Iridium(I)-catalyzed C–H Borylation of α,β-Unsaturated Esters with Bis(pinacolato) diboron

Ikuo Sasaki, [a] Jumpei Taguchi, [a] Hana Doi, [a] Hajime Ito* [a] and Tatsuo Ishiyama* [a]

Abstract: A new process has been developed for the iridium(I)-catalyzed vinylic C–H borylation of α,β-unsaturated esters with bis(pinacolato)diboron. Although this reaction proceeded at room temperature to afford the desired alkenyl boronic esters in good yields, it also afforded the corresponding allyl boronic esters as byproducts. In 2011, Iwasawa’s group reported the dehydrogenative borylation of alkenyl substrates using (PSiP)PdOTf as a catalyst. This borylation reaction proceeded smoothly to give the corresponding alkenyl boronic esters in high yields, although the products were produced as a mixture of E- and Z-isomers in some cases. We recently reported the C–H borylation of alkenes with an iridium catalyst. Although this particular reaction provided facile access to a wide range of alkenylboronates in high yield with good regioselectivity, it was only amenable to cyclic vinyl ether substrates.

We also recently reported the direct regioselective ortho C–H borylation of various benzoates and aryl ketones with the complex [Ir(OMe)(cod)]2/P[3,5-(CF3)2C6H3]3 or AsPh3. Around the same time, several other research groups, including those of Sawamura,[8] Lassaletta,[9] and Hartwig,[10] also reported similar borylation reactions involving functionalized arenes. The selectivity of these reactions has been attributed to the formation of an interaction between the coordinating heteroatom in the carbonyl group and the iridium metal center.[7–9] Herein, we describe the development of a new process for the vinylic C–H borylation of cyclic 1 and acyclic α,β-unsaturated esters 3 with 2, using an in-situ-generated iridium complex consisting of readily available [Ir(X)(cod)]2 (X = OMe or Cl) and AsPh3 as a catalyst with octane as a solvent.[11] This reaction proceeded chemoselectively at 80 or 120 °C to give the corresponding alkenylboronic compounds 4 or 5 in high yields (Scheme 1). The stereoselective borylation of acyclic compounds 3 afforded the (E)-alkenylboronates 5. The mechanism of this reaction was confirmed to involve sequential 1,4-addition/β-hydride reactions based on the results of crossover experiments involving deuterated substrates and the analysis of the products resulting from the reaction of an E/Z isomer mixture. The results also confirmed that iridium C-enolate is involved as a key intermediate in determining the selectivity of the borylation reaction. It is noteworthy that this reaction was also applied to a one-pot borylation/Suzuki–Miyaura cross-coupling procedure to afford the 2-aryl-substituted 1-cycloalkene carboxylate in good yield, which showed biological activity as an antidepressant agent. Some of results in this paper have been reported in a separate communication.[11]
Results and Discussion

We initially established the reaction conditions for the vinylic C–H borylation with methyl 1-cyclohexene carboxylate 1a. The reaction of 1a with 2 (1.1 equiv) in the presence of an Ir\(^{1}\) precursor, [Ir(OMe)(cod)]\(_{2}\) (1.5 mol\%), and AsPh\(_{3}\) (3 mol\%) in octane at 120 °C afforded the desired product 4a in high yield after 16 h (90\% \(^{1}H\) NMR yield, 84\% isolated yield, Table 1, entry 1). A variety of different phosphine ligands, including P(3,5-(CF\(_{3}\))\(_{2}\)C\(_{6}\)H\(_{3}\)), P(C\(_{6}\)F\(_{5}\)), PPh\(_{3}\) and P(4-MeOC\(_{6}\)H\(_{4}\)) were also evaluated in this reaction, but found to be in effective (4a: 0–20\% after 16 h; Table 1, entries 2–5). The yield of 4a decreased when mesitylene was employed as a solvent instead of octane (4a: 51\% after 16 h; Table 1, entry 6). Furthermore, no reaction occurred when dimethylformamide (DMF) was used as the solvent (Table 1, entry 7). The use of [Ir(Cl)(cod)]\(_{2}\) as the iridium precursor led to a small decrease in the yield of 4a to 84\% (Table 1, entry 8). Notably, the borylation proceeded smoothly at the lower temperature of 80 °C (99%, entry 9). Under these conditions, the use of a lower loading of [Ir(OMe)(cod)]\(_{2}\) (0.5 mol\%) also gave 4a in reasonable yield (81%; Table 1, entry 10).

