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C–H Borylation

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

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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 (B_2pin_2). These reactions proceeded in octane at temperatures in the range of 80–120 °C to afford the corresponding alkenylboronic compounds in high yields with excellent regio- and stereoselectivities. The presence of an aryl ester led to significant improvements in the yields of the acyclic alkenylboronates. Crossover experiments involving deuterated substrates as well as a mixture of stereoisomers confirmed that this reaction proceeds via a 1,4-addition/β-hydride elimination mechanism. Notably, this reaction was also used to develop a one-pot borylation/Suzuki–Miyaura cross-coupling procedure.

Introduction

Alkenyl boronic esters are versatile intermediates in synthetic organic chemistry,[1] and their utility for the synthesis of C–C bonds has been well demonstrated in the synthesis of natural products, biologically active compounds, and functional molecules.[2] Conventional methods for the preparation of alkenyl boronic esters include the reaction of $B(OR)_3$ with alkenyl-lithium or -magnesium reagents, and the Pd-catalyzed cross-coupling reaction of alkenyl halides or triflates with (B_2pin_2) (**2**) or pinacolborane (HBpin).[3] However, the application of these methods has been limited by their lack of functional-group compatibility, as well as the fact that many alkenyl halides and triflates are not readily available. Several alternatives to these reactions have recently been reported that involve the transition-metal-catalyzed C–H borylation of alkenyl compounds.[4–6] Notably, these methods are much more cost effective and environmentally friendly than the conventional methods described above. For example, Olsson and Szabó reported a one-pot catalytic C–H borylation/Suzuki–Miyaura coupling sequence of α,β-unsaturated esters in 2008.[6h] The reaction produced the desired products in good yield, however, only terminal alkenes were used as the substrates. Szabó and co-workers also reported the C–H borylation of alkenyl compounds with a palladium pincer complex in 2010.[6c] 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 and co-workers reported the dehydrogenative borylation of alkenyl substrates using (PSiP)PdOTf as a catalyst.[6b] 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.[5] 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-$(CF_3)_2C_6H_3]_3$ (cod = 1,5-cyclooctadiene) or $AsPh_3$.[7] 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 $AsPh_3$ 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 involved sequential 1,4-addition/β-hydride reactions based on the results of crossover experiments involving deuterated substrates and the analysis of

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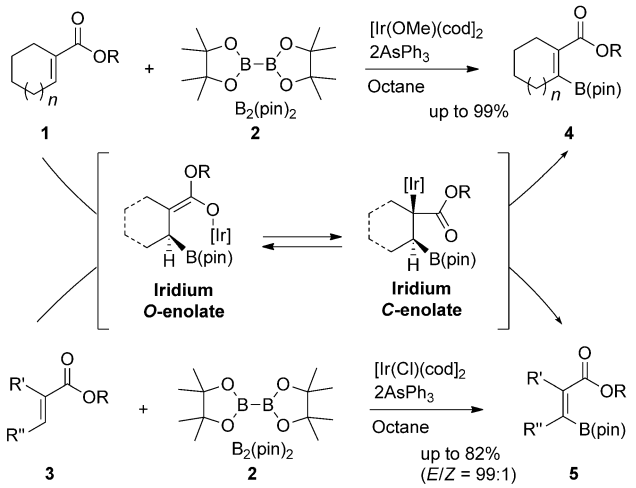
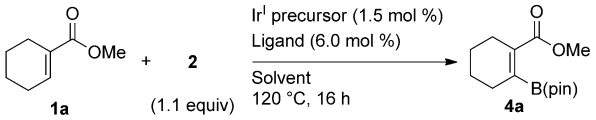


Scheme 1. Vinylic C–H borylation of α,β-unsaturated esters via an iridium *C*-enolate intermediate.

