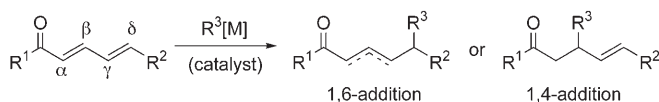


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Highly Selective 1,6-Addition of Aryl Boronic Acids to $\alpha,\beta,\gamma,\delta$ -Unsaturated Carbonyl Compounds Catalyzed by an Iridium Complex**

Takahiro Nishimura, Yuichi Yasuhara, and
Tamio Hayashi*

The transition-metal-catalyzed 1,4-addition of organometallic reagents to electron-deficient olefins is one of the most reliable methods for selective C–C bond formation,^[1] but, on the contrary, there is considerable difficulty in controlling the regioselectivity of the addition to extended conjugate systems; for example, 1,6- or 1,4-addition to electron-deficient dienes (Scheme 1). In this field of research, in which copper

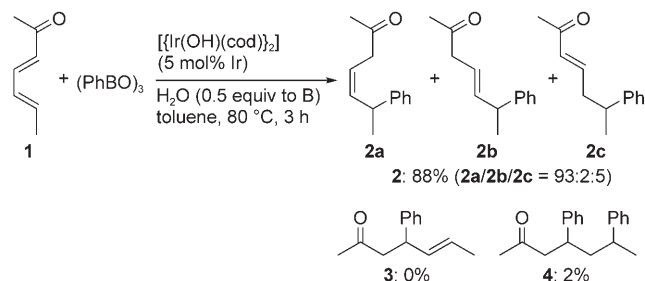


Scheme 1. 1,6-Addition versus 1,4-addition in $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds.

salts have been mainly used as the active catalysts,^[1e,2] Fukuhara and Urabe recently reported notable 1,6-selectivity with iron as a catalyst in the addition of aryl Grignard reagents to 2,4-dienoates and -dienamides.^[3] Although rhodium-catalyzed conjugate addition has been developing very rapidly,^[4] only a few reports have appeared that describe 1,6- or 1,4-selectivity in the addition to electron-deficient dienes.^[5,6] High 1,6-selectivity in the rhodium-catalyzed reactions has been reported for a limited combination of substrates: Examples include the addition of aryl zinc reagents to dienones with β -substituents^[5] and the addition of aryl and alkenyl boronic acids to δ -unsubstituted dienones.^[6] Herein, we report perfect 1,6-selectivity in the addition of aryl boronic acids to a standard type of $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compound, realized by use of an iridium complex as a catalyst.

During our efforts to realize the 1,6-addition of aryl boronic acids to $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds, we found that an iridium complex, $[\text{Ir}(\text{OH})(\text{cod})_2]$ (cod =

cyclooctadiene),^[7] efficiently catalyzes the addition to simple dienones with perfect 1,6-regioselectivity. Thus, treatment of (3*E*,5*E*)-3,5-heptadien-2-one (**1**) with phenylboronic acid (1.0 equiv)^[8] in the presence of a catalytic amount of $[\text{Ir}(\text{OH})(\text{cod})_2]$ (5 mol % Ir) and H_2O (0.5 equiv relative to **1**) in toluene at 80 °C for 3 h gave a mixture of 1,6-adducts, 6-phenylhepten-2-ones **2**,^[5] in 88 % yield (Scheme 2). The

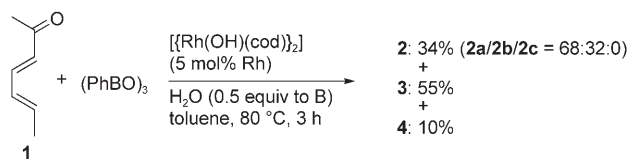


Scheme 2. Iridium-catalyzed 1,6-addition of phenylboronic acid to dienone **1**.

mixture consists of (*Z*)-6-phenyl-4-hepten-2-one (**2a**) as the major isomer (93 %), its *E* isomer **2b** (2 %), and conjugate ketone **2c** (5 %). The formation of the 1,4-addition product **3** was not detected at all under the present reaction conditions. The formation of a small amount of diphenylation product **4** (2 %), probably formed by the 1,4-addition of phenylboronic acid to the conjugate ketone **2c**, was also observed.