Table 1. Optimization of the reaction conditions with 1-cyclohexene carboxylate 1a.\(^{\text{[a]}}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ir(^{1}) precursor</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Ir(OMe)(cod)](_{2})</td>
<td>AsPh(_{3})</td>
<td>Octane</td>
<td>90 (84)(^{\text{[b]}})</td>
</tr>
<tr>
<td>2</td>
<td>[Ir(OMe)(cod)](_{2})</td>
<td>P(3,5-(CF(<em>{3}))(</em>{2})C(<em>{6})H(</em>{3}))</td>
<td>Octane</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>[Ir(OMe)(cod)](_{2})</td>
<td>P(C(<em>{6})F(</em>{5}))</td>
<td>Octane</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>[Ir(OMe)(cod)](_{2})</td>
<td>PPh(_{3})</td>
<td>Octane</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>[Ir(OMe)(cod)](_{2})</td>
<td>P(4-MeOC(<em>{6})H(</em>{4}))</td>
<td>Octane</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>[Ir(OMe)(cod)](_{2})</td>
<td>AsPh(_{3})</td>
<td>Mesitylene</td>
<td>51</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Reaction conditions: 1a (0.5 mmol), 2 (0.55 mmol), Ir\(^{1}\) precursor (1.5 mol\%) and ligand (6.0 mol\%) in solvent (3 mL). \(^{[b]}\) Yields were determined by GC analysis. \(^{[c]}\) Isolated yield. \(^{[d]}\) Reaction was carried out at 80 °C. \(^{[e]}\) 0.5 mol\% [Ir(OMe)(cod)]\(_{2}\) and 2.0 mol\% AsPh\(_{3}\) were used.

With the optimized conditions in hand, we proceeded to examine the scope of this C–H borylation reaction using a variety of cyclic α,β-unsaturated esters (Table 2). Simple alkyl esters, such as those bearing ethyl 1b, isopropyl 1c and tert-butyl 1d alkyl groups, exhibited good reactivity to afford the corresponding alkenylboronates in high yields (4b: 87%, 4c: 77%, 4d: 85%). Phenyl ester 1e, with five C(sp\(^{2}\))–H bonds on its phenyl moiety, reacted exclusively with 2 at its vinylic position to give the desired alkenylboronate 4e in 96% yield at 80 °C.\(^{[7,8]}\) This result highlighted the chemoselectivity of this borylation reaction, with the reaction occurring exclusively at the vinylic C–H position despite the in the presence of aryl C–H bonds, which normally react under conventional Ir-catalyzed borylation conditions. The borylation of 3-chloropropyl ester 1f proceeded exclusively at the vinylic C–H bond to afford 4f in high yield without any side reactions involving the C–Cl bond (86%). The reaction of the CF\(_{3}\)-containing ester 1g afforded 4g in 93% yield. Furthermore, the 3-methoxy ester 1h reacted completely to produce 4h in high yield (83%). The reactions of ketone 1i, ester 1j and carbamate 1k all proceeded smoothly at 120 °C to afford 4i (65%), 4j (74%) and 4k (72%), respectively. Epoxyde 1l reacted without any detectable substrate decomposition under the optimized reaction conditions to give the borylation product 4l in 79% yield after 0.5 h. Although the borylation reactions of various cyclohexene-type substrates produced the corresponding borylated products in high yields, the reactions of cycloalkenyl substrates with five-, seven- and eight-membered rings resulted in low product yields and required much harsher reaction conditions (120 °C with 2.5 mol% [Ir(OMe)(cod)]\(_{2}\) and 10 mol% AsPh\(_{3}\)). Although the reaction of the five-membered ring-containing substrate 1m with 2 led to the complete consumption of both starting materials, the product 4m was obtained in low yield (20%). The reactions of the seven- and eight-membered ring containing substrates 1n and 1o also resulted in low yields of the corresponding alkenylboronates 4n and 4o, respectively, even though the substrates were completely consumed. These results therefore suggested that substrates 1m–o had decomposed under the reaction conditions.

