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Alkene Borylation

Selective C–H Borylation of Alkenes by Palladium Pincer Complex Catalyzed Oxidative Functionalization**

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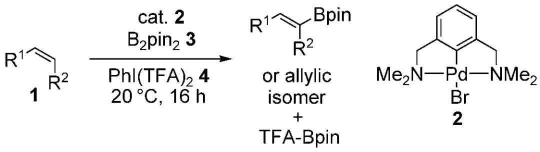
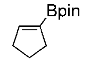
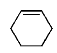
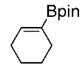
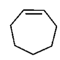
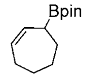
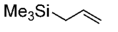
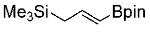
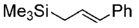
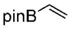
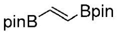
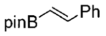
Selective C–H borylation reactions are an important emerging field in synthetic organic chemistry.[1] Using this methodology, easily accessible alkanes, alkenes, and aromatic compounds can be converted into highly value-added organoboronates in a single step.[2–3] Unlike many C–H functionalization processes, C–H borylation reactions can be conducted under relatively mild conditions using moderate temperatures. The majority of the known C–H borylation processes employ iridium,[2a–f,3] rhodium,[2g–m] or ruthenium[2n–o] catalysts. Interestingly, palladium catalysis, which is widely used in both C–H functionalization[4] and borylation reactions,[5] has been employed relatively rarely.[2p–s] In particular, only a limited number of studies[2r–s] have been performed on the palladium-catalyzed borylation of alkenes using C–H functionalization. One possible reason for this is that palladium is not efficient in cleaving vinylic/allylic C–H bonds under the typical reducing conditions of borylation processes, using diboronates or borohydrides as boronate sources. Herein, we present a new concept for the palladium-catalyzed C–H borylation of alkenes (**1**) using oxidative conditions in the presence of diboronates (Scheme 1).



Scheme 1. Palladium-catalyzed C–H borylation of alkenes. TFA = trifluoroacetate.

We have found that simple alkenes (**1**) can be selectively borylated by palladium catalyst **2** using bis(pinacolato)diboron (B$_2$pin$_2$, **3**). An essential component of the borylation reaction is hypervalent iodine[4d–e] species **4**. The borylation reactions can be performed at ambient temperature in neat or diluted alkenes. Simple cycloalkenes **1a–c**, allylsilane **1d**, and vinylboronate **1e** were readily borylated using **3** as the boron source and **4** as the oxidant. In this process, one of the boron atoms of **3** forms a C–B bond with the organic substrate, whilst the other atom is oxidized to boron trifluoroacetate (TFA-Bpin). Accordingly, borohydrides, which are typical side-products in the analogous iridium-catalyzed process,[3] do not form under the oxidative conditions. In fact, very few catalyst systems (such as the rhodium-based system reported by Marder and co-workers[2i,j]) are known to employ borohydrides in C–H borylation reactions.[2t] Usually, the formation of borohydrides leads to subsequent hydroboration of the alkene substrate, which affords an inseparable mixture of alkyl and alkenyl boronates.[3] Therefore, a clear synthetic advantage to applying oxidative conditions is that the alkenyl (or allyl) boronates **5–8** and **10** can be isolated in their pure form (Table 1). The highest yields are obtained using NCN pincer-complex catalyst **2**,[6a–b] which is an efficient catalyst for the preparation[6c–d] of various organometallic compounds. The reaction is also catalyzed by Pd(OAc)$_2$; however, the yields drop substantially (Table 1, c.f. entry 1 with 3; and 4 with 5).

