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Iridium(I)-catalyzed vinylic C–H borylation of 1-cycloalkenecarboxylates with bis(pinacolato)diboron†

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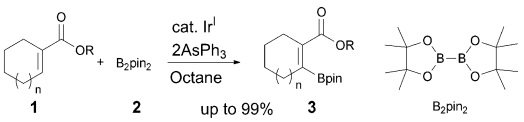
Ikuo Sasaki, Hana Doi, Toshiya Hashimoto, Takao Kikuchi, Hajime Ito* and Tatsuo Ishiyama*

Ir(I)-catalyzed C–H borylation of 1-cycloalkenecarboxylic derivatives with bis(pinacolato)diboron affords various alkenylboronates with functional groups in excellent yields. This reaction was also used in a one-pot borylation/Suzuki–Miyaura cross-coupling procedure.

1-Alkenylboronates are an important class of compounds and are versatile intermediates in synthetic organic chemistry.[1] Their utility has been amply demonstrated in the synthesis of natural products and biologically active compounds *via* C–C bond formation with C–B bonds.[2] Conventional methods for the preparation of alkenylboronates 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 bis(pinacolato)diboron (B_2pin_2) (**2**) or pinacolborane (HBpin).[3] An alternative process involving the transition-metal-catalyzed C–H borylation of alkenyl compounds was recently reported.[4–6] Although this method is more economical and environmentally benign than the above conventional methods, the use of such reactions is still limited for cyclic vinyl ethers[5] and suffers from the formation of a number of different side products such as allylboronates and alkylboronates.[6c,d,f,g,i]

Very recently, we reported the regioselective direct *ortho* borylation of various benzoates or aryl ketones using the complex $[Ir(OMe)(cod)]_2$/P[3,5-$(CF_3)_2C_6H_3]_3$ or $AsPh_3$.[7] At the same time, several groups, including Sawamura's,[8] Lassaletta's,[9] and Hartwig's groups,[10] also reported similar borylation of functionalized arenes. The regioselectivity of these reactions is probably driven by the interaction between the coordinating O and N atoms in the directing group and the Ir metal center.[7–9] So far, these methods have only been used in the C–H borylation of arenes; to the best of our knowledge, C–H borylation at the vinyl position of α,β-unsaturated esters has not been reported previously. In this communication, we describe a vinylic C–H borylation of 1-cycloalkenecarboxylate **1** with **2**, catalyzed using an *in situ*-generated Ir complex consisting of readily available $[Ir(OMe)(cod)]_2$ and $AsPh_3$ in octane solvent. The reaction proceeded chemoselectively at 80 °C or 120 °C to give the corresponding alkenylboronic compounds **3** in high yields (Scheme 1). This reaction was used in a one-pot borylation/Suzuki–Miyaura cross-coupling procedure to afford the 2-aryl-substituted 1-cycloalkenecarboxylate in good yield; this carboxylate showed biological activity.



Scheme 1 Vinylic C–H borylation of 1-cycloalkenecarboxylates.

We initially examined the borylation of methyl 1-cyclohexenecarboxylate **1a** under the optimum conditions for the borylation of 1,4-dioxene; we previously reported that a complex of $[Ir(OMe)(cod)]_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) catalyzed vinylic C–H borylation in good yields and with good selectivities.[5] 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 dtbpy (3 mol%) as the ligand, in octane solvent at 120 °C afforded the desired product **3a** in only 11% yield after 16 h (Table 1, entry 1). We then screened possible ligands (entries 2–8). Notable improvements in yields were not observed in the reactions with various phosphine ligands (**3a**: 4–20% after 16 h, entries 2–7). The use of $AsPh_3$, which can weakly coordinate with an Ir metal center, significantly improved the yield of **3a**, with a shorter reaction time (85%, 1 h, 90%, 16 h, entry 8).[11] The use of less-polar and poorer electron-donating solvents gave much better results than the more-polar and better electron-donating solvents (octane: 90%, mesitylene: 51%, diglyme: 0%, DMF: 0%, entries 8–11). An appropriate choice of Ir catalyst precursor was crucial for this borylation. Although the combination of $[IrCl(cod)]_2$ and $AsPh_3$ gave **3a** in good yield (84%, entry 12), no desired product was obtained when $[Ir(cod)_2]BF_4$ was used (entry 13). The borylation proceeded smoothly, even at 80 °C (99%, entry 14). Under these conditions, a reaction with a lower loading of $[Ir(OMe)(cod)]_2$ (0.5 mol%) also gave **3a** in reasonable

Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan.
E-mail: ishiyama@eng.hokudai.ac.jp; Fax: +81 11 706 6562; Tel: +81 11 706 6562

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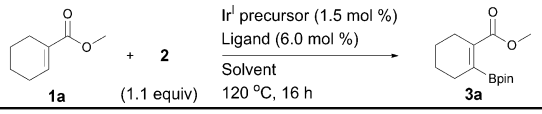
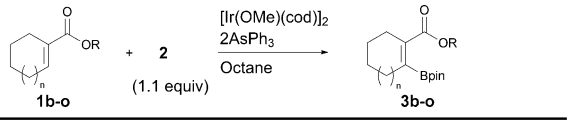
Table 1 Reaction conditions for methyl 1-cyclohexenecarboxylate **1a**[a]

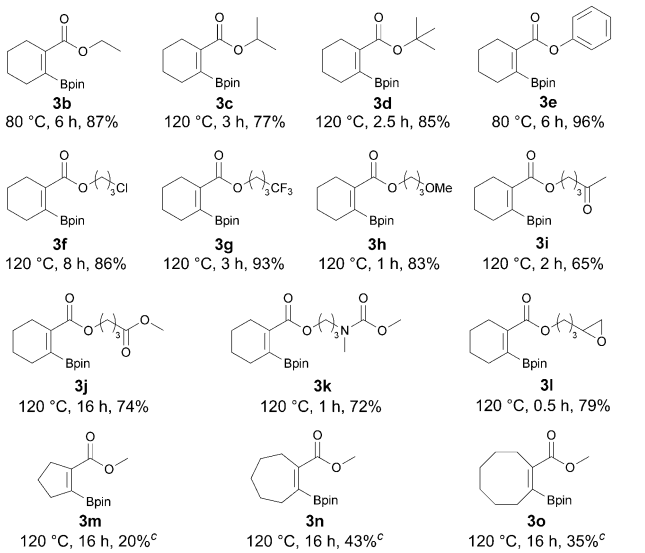


Entry	Ir^I precursor	Ligand	Solvent	Yield[h] (%)
1	$[Ir(OMe)(cod)]_2$	dtbpy[g]	Octane	11
2	$[Ir(OMe)(cod)]_2$	$P(C_6H_5)_3$	Octane	20
3	$[Ir(OMe)(cod)]_2$	$P(OC_6H_5)_3$	Octane	4
4	$[Ir(OMe)(cod)]_2$	$P(4\text{-}MeOC_6H_4)_3$	Octane	0
5	$[Ir(OMe)(cod)]_2$	$P(4\text{-}CF_3C_6H_4)_3$	Octane	19
6	$[Ir(OMe)(cod)]_2$	$P[3,5\text{-}(CF_3)_2C_6H_3]_3$	Octane	14
7	$[Ir(OMe)(cod)]_2$	$P(C_6F_5)_3$	Octane	10
8	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Octane	90 (85)[i]
9	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Mesitylene	51
10	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Diglyme	0
11	$[Ir(OMe)(cod)]_2$	$AsPh_3$	DMF	0
12	$[Ir(Cl)(cod)]_2$	$AsPh_3$	Octane	84
13[b]	$[Ir(cod)_2]BF_4$	$AsPh_3$	Octane	0
14[c]	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Octane	99 (87)[j]
15[c,d]	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Octane	81
16[e]	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Octane	99
17[f]	$[Ir(OMe)(cod)]_2$	$AsPh_3$	Octane	6

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.55 mmol), Ir^I precursor (0.0025–0.0075 mmol), ligand (0.01–0.03 mmol), solvent (3 mL). [b] 3 mol% $[Ir(cod)_2]BF_4$ was used. [c] Reaction was carried out at 80 °C. [d] 0.5 mol% $[Ir(OMe)(cod)]_2$ and 2.0 mol% $AsPh_3$ were used. [e] 5.0 equiv. of **1a** with respect to **2** were used. [f] HBpin (0.55 mmol) was used. [g] 3 mol% dtbpy was used. [h] Yield was determined by GC analysis. [i] Reaction time 1 h. [j] Isolated yield.

