Stockholms universitet

Development of New Synthetic Routes to Organoboronates by Catalytic Allylic Substitution and C-H bond Functionalization

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ISBN 978-91-7155-899-2

Printed in Sweden Edita Sverige AB, Stockholm 2009
Distributor: Department of Organic Chemistry

To my love and family.

Abstract

This thesis describes the development of new catalytic methods for the synthesis and application of organometallic reagents, mainly focusing on allylboronic acid derivatives. Thus, palladium pincer-complex catalysis has been applied for extending the scope of palladium-catalyzed borylation reactions in the synthesis of regio- and stereodefined functionalized allylboronic acid derivatives. These novel allylboronic acids were also employed as substrates in palladium catalyzed regioselective coupling reactions with iodobenzenes. We have also developed a new one-pot sequence based on preparation of allyl- and vinylboronates *via* catalytic carbon-hydrogen bond activation/borylation reactions. The synthetic scope of the reaction as well as mechanistic studies on the borylation process are presented. Finally, the synthesis of new chiral palladium pincer-complexes is described. These species were employed as catalysts in asymmetric electrophilic allyation of imines.

List of Publications

This thesis is based on the following papers, which will be referred to by Roman numerals:

I. *S. Sebelius, V. J. Olsson and K. J. Szabó*: **Palladium Pincer-complex Catalyzed Substitution of Vinyl Cyclopropanes, Vinyl Aziridines and Allyl Acetates with Tetrahydroxydiboron. An Efficient Route to Functionalized Allylboronic Acids and Potassium Trifluoro(allyl)borates**. *J. Am. Chem. Soc.* **2005**, *127*, 10478.

II. *V. J. Olsson, S. Sebelius, N. Selander and K. J. Szabó*: **Direct Boronation of Allyl Alcohols with Diboronic Acid using Palladium Pincer-Complex Catalysis. A Remarkably Facile Allylic Displacement of the Hydroxy Group Under Mild Reaction Conditions.** *J. Am. Chem. Soc.* **2006**, *128*, 4588.

III. *S. Sebelius, V. J. Olsson, O. A. Wallner and K. J. Szabó*: **Palladium-Catalyzed Coupling of Allylboronic Acids with Iodobenzenes. Selective Formation of the Branched Allylic Product in the Absence of Directing Groups.** *J. Am. Chem. Soc.* **2006**, *128*, 8150.

IV. *V. J. Olsson and K. J. Szabó*: **Selective One-Pot Carbon-Carbon Bond Formation by Catalytic Boronation of Unactivated Cycloalkenes and Subsequent Coupling.** *Angew. Chem. Int. Ed.* **2007**, *46*, 6891.

V. *V. J. Olsson and K. J. Szabó*: **Synthesis of Allylsilanes and Dienylsilanes by a One-Pot Catalytic C−H Borylation Suzuki−Miyaura Coupling Sequence.** *Org. Lett.* **2008**, *10*, 3129.

VI. *V. J. Olsson and K. J. Szabó*: **Functionalization of Unactivated Alkenes through Iridium-Catalyzed Borylation of Carbon-Hydrogen Bonds. Mechanism and Synthetic Applications.** *Manuscript.* **2009**.

VII. *O. A. Wallner, V. J. Olsson, L. Eriksson and K. J. Szabó*: **Synthesis of New Chiral Pincer-complex Catalysts for Asymmetric Allylation of Sulfonimines**. *Inorg. Chim. Acta.* **2006**, *359*, 1767.

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Contents

Abbreviations

The abbreviations are used in agreement with standards of the subject.[1] Only non-standard and unconventional ones that appear in the thesis are listed here.