Table 1: Catalytic oxidative C–H borylation of alkenes.[a]

Entry	Substrate		Catalyst	Method[b]	Product		Yield [%][c]
1		**1a**	**2**	A		**5**	73
2		**1a**	**2**	B		**5**	76
3		**1a**	Pd(OAc)$_2$	A		**5**	31
4		**1b**	**2**	A		**6**	61[d]
5		**1b**	Pd(OAc)$_2$	A		**6**	22[d]
6		**1c**	**2**	A		**7**	57[d]
7		**1d**	**2**	B		**8**	51
8		**1d**	**2**	C		**9**	71
9		**1e**	**2**	B		**10**	86
10		**1e**	**2**	C		**11**	86

[a] Catalyst **2** (5 mol%), diboronate **3**, oxidant **4**, and alkene **1** were stirred for 16 hours at 20 °C. [b] Method A: reaction was performed in neat alkene. Method B: CH$_2$Cl$_2$ (0.1 mL) was added. Method C: the reaction was terminated by a Suzuki–Miyaura coupling. [c] Yield of isolated product, (apart from entry 9: yield determined by NMR spectroscopy). [d] Ratio of vinylic/allylic products: 4:1 (entry 4), 1:1 (entry 5), and 1:6 (entry 6).

The reactions were performed either in neat alkene (method A) or using excess of alkene in dichloromethane (method B). Decreasing the alkene concentration usually led to a drop in yield. Addition of base, water, and excess phenyl

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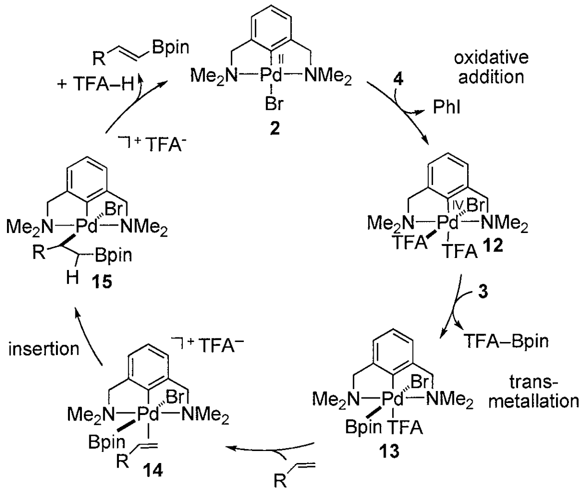
iodide to the crude reaction mixture led to a subsequent Suzuki–Miyaura coupling[7] of the vinylboronates (Table 1, entries 8 and 10). The base and water destroyed pincer-complex **2** and the palladium that was released was able to catalyze the coupling reaction. Accordingly, palladium catalyzes two processes in this one-pot procedure: the C–H borylation and then the Suzuki–Miyaura coupling reactions. The products of the borylation reaction (**5**–**8**) are fairly stable on silica gel; therefore, they were purified by flash chromatography with various losses in yield owing to purification. The exception is diboronate **10**, which completely decomposes under purification by chromatography on silica gel. Therefore, the yield given in Table 1 is determined by ^{1}H NMR spectroscopy of the crude mixture. Although **10** is unstable on silica gel, it reacted in the above described Suzuki–Miyaura coupling (Table 1, entry 10) to afford desymmetrized product **11**.

The borylation reaction usually proceeds with a high vinylic selectivity; however, the substitution pattern of cycloalkenes **1a**–**c** shows an interesting trend. Borylation of cyclopentene (**1a**) provided only vinylic product **5** in high yield; however, the reaction of cyclohexene (**1b**) with **2** as the catalyst resulted in the vinylic (**6**) and allylic forms in a 4:1 ratio (Table 1, entries 1–2 and 4). In the reaction catalyzed by Pd(OAc)$_2$, the selectivity (and yield) dropped, and the vinyl/allyl ratio became 1:1 (Table 1, entry 5). The selectivity was reversed for cycloheptene (**1c**), as the vinylic and allylic products (**7**) were formed in a 1:6 ratio (Table 1, entry 6). Interestingly, Sabo-Etienne and Caballero observed a somewhat similar switch of selectivity in the ruthenium-catalyzed C–H borylation of cycloalkenes.[2o] According to these authors, the allyl/vinyl selectivity is controlled by conformational factors, and the ring flexibility of cycloheptene favors formation of the allylic isomer **7**.