Although rhodium catalysts have been often used for the addition of aryl metal reagents to electron-deficient alkenes,^[4] the iridium catalyst system employed in this addition has not been well demonstrated so far. As a related reaction, Mori and co-workers reported the first example of the iridium-catalyzed addition/elimination reaction of aryl silicon reagents with acrylates to give Mizoroki–Heck-type products.^[9] To the best of our knowledge, the present 1,6-addition is the first example of an iridium-catalyzed addition of aryl boronic acids to electron-deficient alkenes or dienes.^[10] The unique 1,6-selectivity observed in the iridium-catalyzed addition is made clear by comparison with the result obtained with $[\text{Rh}(\text{OH})(\text{cod})_2]$ ^[11] as a catalyst under the same reaction conditions (Scheme 3). The rhodium-catalyzed reaction gave the 1,4-adduct **3** as the main isomer (55 % yield) and a minor amount (34 % yield) of 1,6-adducts **2a** and **2b**.

Competition experiments with a 1:1 mixture of dienone **1** and 3-penten-2-one (**5**) gave us insight into the origin of the difference in regioselectivity between the iridium and rhodium catalysts in the addition of phenylboronic acid to the dienone (Scheme 4). Thus, in the reaction of a 1:1 mixture of **1**

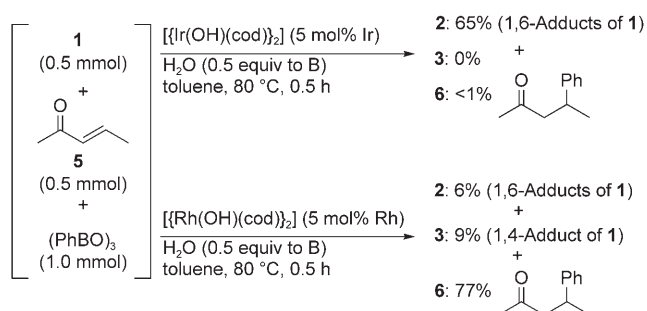


Scheme 3. Rhodium-catalyzed addition of phenylboronic acid to dienone **1**.

[*] Dr. T. Nishimura, Y. Yasuhara, Prof. T. Hayashi
Department of Chemistry
Graduate School of Science
Sakyo, Kyoto 606–8502 (Japan)
Fax: (+81) 75-753-3988
E-mail: thayashi@kuchem.kyoto-u.ac.jp

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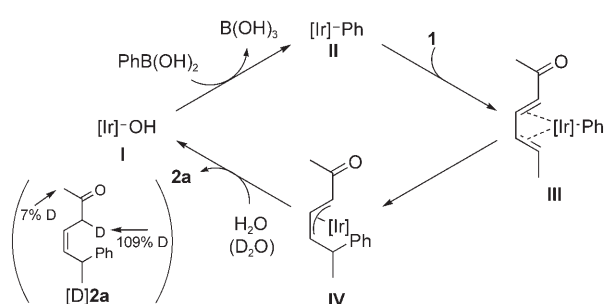
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Scheme 4. Competitive reaction of dienone **1** and enone **5** with phenylboronic acid in the presence of $[\text{Ir}(\text{OH})(\text{cod})]_2$ or $[\text{Rh}(\text{OH})(\text{cod})]_2$.

and **5** with phenylboronic acid in the presence of $[\text{Ir}(\text{OH})(\text{cod})]_2$, dienone **1** was consumed exclusively to give the 1,6-adducts **2** (65%), thus leaving enone **5** unreacted. These results indicate that the iridium catalyst has much a stronger reactivity toward the dienone than enone. On the other hand, the competition experiment with $[\text{Rh}(\text{OH})(\text{cod})]_2$ as a catalyst gave a high yield (77%) of 4-phenyl-2-butanone (**6**), which is the 1,4-addition product of enone **5**, and a small amount of **2** (6%) and **3** (9%), the addition products of the dienone **1**.

On the basis of the high reactivity toward the diene moiety and the high *Z* selectivity in the 1,6-addition product, the catalytic cycle of the present iridium-catalyzed reaction is speculated as shown in Scheme 5. Transmetalation of a phenyl



Scheme 5. Proposed catalytic cycle of the iridium-catalyzed 1,6-addition of phenylboronic acid to enone **1**.

group from the boron to iridium center forms a phenyl-iridium species **II**.^[9,12] The coordination of the dienone to the phenyl-iridium complex with a cisoid diene moiety results in the formation of a $(\eta^4\text{-diene})\text{-Ir}(\text{Ph})$ complex **III**.^[13] Insertion of the diene into the phenyl-iridium bond, thus forming $\pi\text{-allyl-iridium}$ moiety **IV**,^[14] followed by subsequent hydrolysis with the assistance of phenylboronic acid or boric acid gives the 1,6-addition product **2a** with *Z* configuration and the hydroxo-iridium species **I**. The selective incorporation of deuterium at the α -position in **[D]2a** was observed in the addition to dienone **1** by using D_2O in place of H_2O , which aids the hydrolysis step of $\pi\text{-allyl-iridium}$ complex **IV** and gives **2a**.

