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C–H Activation

Selective One-Pot Carbon–Carbon Bond Formation by Catalytic Boronation of Unactivated Cycloalkenes and Subsequent Coupling**

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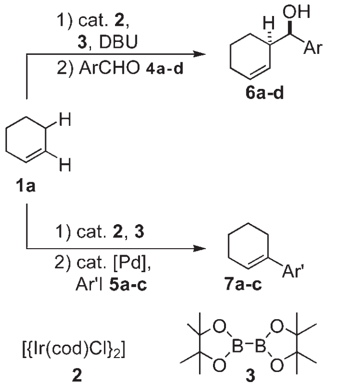
Selective formation of new C–C bonds by activation of allylic or vinylic C–H bonds is a challenging task in organic synthesis. Previous work by Hartwig, Ishiyama, Marder, Miyaura, Smith , and their co-workers[1] has shown that the formation of C–C or C–heteroatom bonds can be initiated by boronation[2a] of aromatic substrates based on C–H activation. Likewise, we[3a–e] and others[3f] have demonstrated previously that catalytic formation of transient allyl boronates[2] followed by one-pot coupling with aldehydes or aryl halides is an efficient route for the synthesis of densely functionalized products from inexpensive starting materials. Nevertheless, the synthetically useful application of unactivated alkenes as substrates for C–C bond-forming reactions raises selectivity issues, as both C(sp^2)–H and C(sp^3)–H bonds are available for functionalization.[4]

We have now found that selective C–C bond formation can be achieved in cycloalkenes such as **1a**–**c** by employing an Ir-catalyzed C–H activation/boronation reaction. The transient organoboranes can react further with either aldehydes or alternatively with aryl iodides in a one-pot sequence (Scheme 1). The regioselectivity can be controlled by addition of 1,8-diazabicyclo[5.4.0]undecane (DBU). Accordingly, when a mixture of Ir catalyst **2** (2 mol %), diboronate **3** (1.0 equiv), and DBU (0.5 equiv) in neat cyclohexene (**1a**) was stirred at 70 °C for 4 h and then aldehydes **4a**–**d** were added, homoallyl alcohols **6a**–**d** were obtained with excellent stereoselectivity[2–3] and good yields (Table 1). On the other hand, when a mixture of **2** and **3** in neat cyclohexene (**1a**) was heated at 70 °C for 16 h, followed by addition of aryl iodides, 5 mol % [Pd(PPh_3)$_4$], and Cs_2CO_3 in dioxane/water (4:1), Suzuki–Miyaura coupling[5] provided the arylated alkenes **7a**–**c** in high yields (Table 1, entries 5–7). The allylation reactions were also attempted using cycloheptene (**1b**) and cyclooctene (**1c**) instead of **1a**; however, in the presence of DBU only unreacted starting material could be observed in the reaction mixture. On the other hand, the functionalization of the vinylic C–H bond (Table 1, entries 8 and 9) occurred at elevated temperatures (90–100 °C).

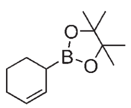


Scheme 1. Selective functionalization of cyclohexene (**1a**). cod = 1,4-cyclooctadiene.

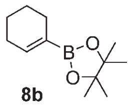
The one-pot C–H activation/C–C bond-formation reaction has a high functional group tolerance as aromatic bromo, chloro, and nitro substituents (Table 1, entries 2, 3, 6, and 7) remained unchanged under the employed reaction conditions. The allylation reactions proceeded with excellent stereoselectivity, providing a single diastereomer for both aryl (Table 1, entries 1–3) and vinyl aldehydes (Table 1, entry 4). So far, the synthetic scope of the reaction is limited to cycloalkenes, as acyclic substrates (such as 1-decene) gave only intractable mixtures under the employed reaction conditions.

We attempted to replace **2** with other catalyst precursors, such as [(η^5-indenyl)Ir(cod)], [Ir(PCy_3)(cod)(py)]PF_6 (Cy = cyclohexyl, py = pyridine), and [{Rh(cod)Cl}$_2$], which have been employed in other C–H activation reactions;[1,4] however these catalysts gave only traces or no product at all under the employed reaction conditions (Scheme 1). Application of other amines instead of DBU (such as Et_3N, tetramethylethylenediamine, and 4,4′-di-*tert*-butyl-2,2′-bipyridine) and phosphine ligands (such as P(OPPh)$_3$, 1,2-bis(diphenylphosphanyl)ethane, and diphenylphosphinoferrocene) did not increase the yields of the allylation reactions (Table 1, entries 1–4).