Table 2 C–H borylation of various esters[a,b]



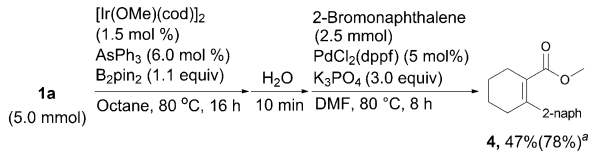


[a] Reaction conditions: ester (0.5 mmol), **2** (0.55 mmol), $[Ir(OMe)(cod)]_2$ (0.0075 mmol), $AsPh_3$ (0.03 mmol), octane (3 mL). [b] Yields were determined by GC analysis. [c] $[Ir(OMe)(cod)]_2$ (0.0125 mmol), $AsPh_3$ (0.05 mmol).

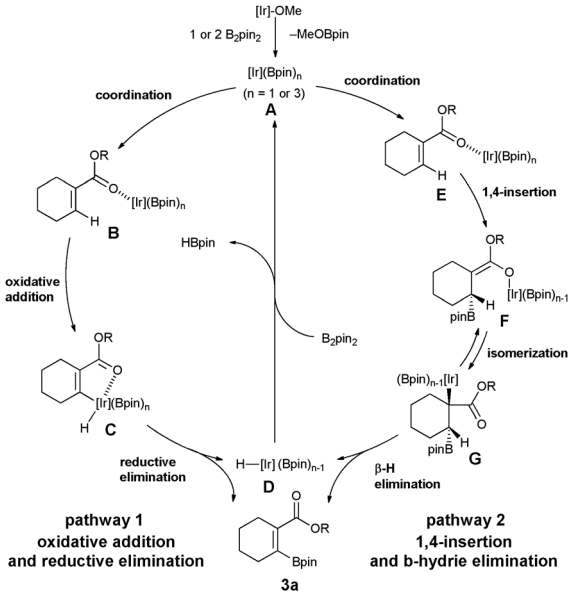
yield (81%, entry 15). No increase in the yield of **3a** was achieved using 5.0 equiv. of **1a** with respect to **2** (99%, entry 16). The product **3a** was obtained in only 6% yield when HBpin was used instead of **2** (entry 17).

With the optimized conditions in hand, we next investigated the availability of the ester side-chain and the reactivity dependence on the ring size of the substrate; the borylation of various 1-cycloalkenecarboxylic substrates was examined (Table 2). Ethyl ester **1b** exhibited similar reactivity to that of methyl ester **1a**, producing the corresponding alkenylboronate **3b** in 87% yield. Even the more sterically congested substrates isopropyl ester **1c** and *tert*-butyl ester **1d** showed good reactivity at 120 °C, affording the corresponding **3c** and **3d** in 77% and 85% yields, respectively. Reaction of phenyl ester **1e** gave only the vinylic borylation product **3e** in 96% yield at 80 °C. It is noteworthy that the phenyl group, which has five $C(sp^2)$–H bonds and would be reactive in Ir-catalyzed borylation, remained intact in the reaction with **1e**.[7,8] Although some transition-metal complexes exhibit high reactivity toward C–Cl bonds, 3-chloropropyl ester **1f** underwent borylation at the vinylic C–H bond, in high yield, without any side reactions involving the C–Cl bond (86%). We then examined the borylation of CF_3-containing ester **1g**; the CF_3 group is very important in drug design because it enhances the biological activity. The reaction of **1g** afforded **3g** in 93% yield. The 3-methoxy ester **1h** reacted completely with **2** within 1 h to produce **3h** in high yield (83%). The reactions of ketone **1i**, ester **1j**, and carbamate **1k** proceeded at 120 °C to afford **3i** (65%), **3j** (74%), and **3k** (72%), respectively. Although competitive coordination of the carbonyl group in the side-chain would inhibit direct borylation, these results showed that the side-chain carbonyl group did not have a serious detrimental effect on the reactivity of the borylation. Epoxide **1l** reacted without substrate decomposition, and the borylation product **3l** was obtained in 79% yield after 0.5 h. Unlike the cyclohexene-type substrate discussed above, the reactions of cycloalkenyl substrates with five-, seven-, and eight-membered rings resulted in low product yields, even under harsher reaction conditions (120 °C with 2.5 mol% $[Ir(OMe)(cod)]_2$ and 10 mol% $AsPh_3$) than those used for the cyclohexene-type substrate. Although the five-membered ring **1m** and **2** were completely consumed in the reaction, the product **3m** was obtained in low yield (20%). The reactions of the seven-membered ring **1n** and eight-membered ring **1o** also gave the alkenylboronates **3n** and **3o** in low yields, though the substrates were completely consumed. We speculate that **1m–1o** decomposed under the reaction conditions.