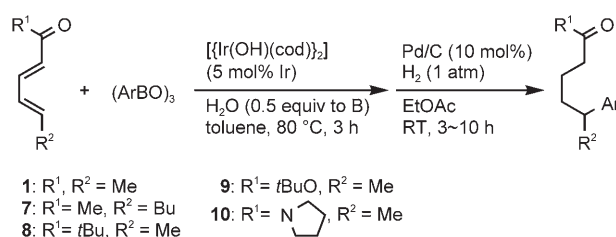
The results of the 1,6-addition of aryl boronic acids to $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds are summarized in Table 1. The addition products provided by the iridium-

Table 1. Iridium-catalyzed 1,6-addition to dienes.^[a]

Entry	Diene	Ar	Yield [%] ^[b]
1	1	Ph	86 (11) ^[c]
2	1	4-MeC ₆ H ₄	82 (12) ^[c]
3	1	4-MeOC ₆ H ₄	88 (13) ^[c]
4	1	4-CF ₃ C ₆ H ₄	75 (14)
5	1	4-FC ₆ H ₄	84 (15) ^[c]
6	1	2-naphthyl	86 (16)
7	7	Ph	86 (17)
8	8	Ph	94 (18)
9	9	Ph	82 (19)
10	10	Ph	90 (20)

[a] Reaction conditions: $[\text{Ir}(\text{OH})(\text{cod})]_2$ (0.025 mmol Ir), diene (0.50 mmol), $(\text{ArBO})_3$ (0.50 mmol), H_2O (0.75 mmol), toluene (1.0 mL), 80 °C, 3 h. After short column chromatography on silica gel, the products were subjected to hydrogenation in the presence of Pd/C (10 mol%) under H_2 (1 atm). [b] Yield of the isolated products. [c] A diarylation product was also obtained in 2% yield in each case.

catalyzed hydroarylation were subjected to palladium-catalyzed hydrogenation to give saturated ketones (Scheme 6).



Scheme 6. Iridium-catalyzed 1,6-addition of aryl boronic acids to electron-deficient dienes.

The reaction of dienone **1** with several aryl boronic acids with electron-donating and -withdrawing substituents on the benzene ring gave the corresponding δ -aryl ketones in high yields (75–88% yields, entries 1–6) after hydrogenation. The 1,4-addition to dienone **1** was not detected in any case. The 1,6-selectivity was also observed in the addition to dienones **7** ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Bu}$) and **8** ($\text{R}^1 = t\text{Bu}$, $\text{R}^2 = \text{Me}$; entries 7 and 8, respectively). This iridium-catalyzed reaction can be applied to $\alpha,\beta,\gamma,\delta$ -unsaturated ester **9** and amide **10** to give the corresponding 1,6-addition products in 82 and 90% yield, respectively (entries 9 and 10).

In summary, the catalytic 1,6-addition of aryl boronic acids to electron-deficient dienes was realized by use of an iridium catalyst, which gave high yields of the corresponding δ -arylated carbonyl compounds with perfect 1,6-selectivity.

Experimental Section

(3*E*,5*E*)-3,5-Heptadien-2-one (**1**; 55.1 mg, 0.50 mmol) and H_2O (13.5 μL , 0.75 mmol) were added to a solution of $[\text{Ir}(\text{OH})(\text{cod})]_2$ (8.3 mg, 0.025 mmol Ir) and phenylboroxine (156 mg, 0.50 mmol) in toluene (1.0 mL) at room temperature. The reaction mixture was heated at 80 °C for 3 h. After the usual workup, column chromatography on silica gel gave a mixture of the 1,6-addition products. The mixture was hydrogenated in the presence of Pd/C (10 mol% Pd)

under H_2 (1 atm) in EtOAc (2.0 mL) at room temperature for 3 h to give 6-phenyl-2-heptanone (83.0 mg, 86 %).

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