Table 1. Optimization of the reaction conditions with 1-cyclohexenecarboxylate **1a**.[a]



Entry	Ir^I precursor	Ligand	Solvent	Yield [%][b]
1	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Octane	90(84)[c]
2	$[Ir(OMe)(cod)]_2$	$P[3,5\text{-}(CF_3)_2C_6H_3]_3$	Octane	14
3	$[Ir(OMe)(cod)]_2$	$P(C_6F_5)_3$	Octane	10
4	$[Ir(OMe)(cod)]_2$	PPh_3	Octane	20
5	$[Ir(OMe)(cod)]_2$	$P[4\text{-}MeOC_6H_4]_3$	octane	0
6	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Mesitylene	51
7	$[Ir(OMe)(cod)]_2$	$AsPh_3$	DMF	0
8	$[Ir(Cl)(cod)]_2$	$AsPh_3$	Octane	84
9[d]	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Octane	99 (87)
10[e]	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Octane	81

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.55 mmol), Ir^I 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.

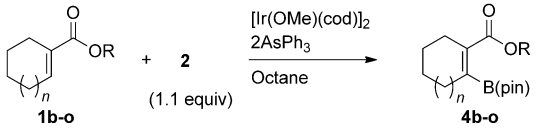
the products resulting from the reaction of an *E*/*Z* isomer mixture. The results also confirmed that an iridium *C*-enolate is involved as a key intermediate in determining the selectivity of the borylation reaction. It is noteworthy that this reaction was also applied to a one-pot borylation/Suzuki–Miyaura cross-coupling procedure to afford the 2-aryl-substituted 1-cycloalkenecarboxylate in good yield, which showed biological activity as an antidepressants agent. Some of results in this paper have been reported in a separate communication.[11]

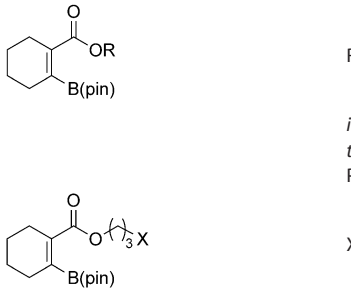
Results and Discussion

We initially established the reaction conditions for the vinylic C–H borylation with methyl 1-cyclohexenecarboxylate **1a**. The reaction of **1a** with **2** (1.1 equiv) in the presence of an Ir^I 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% ^1H NMR yield, 84% isolated yield, Table 1, entry 1). A variety of different phosphine ligands, including $P[3,5\text{-}(CF)_2C_6H_3]_3$, $P(C_6F_5)_3$, PPh_3, and $P(4\text{-}MeOC_6H_4)$ 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 *N*,*N*-dimethylformamide (DMF) was used as the solvent (Table 1, entry 7). Using $[IrCl(cod)]_2$ 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%, Table 1, entry 9). Under these conditions, a lower loading of $[Ir(OMe)(cod)]_2$ (0.5 mol%) also gave **4a** in reasonable yield (81%; Table 1, entry 10).

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, showed 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 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. Epoxide **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% $AsPh_3$). The reaction of the five-membered ring-containing substrate **1m** with **2** led to the complete consumption of both starting materials, however, 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.[a]





R = Et (**4b**): 87% (80 °C, 6 h)

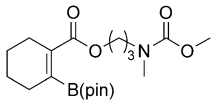
*i*Pr (**4c**): 77% (120 °C, 3 h)
*t*Bu (**4d**): 85% (120 °C, 2.5 h)
Ph (**4e**): 96% (80 °C, 6 h)

X = Cl (**4f**): 86% (120 °C, 8 h)

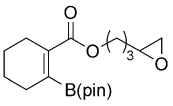
CF_3 (**4g**): 93% (120 °C, 3 h)
OMe (**4h**): 83% (120 °C, 1 h)

R = Me (**4i**): 65% (120 °C, 2 h)

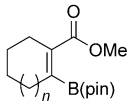
OMe (**4j**): 74% (120 °C, 16 h)



(**4k**)
72% (120 °C, 1 h)



(**4l**)
79% (120 °C, 0.5 h)