Table 2. C–H borylation of various cyclic α,β-unsaturated esters.\(^{[9]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ir(^{1}) precursor</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>[Ir(OMe)(cod)](_{2})</td>
<td>AsPh(_{3})</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>[Ir(Cl)(cod)](_{2})</td>
<td>AsPh(_{3})</td>
<td>Octane</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>[Ir(OMe)(cod)](_{2})</td>
<td>AsPh(_{3})</td>
<td>Octane</td>
<td>99 (87)</td>
</tr>
</tbody>
</table>

\(^{[9]}\) Reaction conditions: 1b-o (0.5 mmol), 2 (0.55 mmol), Ir\(^{1}\) precursor (1.5 mol\%) and ligand (6.0 mol\%) in solvent (3 mL).
To further expand the utility of our newly developed vinylic C–H borylation, we investigated its application to acyclic α,β-unsaturated esters (Table 3). The reaction of methyl (E)-2-methylbut-2-enoate 3a with 2.0 equiv of 2 proceeded at 120 °C in the presence of [Ir(Cl)(cod)]2 (1.5 mol%) as the catalyst precursor and AsPh3 (3 mol%) as the ligand to afford the (E)-alkenylboronate 5a in moderate yield with excellent stereoselectivity. Several other alkyl (E)-2-methylbut-2-enoates, including the methoxy 3b and ethyl thiocyano 3c substrates exhibited low to moderate reactivity with both reactions providing the E-isomer exclusively (5b: 48%, 5c: 21%). When phenyl ester 3d was used as the substrate, the yield of the corresponding alkylboronate 5d increased (5d: 62%). Based on the higher yield of this reaction, we proceeded to examine the borylation of various ary esters. The reactions of the para- and ortho-methoxyphenyl esters 3e and 3f proceeded smoothly to give the desired alkylboronates 5e and 5f in 76 and 74% yields, respectively. Notably, 2,4-dimethoxyphenyl ester 3g exhibited better reactivity than 3e or 3f to afford the corresponding (E)-alkenylboronate 5g in 82% yield. However, the reaction of 2,4,6-trimethoxyphenyl ester 3h afforded only a moderate yield of the corresponding (E)-alkenylboronate 5j (64%). The benzodioxole ester 3i, bearing an orthodialkoxyphenyl moiety, reacted with 2 to afford the boronate 5i in moderate yield (65%). The borylation of para-dimethylaminophenyl ester 3j produced alkylboronate 5j in 77% yield. Several sterically congested substrates, including 4-methoxyphenyl(2)-2-methylpent-2-enoates 3k and 4-methoxynaphthyl(2)-2-methyl-3-phenylacrylate 3l, were also evaluated but exhibited low reactivity, with the borylated products being isolated in low yields (5k: 41%, 5l: 19%). In all cases, the stereoselectivity of the product was completely retained, whilst the yield of the borylated compounds varied considerably.

Table 3. C–H borylation of various acyclic α,β-unsaturated esters.3k

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Yields (α: β)</th>
<th>α: β</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Cl</td>
<td>62% (52%)</td>
<td>3h</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>65% (1h)</td>
<td>5i</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>77% (1h)</td>
<td>5j</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>64% (4%)</td>
<td>5h</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>82% (55%)</td>
<td>5g</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>65% (1h)</td>
<td>5i</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>77% (51%)</td>
<td>5j</td>
<td></td>
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</tr>
<tr>
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<td>OMe</td>
<td>77% (51%)</td>
<td>5j</td>
<td></td>
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</tbody>
</table>

We then investigated the one-pot synthesis of a bioactive compound via a sequential vinylic C–H borylation/cross-coupling reaction (Scheme 2).13 Compound 6 has been reported to be an inhibitor of monoamine transporters.14 The alkynylboronate 4a was prepared from 1a under the optimized conditions shown in Table 1. Distilled water was added to the reaction mixture in this case to hydrolyze the HBpin byproduct generated during the course of the Ir-catalyzed borylation because this material inhibited the subsequent cross-coupling reaction. Finally, the cross-coupling reaction was conducted by adding 2-bromonaphthalene (2.5 mmol), K2PO4 (3.0 equiv), and PdCl2(dpff) (5 mol%) to the reaction mixture without the

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evaporation of the solvent or the prior purification of the product. The cross-coupling product 6 was obtained in 47% yield (78%, GC yield) from this two-step reaction.

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According to pathway 1, the electron-oxidative insertion reaction to the iridium enolate would undergo a 1,4-insertion reaction as opposed to an elimination of the Ir–hydride complex. The subsequent reductive elimination of the vinylic C–H bond to produce the boryliridium complex 4. According to pathway 2, complex B would result in the formation of desired products 4 or 5. Finally, the oxidative addition of HBpin to D, followed by the reductive elimination of HBpin, would regenerate A. According to pathway 2, complex B would undergo a 1,4-insertion reaction as opposed to an oxidative addition reaction to the iridium enolate E. The subsequent isomerization of E would afford the Ir complex F, which would have an Ir–C bond with a syn configuration between the Ir center and the β-H atom. Finally, the β-hydride elimination of complex F would result in the formation of desired products 4 or 5 and D.