BINOL	1,1'-Bi-2-naphtol
Bs	Benzenesulfonyl
Cond	Conditions
COD	1,4-Cyclooctadiene
Cy	Cyclohexyl
Equiv	Equivalents
L_n	Unspecified number of ligands
Py	Pyridine
Pin	Pinacol
TMEDA	Tetramethylethylenediamine

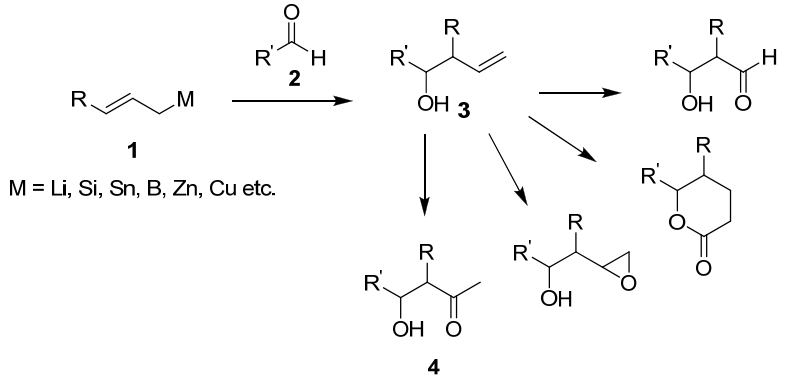
[1] *Org. Lett.* **2009**, *11*, 24A-22A.

1. **Introduction**

Transition metal complexes are extensively employed as catalysts in modern preparative organic chemistry, natural product synthesis and manufacturing of drugs and specialized chemicals.[1-16] This thesis is mainly focused on the development of new innovative palladium and iridium catalyzed methods for the synthesis of allylboronate derivatives. The main attention has been directed to finding catalytic reactions affording functionalized allylboronates with broad synthetic scope and high regio- and stereoselectivity.

1.1 Allyl metal reagents in organic synthesis

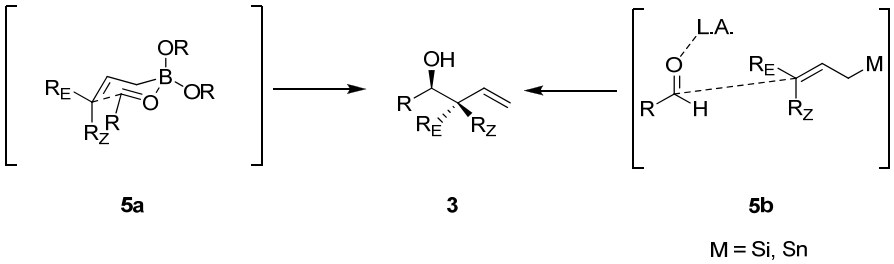
Allylic organometallic compounds (**1**) are extensively used as reagents for the organic transformation[17-31] of aldehydes (**2**) affording homoallylic alcohols (**3**) (Scheme 1). This reaction is also a synthetic alternative to the aldol reaction[31] since the homoallyl alcohol products can easily be converted to the corresponding aldol **4**. Moreover, the alkene group may readily be converted to other functionalities such as aldehydes, β–lactones, or epoxides (Scheme 11).[32-33]



Scheme 1. Synthetic scope of the allylmetal-aldehyde condensation.[33]

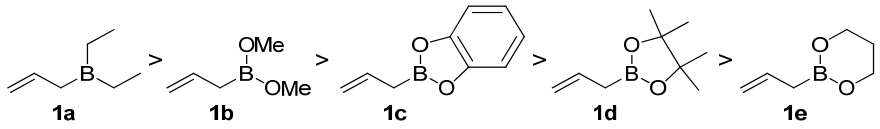
Selectivity of the allylation reactions. Allylboron reagents have become one of most widely applied class of allylic substrates because of

their high stereoselectivity in the reaction with aldehydes.[17-44] The high diastereoselectivity can be explained by reaction *via* a so called "type I" mechanism,[45] (Scheme 2) which features a coordination bond between the carbonyl oxygen and the boron atom in a compact six-membered chair-like transition state (**5a**). This mechanism contrasts with the reaction of allylsilanes and allylstannanes, which proceed by a type II mechanism (Scheme 2) *via* an open transition structure (**5b**) and generally requires external Lewis acid activators. This mechanistic model can also account for the observed diastereospecificity[46] in the allylation of aldehydes when employing γ-substituted allylboronates such as crotylboronates. For example, (*E*)-crotylboronate (Scheme 2, **5a**, R_E=Me, R_Z=H) and (*Z*)-crotylboronate (Scheme 2, **5a**, R_E=H, R_Z=Me) yields the corresponding *anti* and *syn* condensation products, respectively. In both cases the aldehyde substituent (Scheme 2, group R) resides in a pseudo-equatorial position.