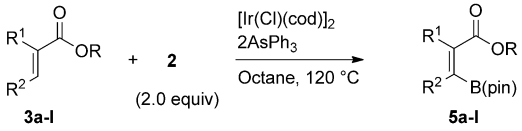


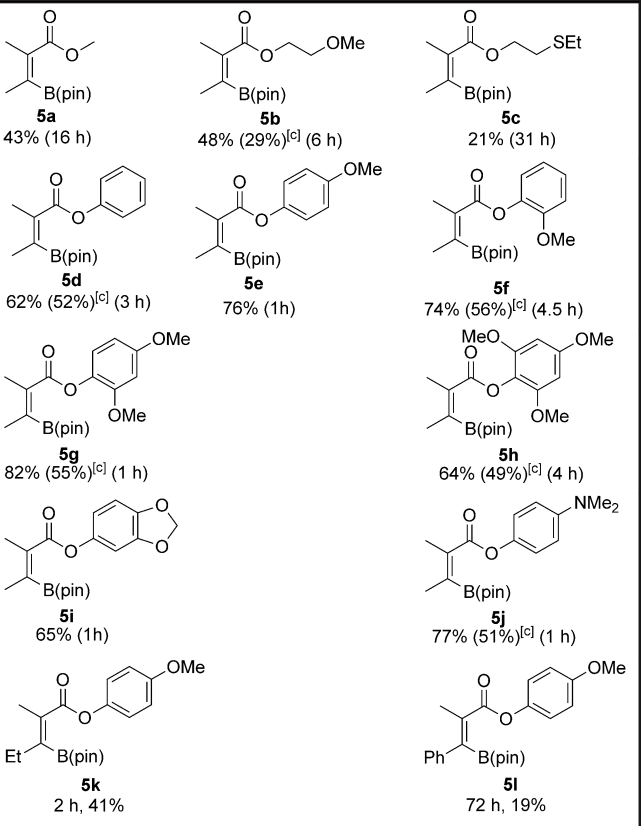
n = 0 (**4m**): 20% (120 °C, 16 h)

2 (**4n**): 43% (120 °C, 16 h)
3 (**4o**): 35% (120 °C, 16 h)

[a] Reaction conditions: esters **1b–o** (0.5 mmol), **2** (0.55 mmol), $[Ir(OMe)(cod)]_2$ (1.5 mol%), $AsPh_3$ (6.0 mol%) in octane (3 mL). [b] Yields were determined by GC analysis. [c] 2.5 mol% $[Ir(OMe)(cod)]_2$ and 10.0 mol% $AsPh_3$ were used.

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





5a
43% (16 h)

5b
48% (29%)[c] (6 h)

5c
21% (31 h)

5d
62% (52%)[c] (3 h)

5e
76% (1h)

5f
74% (56%)[c] (4.5 h)

5g
82% (55%)[c] (1 h)

5h
64% (49%)[c] (4 h)

5i
65% (1h)

5j
77% (51%)[c] (1 h)

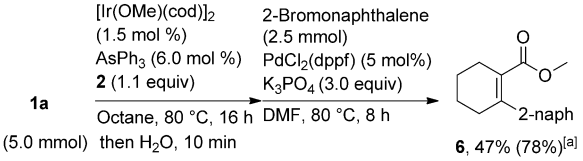
5k
2 h, 41%

5l
72 h, 19%

[a] Reaction conditions: esters **3a–l** (0.5 mmol), **2** (1.0 mmol), $[Ir(Cl)(cod)]_2$ (1.5 mol%), and $AsPh_3$ (6.0 mol%) in octane (3 mL). [b] Yields were determined by GC analysis. [c] Isolated yield.

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 equivalents of **2** proceeded at 120 °C in the presence of $[Ir(Cl)(cod)]_2$ (1.5 mol%) as the catalyst precursor and $AsPh_3$ (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 thioether **3c** substrates showed moderate-to-low 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 alkenylboronate **5d** increased (**5d**: 62%). Based on the higher yield of this reaction, we proceeded to examine the borylation of various aryl esters. The reactions of the *para*- and *ortho*-methoxyphenyl esters **3e** and **3f** proceeded smoothly to give the desired alkenylboronates **5e** and **5f** in 76 and 74% yields, respectively. Notably, 2,4-dimethoxyphenyl ester **3g** showed 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 **5g** (64%). The benzodioxole ester **3i**, bearing an *ortho*-dialkoxyphenyl moiety, reacted with **2** to afford the boronate **5i** in moderate yield (65%). The borylation of *para*-dimethylaminophenyl ester **3j** produced alkenylboronate **5j** in 77% yield. Several sterically congested substrates, including 4-methoxyphenyl-(*E*)-2-methylpent-2-enoates **3k** and 4-methoxyphenyl-(*E*)-2-methyl-3-phenylacrylate **3l**, were also evaluated but showed 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.