At present, the catalytic process requires cyclic (e.g. **1a**–**c**) or functionalized, terminal acyclic alkene substrates (e.g. **1d** and **1e**) to obtain synthetically useful amounts of pure borylated products. For example, 1-decene undergoes isomerization of the double bond under these catalytic conditions, whilst 3-hexene shows very poor reactivity. An important task is to improve this catalytic procedure with regard to substrate scope, for example by replacing **4** with other oxidants.



Scheme 2. Mechanism for the C–H borylation reaction.

Although the reaction mechanism is not fully understood, the results of this and previous studies[8] help to construct a plausible catalytic cycle (Scheme 2). Our stoichiometric studies (see the Supporting Information) show that **4** easily oxidizes complex **2** into **12**. We recently reported[8a] that the acetate analogue of **4** is able to oxidize the Pd^{II} atom of **2** into Pd^{IV} and the groups of van Koten[8c] and Canty[4a,8d] also reported that NCN complex **2** is readily oxidized by various I^{III} salts.[4d–e] The electron-deficient Pd^{IV} complex **12** would then undergo facile transmetalation with B$_2$pin$_2$ (**3**) to provide complex **13**. The transmetalation probably proceeds via a four-center transition state, in which fission of the B–B bond occurs simultaneously with the formation of a Pd–Bpin bond and TFA–Bpin bond.[5h] This process probably involves a temporary dissociation of the other TFA ligand to generate a free coordination site for the transmetalation process. Initial formation of the active borylation reagent from **3** and **4** cannot be ruled out; however, we were not able to verify such a process by monitoring the reaction by NMR spectroscopy. After transmetalation, an alkene (e.g. **1**) is coordinated (**14**) and the Bpin ligand undergoes insertion into the double bond to give **15**, which, after an elimination–decomplexation sequence, provides the corresponding organoboronate product and regenerates catalyst **2**. Without the transmetalation step (**12**→**13**), a nucleophilic attack or insertion of the trifluoroacetate ligand would have been expected, as we previously reported that under catalytic conditions, PhI(OAc)$_2$ (in the absence of **3**) is able to acetoxylate alkenes.[8a] The use of **4** has some important benefits, such as its high oxidation potential and the relatively poor nucleophilicity of the released trifluoroacetate. Probably the most important conceptually new feature of this C–H borylation reaction is the possible formation of Pd^{IV} intermediates, such as **12**, which presumably transmetalates with B$_2$pin$_2$ more readily than the Pd^{II} species, the most oxidized species in typical palladium-catalyzed borylation reactions.[5] To the best of our knowledge, there have been only two papers, published by Sneddon and co-workers,[2r–s] on the palladium-catalyzed C–H borylation of alkenes. However, in these studies, borane clusters (pentaborane) were used as the boronate source and the catalytic reaction afforded an isomeric mixture of alkyl/vinyl pentaborane derivatives.

In summary, we have presented a palladium-catalyzed C–H borylation reaction based on an oxidative-functionalization–transmetalation concept. The key steps involve oxidation of the catalyst to a Pd^{IV} species, which then undergoes a facile transmetalation with B$_2$pin$_2$ to deliver the metal-bound boronate moiety for subsequent reaction with the organic substrate. The byproduct is TFA–Bpin, which is inert under the catalytic conditions and can be easily removed during purification. This reaction provides an easy access to pinacolboronates **5**–**8** and offers the possibility of a one-pot Suzuki–Miyaura coupling. This C–H borylation reaction, which uses oxidative functionalization, opens new synthetic routes to organoboronates, which are very important, environmentally benign reagents in modern organic synthesis.[1–3,5,7]

Experimental Section

General procedure: **2** (5 mol%), **3** (0.30 mmol), and **4** (0.15 mmol) were dissolved in alkene **1** (1.875 mmol). For Table 1, entries 2 and 7–10, 0.1 mL of dichloromethane was added. Then the reaction mixture was stirred at 20°C for 16 hours and thereafter purified by column chromatography on silica gel. The procedure for the one-pot borylation/vinyl functionalization is given in the Supporting Information.

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