Scheme 2. Mechanism of type I (**5a**) vs. type II (**5b**) allylmetal reagents.[45]

Reactivity and stability of allylboron reagents. Studies by Brown and co-workers[22] have revealed that the relative reactivity and stability of allylboron reagents is highly dependent on the substituents directly attached to the boron atom (Scheme 3). Due to their relatively high stability towards oxidation, allylboronates (**1b-e**) are much easier to handle than the corresponding allylboranes (**1a**). The higher stability of allylboronates can be explained by a π-interaction between the oxygen lone pair and the empty p_π-orbital on boron resulting in decreased electrophilicity of the boron atom. Furthermore enhanced stability can be achieved in cyclic boronate derivatives (borolanes **1c-e**), where six-membered analogues such as **1e** are more stable than the corresponding five-membered ones (**1c-d)**. The lower kinetic stability of catecol boronate **1c** compared to cyclic analogue **1d** can be attributed to the lower availability of the oxygen lone pairs in **1c** due to delocalization on the aromatic ring.

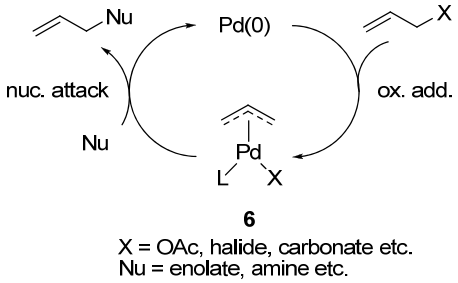


Scheme 3. Relative reacticvities of allylboron derivatives.

Furthermore, allylboranes such as **1a** are known to easily undergo reversible borotropic rearrangements, which, in the case of substituted analogues, may result in scrambling of the *E/Z* geometry of the double bond and thereby loss of stereochemical information. Allylboronates (such as **1b-e**) on the other hand are much less prone to this type of rearrangement and thereby posses higher configurational stability.[47]

1.2 Reactivity of allylpalladium complexes

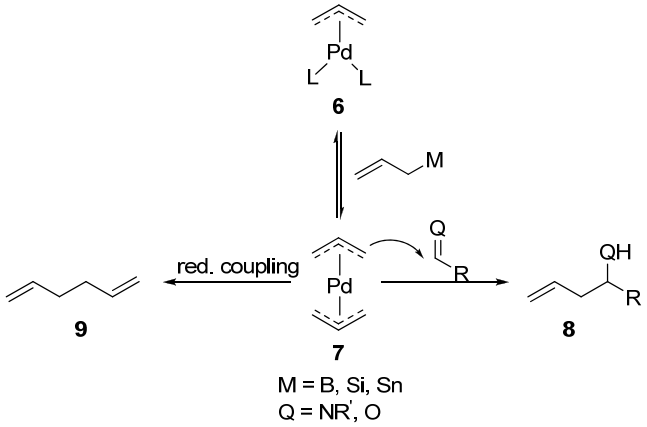
Palladium catalyzed nucleophilic allylic substitution is a well established procedure in organic synthesis.[1-16] The reactions proceed via electrophilic mono-allylpalladium intermediates (**6**) generated from palladium(0) by oxidative addition of the allylic substrates (Scheme 4). Subsequent nucleophilic attack on the η^3-allyl moiety yields the allylated product and regenerates the palladium(0) catalyst (Scheme 4).



Scheme 4. Reactivity of mono-η^3allylpalladium complexes.

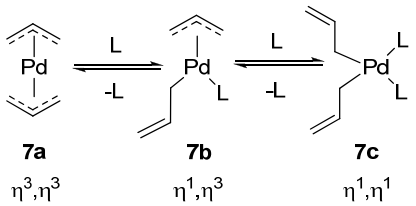
Interestingly, it has also been shown that umpolung of the allyl reactivity may be achieved upon the formation of a bis-allylpalladium complexes (**7**),[48-69] by transmetallation of allylmetal species and mono-allylpalladium complex **6** (Scheme 5). Bis-allylpalladium com-

plexes are known to react with electrophiles, such as aldehydes and imines under catalytic conditions yielding the corresponding homoallylic alcohols or amines (Scheme 5).[70-78]



Scheme 5. Reactivity of bis-allylpalladium complexes.