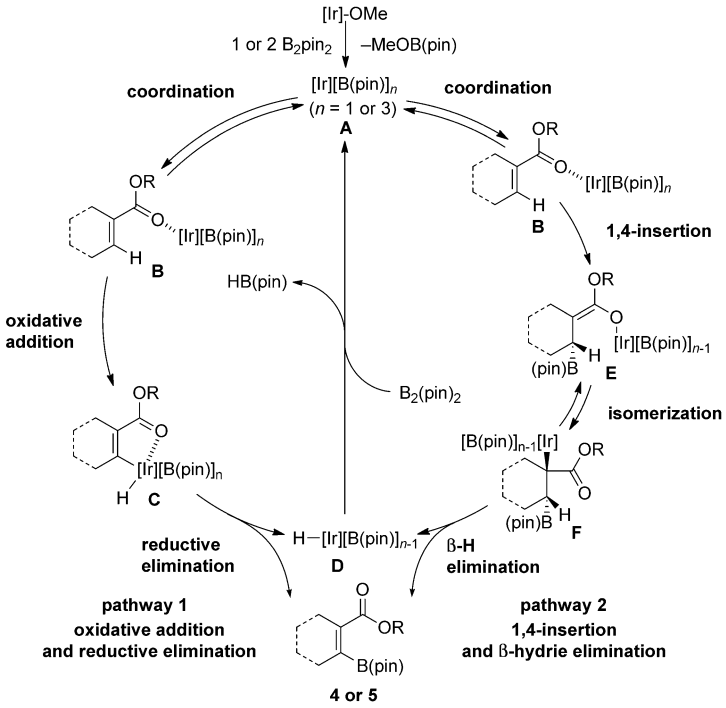
We then investigated the one-pot synthesis of a bioactive compound through a sequential vinylic C–H borylation/cross-coupling reaction (Scheme 2).[13] Compound **6** has been reported to be an inhibitor of monoamine transporters.[14] The alke-



Scheme 2. One-pot borylation/Suzuki–Miyaura cross-coupling procedure. [a] GC yield based on 2-bromonaphthalene.

nylboronate **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), K_3PO_4 (3.0 equiv), and $PdCl_2$(dppf) (5 mol%) (dppf = diphenylphosphinoferrocene) to the reaction mixture without evaporating 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.

The two catalytic cycles proposed for the current transformation are shown in Scheme 3. Both of these cycles would involve the initial formation of the mono- ($n=1$) or tris- ($n=3$) boryliridium complex **A** by the reaction of the corresponding Ir^{I} complex with B_2pin_2.[15] According to pathway 1, the electron-donating oxygen atom of the ester group would coordinate to the Ir metal center of complex **A** to give complex **B**, which would undergo an oxidative addition to the vinylic C–H bond to produce the pseudo metallacycle **C**. The subsequent reductive elimination of the Ir-hydride complex **D** would lead to the formation of the desired products **4** or **5**. Finally, the oxidative addition of B_2pin_2 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 insertion reaction to the iridium enolate **E**.[16] 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**.



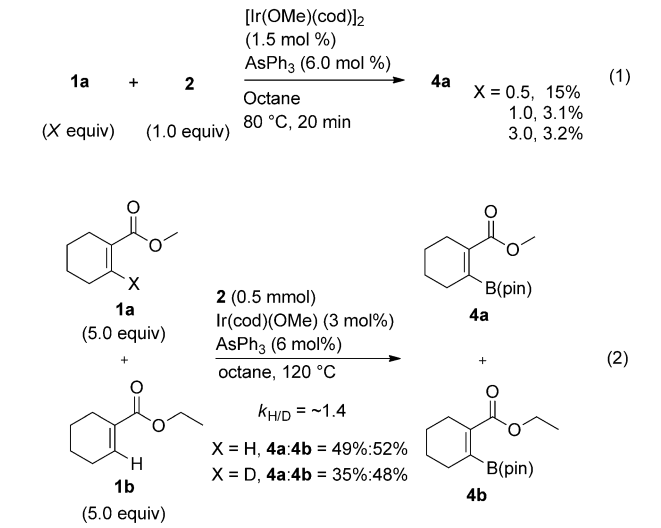
Scheme 3. Proposed mechanism.