Analysis of the ^{1}H NMR spectrum of the boronation reactions (step 1 in Scheme 1) clearly indicated formation of allyl boronate **8a** and vinyl boronate **8b** as intermediates. A 1:1 mixture of **8a**/**8b** was observed after 3 h at 70 °C; in contrast after 16 h at 70 °C exclusively **8b** was observed.



8a



8b

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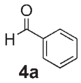
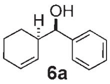
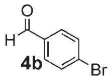
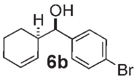
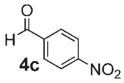
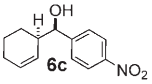
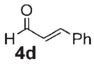
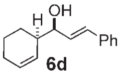
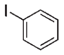
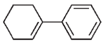
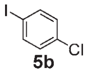
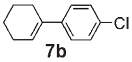
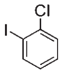
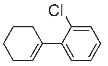
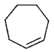
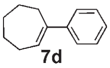
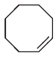
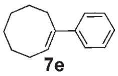
Table 1: One-pot synthesis of stereodefined homoallyl alcohols **6** and aryl cycloalkenes **7** by catalytic C–H activation.[a]

Entry	Substrates		Boronation T [°C]/t [h]	Method[b]	Coupling T [°C]/t [h]	Product	Yield [%][c]
1	 **1a**	 **4a**	70/4	A	40/16	 **6a**	61
2	**1a**	 **4b**	70/4	A	40/3	 **6b**	60
3	**1a**	 **4c**	70/4	A	20/4	 **6c**	57
4	**1a**	 **4d**	70/4	A	40/4	 **6d**	53
5	**1a**	 **5a**	70/16	B	60/16	 **7a**	99
6	**1a**	 **5b**	70/16	B	70/18	 **7b**	90
7	**1a**	 **5c**	70/16	B	70/16	 **7c**	70
8	 **1b**	**5a**	90/4	B	60/16	 **7d**	97
9	 **1c**	**5a**	100/4	B	70/16	 **7e**	72

[a] Reaction conditions: A mixture of catalyst **2** (2 mol%), diboronate **3**, and DBU (entries 1–4) dissolved in neat cycloalkene (**1a–c**) was stirred for the times and temperatures given in the column labeled Boronation followed by application of Method A or B. [b] Method A: After addition of the corresponding aldehyde, the reaction mixture was stirred under the conditions given in the column labeled Coupling. Method B: After addition of a mixture of dioxane/water (4:1), [Pd(PPh$_3$)$_4$] (5 mol%), and base, the reaction mixture was stirred under the conditions given in the column labeled Coupling. [c] Yield of isolated product.

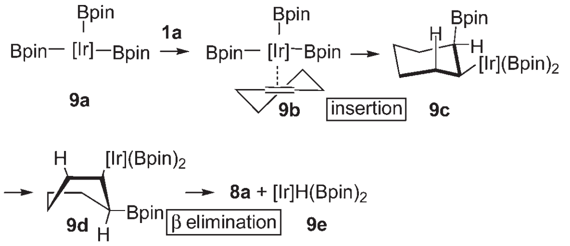
Addition of 0.5 equiv DBU led to a dramatic increase of the **8a**/**8b** ratio (5:1 after 3 h at 70 °C); however, after an extended reaction time (16 h) the amount of **8b** started to increase. The addition of 1.0 equiv DBU strongly retarded the reaction, decreasing the formation of both **8a** and **8b**. In contrast to the reactions with cyclohexene (**1a**), the allyl selectivity could not be increased for **1b** and **1c**, as addition of DBU efficiently inhibited the C–H activation process.