It is noteworthy that the borylation of acyclic compounds under these conditions afforded the (E)-products selectively. When a 50:50 (mol/mol) mixture of the (E) and (Z)-isomers of 3e was used as the substrate, both of the isomers were consumed at the same rate. However, this reaction afforded the (E)-isomer 5e as the major product (98:2) in 44% yield (Scheme 5a). To develop a better understanding of this reaction, we investigated the borylation of a mixture of (Z)-3e and (E)-paraethoxyphenyl ester 3m (Scheme 5b). The mixture of (Z)-3e and (E)-3m reacted with 2 to afford (E)-5e and (E)-5m in 15 and 71% yields, respectively. Notably, the reaction of (Z)-3e alone under the optimized conditions also gave (E)-5e in 13% yield. These results therefore suggested that the (E) and (Z)-isomers were both reacting under these conditions to give a single isomer. The selectivity observed in this case therefore most likely occurred as a consequence of steric repulsion between the β-methyl group and the carbonyl group of the ester moiety (Scheme 5c).

To elucidate the mechanism of this C–H borylation reaction, we investigated the effect of varying the number of equivalents of 1a added to 2 under the optimized conditions (eq.1). The results revealed that the addition of 0.5 equivalents was optimal, with larger charges (i.e., 1.0 or 3.0 equiv) leading to a 5-fold decrease in the yield. This indicates that the coordination step might not be the rate determining step. We also conducted a competition experiment with 1a (X = H or D) and 1b at 120 °C, which revealed that the reaction proceeded without any discernible isotope effect (Scheme 4, eq. 2). This result indicates that pathway 1 is less plausible because the oxidation step proposed in pathway 1 would cause large isotope effect if it is the rate limiting step. Although the above two mechanistic experiments could not give a decisive result, we currently suppose pathway 2 is more plausible. This mechanism can explain the following stereo-divergent results by considering the enolate intermediate in pathway 2.
addition/involving a deuterated substrate and a mixture of functional groups, including halogen, acyl, alkoxycarbonyl, exhibited good functional group tolerance towards a wide range even for substrates bearing an aryl group, which would normally react though their own C–H bonds under conventional Ir-at the vinylic position with good chemo- and stereoselectivity, unsaturated esters with

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Scheme 5. Selectivity of the borylation of acyclic esters.

Conclusions

In summary, the iridium complexes prepared by the reaction of [Ir(OMe)(cod)]2 and [Ir(Cl)(cod)]2 with AsPh3 have been shown to be efficient catalysts for the vinylic C–H borylation of α,β-unsaturated esters with 2. These borylation reactions proceeded at the vinylic position with good chemo- and stereoselectivity, even for substrates bearing an aryl group, which would normally react though their own C–H bonds under conventional Ir-catalyzed borylation conditions. Furthermore, this reaction exhibited good functional group tolerance towards a wide range of functional groups, including halogen, acyl, alkoxycarbonyl, carbamoyl and epoxy groups. The results of crossed reactions involving a deuterated substrate and a mixture of E/Z-isomers suggested that this transformation proceeded via sequential 1,4-addition/β-hydride elimination reactions. We also achieved a one-pot borylation/cross-coupling procedure for the rapid synthesis of a drug candidate; further highlighting the synthetic utility of this reaction.

Experimental Section

A Representative Procedure for the Iridium(I)-Catalyzed Vinylic C–H Borylation of 1a (Table 1).

[47.2 mmol] of [Ir(OMe)(cod)]2 and [Ir(Cl)(cod)]2 was then added to the reaction mixture, and the resulting mixture was stirred at 80 or 120 °C. Upon completion of the reaction, the mixture was concentrated to give a residue, which was purified by flash chromatography over silica gel (EtOAc/hexane, 1:99–5:95) to give the corresponding alkenylboronate 4a as a colorless oil.

Acknowledgements ((optional))

This work was financially supported by a Grant-in-Aid for Scientific Research (B) (No. 21350049) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan and the MEXT (Japan) program “Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions” of Hokkaido University.

Keywords: iridium • borylation • alkenyl boronate • α,β-unsaturated esters • diboron

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A new method has been developed for the vinylic C–H borylation of α,β-unsaturated esters with B_2(pin)_2 using iridium(I) catalysts. These reactions proceeded in octane at 80 to 120 °C to afford the alkenylboronic compounds in high yields with excellent regio- and stereoselectivities. The use of an aryl ester group was important for the mechanism of the reaction, which was elucidated by crossover experiments with a deuterated substrate and a mixture of stereoisomers.