ligand and palladium. We have proposed the possible catalytic cycles of these reactions.[9] At first, phosphine-ligated dichloromethylpalladium(II) chloride intermediate **2** is generated by oxidative addition of chloroform to phosphine-coordinated palladium(0) complex **1**, and hydroxy palladium(II) species **3** is derived from **2** by ligand exchange (Scheme 1).

In this study, a ferrocene-based phosphine ligand, [1-(2-bromoferrocenyl)ethyl]diphenylphosphine (**4**) was synthesized, and applied for palladium-catalyzed 1,4-addition reaction of arylboronic acids to enones. We speculated that the ligand **4** could form a complex **5** with palladium(0) precursor. Formation of a complex **6** would be followed by ligand exchange through the same manner from **2** to **3**. We expected that this complex **6** would have the similar catalytic activity (Scheme 2). We already reported this study in several conferences.[10] Independently, Hu et al. reported the similar chemistry without asymmetric reaction very recently.[11]



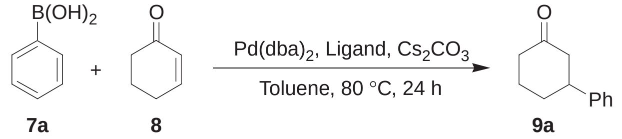
Scheme 1.



Scheme 2.

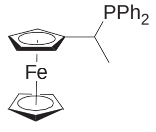
First, a racemic ligand **4** was synthesized from ferrocene by six reaction steps in excellent yield in every step.[12] 1,4-Addition reaction of phenylboronic acid to 2-cyclohexen-1-one was attempted with a racemic ligand **4**. At the same time, we applied the other ferrocene-based ligands **10**–**12** to the same reaction. Representative results are summarized in Table 1.

Table 1. Effect of ligands[a]



Entry	Ligand	Yield/%[b]
1	None	0
2	PPh_3	0
3	**4**	82
4	**10**	Trace
5	**10**[c]	85
6	**11**	0
7	**11** + PPh_3 (1 equiv.)	0
8	**11** + PPh_3 (2 equiv.)	0
9	**11** + PPh_3 (3 equiv.)	0
10	**12**	0

[a]Reaction conditions; 2-cyclohexen-1-one (1.0 mmol), phenylboronic acid (1.0 mmol), Pd(dba)$_2$ (0.05 mmol), ligand (0.05 mmol), Cs_2CO_3 (2.0 mmol). [b]Isolated yield. [c]Under air atmosphere.



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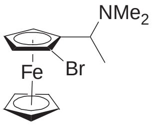

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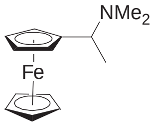

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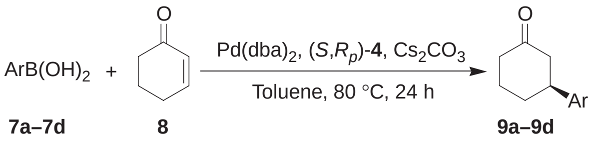
The reaction with ligand **4** afforded, as we expected, the 1,4-addition product, 3-phenylcyclohexanone (**9a**) in 82% isolated yield (Entry 3). The yield was trace when we used ligand **10** having no bromo substituent on it (Entry 4). However, **9a** was provided when we used ligand **10** under air atmosphere (Entry 5). We suppose that this reactivity is attributed to formation of a palladium(II) hydride complex derived from Pd and

Table 2. Asymmetric 1,4-addition reaction[a]



Entry	ArB(OH)$_2$	Ar	Yield/%[b]	ee/%[c]
1	**7a**	C_6H_5	82	42 (*S*)
2	**7b**	*o*-MeC_6H_4	93	25 (*S*)
3	**7c**	*m*-MeC_6H_4	63	58 (—)
4	**7d**	*p*-MeC_6H_4	88	61 (—)

[a]Reaction conditions; 2-cyclohexen-1-one (1.0 mmol), arylboronic acid (1.0 mmol), $Pd(dba)_2$ (0.05 mmol), ligand (0.05 mmol), Cs_2CO_3 (2.0 mmol). [b]Isolated yield. [c]Determined by HPLC analysis with chiral column chiralcel OD–H (eluent; hexane/*i*-PrOH = 98/2), and chiralpak AD–H (eluent; hexane/*i*-PrOH = 98/2).

ligand **10**, followed by insertion of oxygen into it to form palladium(II) hydroperoxy complex,[13] which would also possess the similar reactivity to one of the complex **6**. **9a** was not provided by using the other ferrocene ligands **11** and **12** (Entries 6–10). In addition, when we used triphenylphosphine as an extra ligand (Entries 2, and 7–9), or used no ligand (Entry 1), **9a** was not provided. From these results, the ligand **4** appeared to exhibit the same effect on the catalysis as chloroform did previously.

Next, an optically active ligand **4** was synthesized and applied for enantioselective 1,4-addition reaction of several arylboronic acids to 2-cyclohexen-1-one. The results are summarized in Table 2.

When phenylboronic acid was used, the desired product **9a** was obtained in 82% isolated yield and 42% ee (Entry 1). By using several methylphenylboronic acids **7b**–**7d**, the corresponding optically active β-arylcyclohexanones **9b**–**9d** were obtained in moderate to excellent yield (Entries 2–4). Among them *p*-methylphenylboronic acid afforded the highest enantiomeric excess as 61%. The good ee values observed in Table 2 clearly indicated that the chiral compound **5** or **6** would be an active catalyst.

Then, the effect of reaction temperature was examined for this catalysis, and the results were listed in Table 3. A significant difference was not observed in enantioselectivity when the reaction temperature was decrease from 80 to 60 °C (Entries 1 and 2). However, obvious improvement of enantioselectivity was observed when the reaction was carried out at room temperature with slight decrease of yield (Entry 3). The best enantiomeric excess (90% yield, 71% ee) was achieved by using **7d** at room temperature (Entry 5).

In summery, we found that efficient 1,4-addition reaction of 2-cyclohexen-1-one with arylboronic acid catalyzed by palladium complex having ferrocene-based phosphine ligand, which has an ability of oxidative addition to palladium center was achieved. Asymmetric reaction was also demonstrated using chiral one. Further applications and development of ligand are underway.

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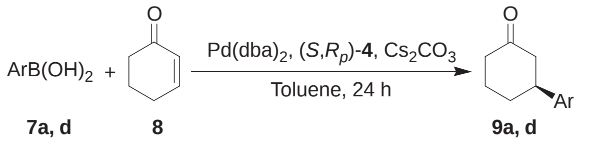
Table 3. Effect of reaction temperature[a]



Entry	ArB(OH)$_2$	Temp/°C	Yield/%[b]	ee/%[c]
1	**7a**	80	82	42 (*S*)
2	**7a**	60	83	46 (*S*)
3	**7a**	rt	79	66 (*S*)
4	**7d**	80	88	61 (—)
5	**7d**	rt	90	71 (—)

[a]Reaction conditions; 2-cyclohexen-1-one (1.0 mmol), arylboronic acid (1.0 mmol), $Pd(dba)_2$ (0.05 mmol), ligand (0.05 mmol), Cs_2CO_3 (2.0 mmol). [b]Isolated yield. [c]Determined by HPLC analysis with chiral column chiralcel OD–H (eluent; hexane/*i*-PrOH = 98/2), and chiralpak AD–H (eluent; hexane/*i*-PrOH = 98/2).

This paper is dedicated to the heartfelt memory of the late Professor Yoshihiko Ito of Doshisha University.

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