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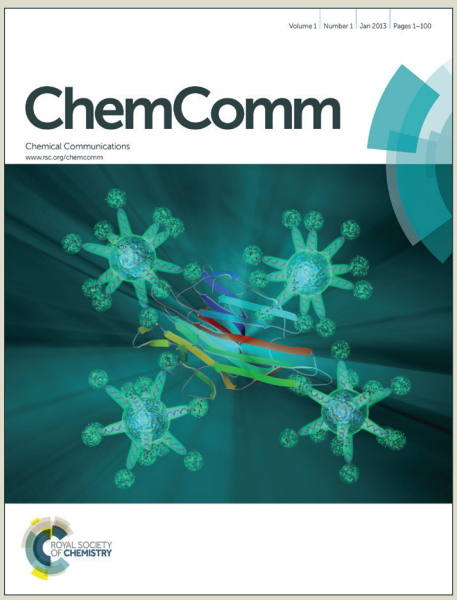

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ARTICLE TYPE

Allylic sp^3 C-H borylation of alkenes via allyl-Pd intermediates. An efficient route to allylboronates†

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Abstract: Palladium catalyzed allylic C-H functionalization was performed using exocyclic alkene substrates. Multi-component synthesis of stereodefined homoallylic alcohols could be performed using a reaction sequence involving allylic C-H borylation and allylation of aldehydes.

Catalytic C-H borylation has become a practically useful synthetic method for preparation of organoboronates.[1] The main reason is that these transition metal catalyzed C-H functionalization reactions can be performed under relatively mild conditions with remarkably high selectivity[1b,c] using usually B_2Pin_2 as boronate source. The largest efforts have been focused on sp^2 C-H borylation of aromatic and alkene substrates to obtain aryl/heteroaryl[2] and vinyl[3]boronates. However, in the last couple of years an increased attention has been focused on development of sp^3 C-H functionalization methods.[4] These studies involved functionalization of aliphatic C-H bonds[4d-h,4l,m,4o-q] usually directed by heteroatoms, benzylic C-H bonds[4i-k] and there are a few examples for allylic C-H borylation[4a-c] as well. A selective allylic C-H borylation[4a-c] is particularly challenging to achieve by two main reasons: i) Under catalytic conditions allylboronates very easily rearrange to the more stable vinylboronates.[3b,c,f,4c] Thus, even if the kinetic product is an allylboronate, the thermodynamic (final) product of the C-H borylation of alkenes give vinylboronate; i.e. an overall sp^2 instead of sp^3 C-H bond functionalization; and ii) For non-symmetrical organometallic intermediates (e.g. allyl or alkyl-metal species) the regioselectivity of the borylation is difficult to control. Therefore, only a very few transition metal catalyzed methods are available for allylic C-H borylation of alkenes[4a-c] and because of i-ii the substrate scope is also very narrow.

The previously developed procedures providing predominantly allylboronate products are based on C-H functionalization of simple cycloalkenes (Figure 1). Sabo-Etienne and Caballero[4a] have shown that cycloheptene undergoes hydroboration and allylic C-H borylation in the presence of catalytic amounts bis(dihydrogen)Ru complex. We have shown[4b,c] that simple cycloalkenes can be reacted with B_2pin_2 in the presence of Ir-catalysts to give allyl-Bpin compounds.

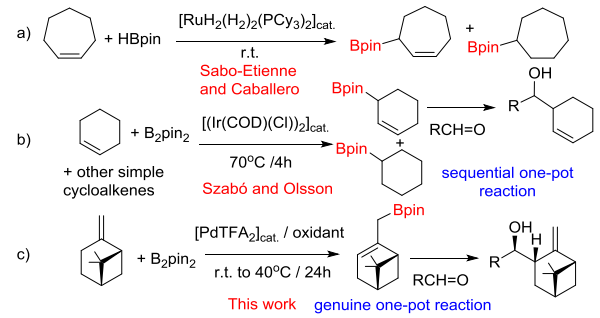
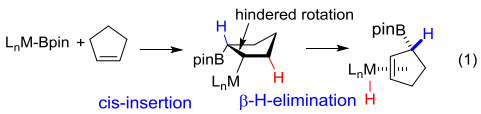


Fig.1 Overview of catalytic allylic C-H borylations

Interestingly, other catalytic conditions with the above endo-cyclic alkene substrates using rhodium[3g] or palladium[3c,f] catalysts also give allyl-Bpin products in varying amounts. However, for substrates with exo-cyclic double bond allylic C-H borylation has never been reported. This can probably be explained by the mechanistic features of the currently available Ru, Rh, Ir and Pd catalyzed methods. In all cases an initial formation of M-Bpin complex can be postulated (eq 1), which undergoes to a syn insertion to the double bond followed by a syn selective β-hydride elimination. However, acyclic compounds can undergo unhindered rotation of the σ-bonds, and therefore the β-hydride elimination may easily result in the thermodynamically more stable vinyl-Bpin form.[4c]