We performed a one-pot synthesis of a bioactive compound *via* a vinylic C–H borylation/cross-coupling sequence (Scheme 2).[12] Compound **4** has been reported to be an inhibitor of monoamine transporters.[13] The alkenylboronate **3a** was prepared from **1a** under the optimized conditions shown in Table 1, and then distilled water was added to the mixture to hydrolyse HBpin that was generated by the Ir-catalyzed borylation. Finally, the subsequent cross-coupling reaction was conducted by adding 2-bromonaphthalene (2.5 mmol), K_3PO_4 (3.0 equiv.), and $PdCl_2$(dppf) (5 mol%), without solvent evaporation and product purification.



Scheme 2 One-pot synthesis of **4**. [a] GC yield based on 2-bromonaphthalene.



Scheme 3 Proposed catalytic cycle.

The cross-coupling product **4** was obtained in 47% yield (78%, GC yield) from the two-step reaction.

Two proposed catalytic cycles are shown in Scheme 3. In both the catalytic cycles, the mono- (n = 1) or tris- (n = 3) boryliridium complex **A** is first produced by reactions of Ir(I) complexes with B_2pin_2.[14] In pathway 1, involving oxidative addition and reductive elimination, the electron-donating oxygen atom in the ester group coordinates with the Ir metal center (complex **B**, Scheme 3), and then oxidative addition of the vinylic C–H bond to **A** produces the pseudo-metallacycle **C**. After reductive elimination, the Ir–hydride complex **D** and the product **3a** are produced. Finally, oxidative addition of B_2pin_2 to **D**, followed by reductive elimination of HBpin, regenerates **A**. In pathway 2, involving a 1,4-insertion and β-hydride elimination, the 1,4-insertion of the carbonyl-coordinated complex **E** produces the iridium enolate **F**.[15] The subsequent isomerization of **F** affords the Ir complex **G**, which has an Ir–C bond with a *syn* configuration between the Ir center and the β-H. The product **3a** and **D** are then formed through β-hydride elimination from the C-enolate Ir complex **G**.

In summary, an iridium complex consisting of $[Ir(OMe)(cod)]_2$ and $AsPh_3$ was found to be an efficient catalyst for the vinylic C–H borylation of 1-cycloalkenecarboxylic derivatives with **2**. This borylation proceeded at the vinylic position with good selectivity, even though substrates have a phenyl group which would be reactive in Ir-catalyzed borylation. Additionally, the borylation of substrates containing various functional groups such as halogen, acyl, alkoxycarbonyl, carbamoyl, and epoxy groups afforded the corresponding products. Bipyridine, phosphine, and NHC ligands have been used for aromatic and alkenyl C–H borylation, but the present results show the first vinylic C–H borylation using $AsPh_3$. Additionally, a one-pot borylation/cross-coupling procedure for the rapid synthesis of a drug candidate was also conducted, and shows the synthetic usefulness of this reaction.

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