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 a 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.

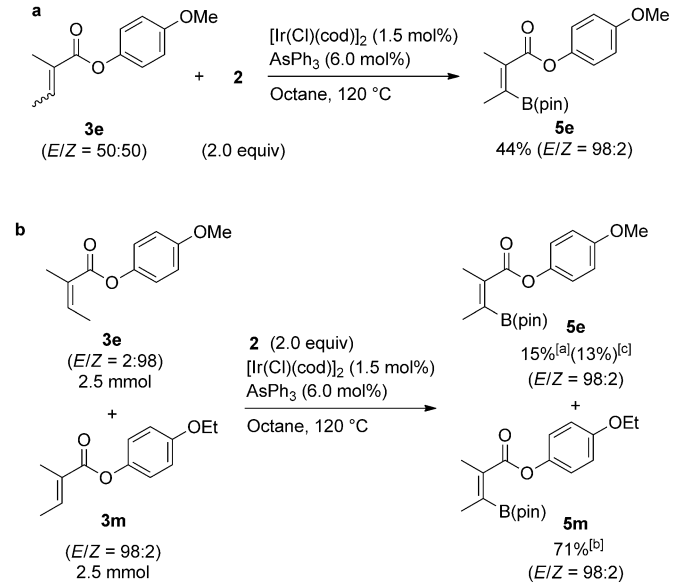
It is noteworthy that the borylation of acyclic compounds under these conditions afforded the (*E*)-products selectively. When a 50:50 (mol/mol) mixture of the (*E*)- and (*Z*)-isomers of **3e** was used as the substrate, both of the isomers were consumed at the same rate. However, this reaction afforded 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*)-*para*-ethoxyphenyl 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)

Conclusions

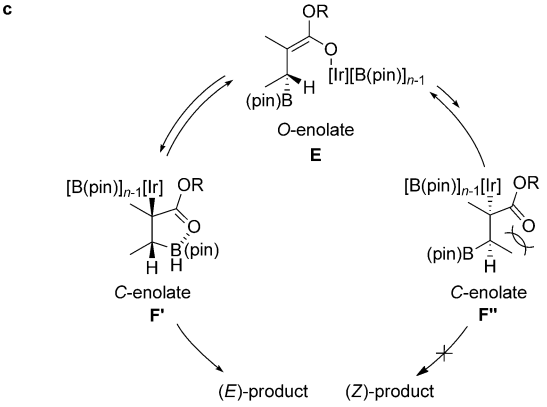
In summary, the iridium complexes prepared by the reaction of $[Ir(OMe)(cod)]_2$ and $[Ir(Cl)(cod)]_2$ with $AsPh_3$ have been shown to be efficient catalysts for the vinylic C–H borylation of α,β-unsaturated esters with **2**. These borylation reactions proceeded at the vinylic position with good chemo- and stereoselectiv-



Scheme 4. Investigation of the reaction mechanism.



[a]GC yield based on (*Z*)-**3e**. [b]GC yield based on (*E*)-**3m**.
[c]2.5 mmol of **3m** was only employed in the borylation.



Scheme 5. Selectivity of the borylation of acyclic esters.

ity, 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 showed good functional group tolerance towards a wide range of functional groups, including halogen, acyl, alkoxycarbonyl, carbamoyl, and epoxy groups. The results of crossover 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).

$[Ir(OMe)(cod)]_2$ (4.97 mg, 0.0075 mmol), bis(pinacolato)diboron (**2**) (140 mg, 0.55 mmol), and $AsPh_3$ (9.19 mg, 0.030 mmol) were placed in an oven-dried two neck flask. The flask was subsequently connected to a vacuum/nitrogen manifold through a rubber tube and vacuum purged with nitrogen three times. Octane (3 mL) was added to the flask through a rubber septum, and the resulting mixture was stirred at room temperature for 10 min. Compound **1a** (70.1 mg, 0.5 mmol) 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 column chromatography over silica gel (EtOAc/hexane, 1:99–5:95) to give the corresponding alkenylboronate **4a** as a colorless oil.

Acknowledgements

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Keywords: alkenyl boronates · borylation · diboron · iridium · α,β-unsaturated esters

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