Therefore, we decided to develop a new sp^3 allylic C-H borylation reaction based on an alternative mechanistic concept. We hypothesized that a Pd-catalyzed process based on initial formation of an allyl-Pd complex followed by transmetallation[5] with B_2pin_2 may avoid the termination of the reaction with a β-hydride elimination. The realization of this idea is very challanging, as closing the catalytic cycle (see bellow) requires use of oxidants, while B_2pin_2 is a reductant and allylboronates are sensitive to oxidation.[6]

We directed the initial studies to C-H functionalization of β-pinene **1a**, as these compounds readily form[7] (η^3-allyl)palladium complexes with stoichiometric amounts of Pd-salts. Indeed, when **1a**, **3a,** an appropriate oxidant and catalytic amounts of Pd(TFA)$_2$

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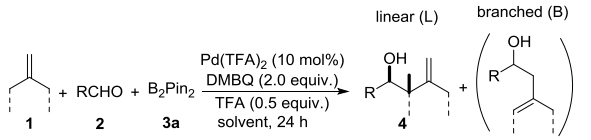
were mixed in $(CD_3)_2CO$, formation of borylated β-pinene was observed (Figure 1c). Using deuterated acetone enabled us to follow the reaction by ^1H NMR. The ^1H NMR of the reaction mixture showed that the reaction was not completed, probably because of product inhibition. When the allylbornate product was quenched with nitro-benzaldehyde (**2**), the corresponding homoallylic alcohol **4a** was formed selectively as a single, regio-stereoisomer.

Table 1. Allylic C-H borylation of alkenes.[a]

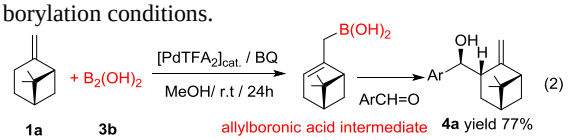


Entry	Alkene	Temp. (°C)/Solvent	Yield (%)[b]	B:L
1	**1a**	rt/$(CD_3)_2CO$	**4a** 78	>50:1
2	**1a**	rt/$(CD_3)_2CO$	**4b**[c] 58	>26:1
3	**1a**	rt/$(CD_3)_2CO$	**4c**[c] 56	>50:1
4	**1b**	40/$PhCF_3$	**4d** 53	>50:1
5	**1c**	40/$PhCF_3$	**4e** 51	>50:1
6	**1d**	40/$PhCF_3$	**4f** 43	>50[d]:1
7[e]	**1e**	rt/$(CD_3)_2CO$	**4g** 51	>50:1
8	**1f**	40/$(CD_3)_2CO$	**4h** 69	8:1
9	**1g**	40/$(CD_3)_2CO$	**4i** 80	2.5:1
10[f]	**1h**	40/$PhCF_3$	**4j** 38	>50:1
11	**1i**	40/$(CD_3)_2CO$	**4k** 14	15[g]:1

[a] Unless otherwise stated the reactions were carried out with **1** (0.1 mmol), **2,** nitro-benzaldehyde (0.2 mmol), **3a** (0.2 mmol), Pd(TFA)2 (0.01 mmol), DMBQ (0.2 mmol) and TFA (0.05 mmol) in solvent (0.2-0.5 mL) for 24 h. [b]Isolated yields for the linear (L) and branched (B) products together. Unless otherwise stated the branched product was isolated as a single diasteromer. [c]PhCHO (entry 2) and n-C_6H_{13}CHO (entry 3) was used instead of nitro-benzaldehyde. [d]d.r. = 9:1. [e]Tetramethyl-benzoquinone instead of DMBQ. [f] Reaction was carried out with **1h** (0.2 mmol) and **2a** (0.1 mmol). [g]d.r. = 3:2. Ar = 4-$NO_2C_6H_4$, DMBQ = 2,6-dimethylbenzoquinone.

Gratifyingly, the entire procedure with **1a**, **2**, **3a**, the oxidant (BQ), TFA and the Pd-catalyst could be performed as a multi-component[8] (or genuine one-pot) reaction (Table 1, entry 1). As we used optically active β-pinene, the multicomponent C-H borylation - allylation sequence gave enantiomerically pure product (**4a**). The structure of **4a** was assigned on the basis of single crystal X-ray diffraction. Subsequently, we studied the synthetic scope of the reaction. We have found that cyclic substrates with exocyclic double bond give synthetically useful yields in the C-H borylation based allylation of aldeheydes (Table 1). In most cases (except with **1a**) we obtained complex mixtures and low yields, when we used BQ as oxidant. However, 2,6-dimethyl BQ (DMBQ) successfully replaced BQ. Deutereted acetone proved to be an ideal solvent in most cases as it allowed to study the crude mixtures by ^1H NMR. In some cases, the process was slow in acetone (e.g. entries 4-6 and 10) and therefore the solvent was changed to trifluoro toluene, which gave a higher reaction rate.