According to the extensive studies of Hartwig, Ishiyama, Marder, Miyaura, Smith, and their co-workers[1d,f,6] the special features of the Ir-catalyzed C–H activation boronation reactions arise from the formation of a tris(boryl)Ir complex such as **9a** (Scheme 2). Although the majority of the Ir-catalyzed C–H activation/boronation studies are described for aromatic substrates, there are a few studies on Rh-[4a] and Ru-catalyzed[4b] processes employed for alkenes. Marder and co-workers[4a] suggested that alkenes can undergo dehydrogenative borylation, which involves insertion of the substrate to the metal–boron bond of the active catalyst (such as **9a**) followed by β-hydride elimination to give vinyl boronates. Probably the same process is the key step of our process (Scheme 1) as well. Thus, the double bond of cyclohexene is inserted into the Ir–B bond of **9b** to give **9c**. Assuming that the insertion proceeds by a *syn* mechanism, the C–B and C–Ir bonds are in *cis* position in adduct **9c**. Because of the hindered rotation of the C–C bonds in **9c**, only the allylic C–H bond is able to adapt to the *syn* conformation (**9d**) required for the β-hydride elimination. This would explain the initial formation of allyl product **8a**. Subsequently, allyl rearrangement of **8a** leads to formation of **8b**, which can be retarded by application of DBU. The molecular geometry required for the β-hydride elimination is probably easiest to realize in the cyclohexane derivative **9d**, while this elimination step is expected to be sluggish for the cycloheptane and cyclooctane analogues for conformational reasons. This may explain the lower reactivity of **1b**,**c** relative to **1a** in the C–H bond-functionalization processes.

The β-elimination reaction results in **9e**, which undergoes reductive elimination to give pinacolborane (HBpin) and to regenerate the catalyst. Pinacolborane is known[4c] to undergo Ir-catalyzed hydroboration of alkenes affording saturated boronates. Thus only one of the boron atoms of **3** can be employed in the above C–H functionalization reactions, as the other one is sacrificed for hydroboration of **1a**, which is present in large excess in the reaction mixture.

The special regioselectivity of the C–H activation of cycloalkenes is probably not restricted to Ir-catalyzed reactions. Sabo-Etienne and Caballero[4b] have shown that the Ru-catalyzed hydroboration (with HBpin) of cycloheptene (**7b**) leads to formation of significant amounts of allyl boronate together with the expected saturated species. Interestingly, this reaction did not give allyl product **8a** when **1a** was used as substrate.[4b]

In summary, we have shown that selective C–C bond formation can be achieved in a one-pot Ir-catalyzed C–H



Scheme 2. Sugegsted mechanism of the boronation of **1a**.

activation/borylation reaction. The regioselectivity of the process can be switched by a slight change in the reaction conditions. To our knowledge this is the first one-pot C–C bond-forming reaction that involves catalytic C–H bond functionalization of unactivated alkenes based on boronation.

Experimental Section

Allylation reactions (Method A): A mixture of catalyst **2** (0.003 mmol, 2 mol%, 2 mg), boronate **3** (0.15 mmol, 38 mg), and DBU (0.075 mmol, 11.4 mg) was dissolved in neat **1a** (1.97 mmol, 0.2 mL). Then this reaction mixture was stirred at 70 °C for 4 h. After the reaction mixture had cooled to room temperature, the appropriate aldehyde **6a–d** (0.18 mmol) was added to the mixture, and stirring was continued for the times and temperatures given in Table 1 (see column labeled Coupling). The crude reaction mixture was concentrated to dryness, and the residue was purified by silica gel column chromatography.

Vinyl functionalization (Method B): A mixture of catalyst **2** (0.003 mmol, 2 mol%, 2 mg) and boronate **3** (0.15 mmol, 38 mg) was dissolved in neat **1a–c** (0.1 mL). The reaction mixture was stirred for the given times and temperatures in Table 1 (Boronation). After the reaction mixture had cooled to room temperature, it was diluted with a dioxane/water (4:1) mixture (0.25 mL). The appropriate aryl iodides **5a–c** (0.15 mmol), Cs_2CO_3 (0.30 mmol, 97 mg), and $[Pd(PPh_3)_4]$ (0.0075 mmol, 5 mol%, 8 mg) were added. The reaction mixture was stirred for the times and temperatures given in Table 1 (Coupling).

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