Nitro-benzaldehyde **2** could be replaced by benzaldehyde or aliphatic aldehyde (entries 2-3). The multicomponent reaction is still very selective but the yield was dropped (cf entries 1 and 2-3). The reaction with six-membered ring based substrates **1b-d** gave exclusively the branched allylic products **4d-e** (entries 4-5). There are three stereogenic carbons in product **4f**, thus statistically four diastereomers could be formed. However, the reaction proceeds with a remarkably high stereoselectivity, as only two diastereomers were obtained in a ratio of 9:1 (entry 6). The reactions for the five membered ring based substrate **1e** proceeded faster than for the six membered ring analogs, and therefore the reaction could be conducted at rt. The best yield and selectivity was obtained, when DMBQ was replaced by tetramethyl BQ as oxidant (entry 7). The seven membered ring based substrate **1f** reacted with high yield (entry 8) but the regioselectivity was also lower than for the six-membered ring based substrates. In case of **1g** containing an eight-membered ring the regioselectivity drops to 2.5:1 (entry 9). We had a limited success with borylation of heterocyclic substrates, such as **1h** (entry 10). This compound can also be transformed to **4j** with a high selectivity but the yield is poor and we could not improve it by extensive optimization. For acyclic analogs the yield and the selectivity drops dramatically (entry 11). For example **1i** reacts very slowly and with low conversion probably because of inhibition of the Pd-catalyst. Interestingly, the reaction can be performed with diboronic acid (**3b)** instead of B_2pin_2 with a slight alteration of the reaction conditions (eq 2). This is a reamarkable result, as it shows that highly oxidation sensitive allylboronic acids[6] can also be reaction intermediates under oxidative allylic C-H borylation conditions.



We suggest that the first step of the process is formation of the allyl-palladium complex **5** by deprotonation and palladation of the allylic position of the substrate, such as **1b** (Figure 2).[7] The subsequent step is transmetallation by B_2pin_2. It was shown[5] that these reactions proceed easily, when weakly coordinating ligands are on Pd. This could explain that $Pd(TFA)_2$ is an excellent

catalyst for the process, while $Pd(OAc)_2$ with chelating acetate group is inefficient. Iwasawa and co-workers[9] have recently shown that Pd-Bpin complexes are stable species. The reductive elimination of the Bpin group in **6** is supposed to be fast[5] due to the strong trans influence of the Bpin ligand.[10] It proceeds with a very high regioselectivity leading to the linear allylboronate product. This high regioselectivity is a prerequisite of the high selectivity of the allylation of aldehyde **2** affording the branched homoallylic product **4d**. The reductive elimination involves formation of Pd(0), which have to be reoxidized to close of the catalytic cycle. The main role of the used quinone is reoxidation of Pd(0) to Pd(II). Added trifluoroacetic acid increases the oxidation potential of the quinones and also catalyze the allylboration of the aldehydes.[11]

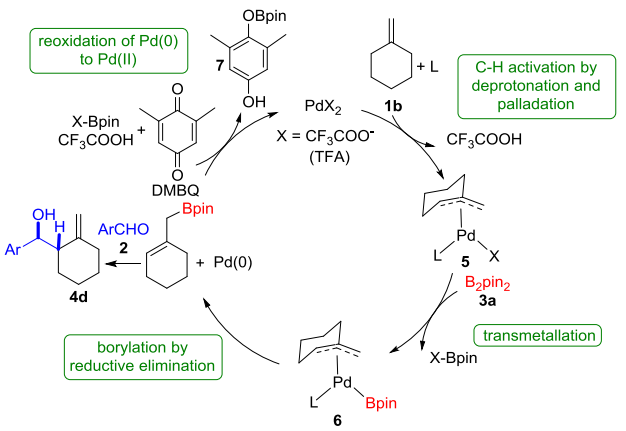


Fig. 2 Suggested catalytic cycle exemplified by substrate **1b**.

In summary, we have shown the first time that allylic C-H borylation can be performed with exocylic alkenes. Multicomponent reaction involving this new C-H borylation – allylboration sequence can be performed to obtain stereodefined homoallylic alcohols. The reaction proceeds via regioselective borylation and a subsequent regio- and stereoselective allylation. The mechanistically novel element in this reaction is that it proceeds via initial formation of an allyl-palladium intermediate, which then undergoes transmetallation with B_2pin_2 and a subsequent regioselective reductive elimination of the allylboronate product.

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