Unfortunately, a known side reaction in these processes is reductive allyl-allyl coupling providing hexadiene (**9**) byproducts (Scheme 5).[70-72] This process is believed to proceed *via* isomerization to the η^1, η^1–bis allyl complex **7c** (Scheme 6).[70-78]

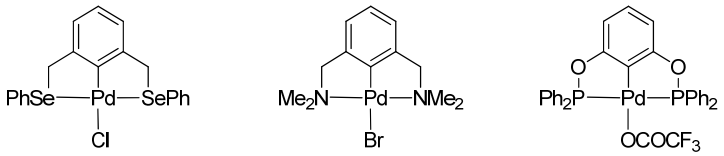


Scheme 6. Dynamic properties of bis-allylpalladium complexes.

1.3 Palladium pincer-complexes

In the past decade, a number of catalytic applications employing pincer-complexes[79-84] have appeared.[85-97] Pincer complexes are organometallic species containing a tridentate monoanionic ligand. They are classified according to the heteroatoms on the ligand, for example SeCSe[80] **10a**, NCN[81] **10b** or PCP[82] **10c** (Scheme 7). Their success as catalysts is attributed to number of attractive features as air-, moisture-, and thermostability. Moreover, a strong terdentate coordination pre-

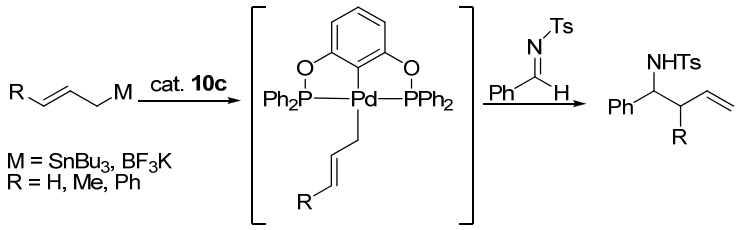
vents undesired ligand exchange processes such as allyl-allyl coupling (Section 1.2).



10a **10b** **10c**

Scheme 7. Selected palladium pincer-complexes employed in this thesis.

For example, palladium pincer-complex **10c** has been found to be an effective catalyst for the allylation of sulfonylimines with allylstannanes[85-86] or allyltrifluoroborates[89-90] yielding tosyl-protected homoallylic amines with high diastereoselectivity. Mechanistic studies have revealed that the reactions proceed *via* η^1-mono-allylpalladium intermediates (Scheme 8).[86,90]



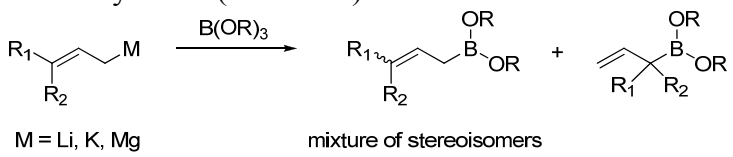
Scheme 8. Allylation of sulfonimines with palladium pincer-complex catalysis.

1.4 Synthesis of allylboronates

In the literature, there are several methods for the preparation of allylboronate derivatives.[37,96-131] In these procedures, the boronate group is either introduced directly into the substrate (direct method) or an organoborate is modified to create the allyl functionality (indirect method).[37] The focus in this thesis is on the direct methods, which are perhaps the most general and elegant approaches for the synthesis of this highly important class of organic reagents.

Allylboronates from transmetallation of allylmetal reagents. Perhaps the most straightforward method for the synthesis of allylboronates is that involving transmetallation of reactive allylmetal interme-

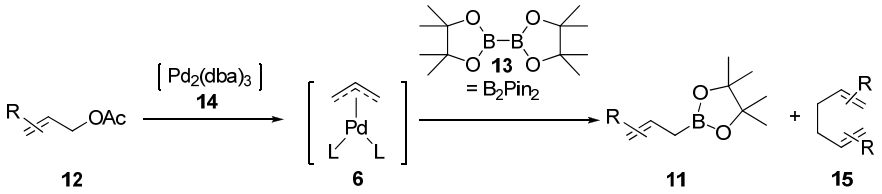
diates such as allyllithium, allyl-Grignard or allylpotassium reagents with a trialkoxyborate (Scheme 9).[96-113]



Scheme 9. Synthesis of allylboronates employing reactive allylmetal reagents

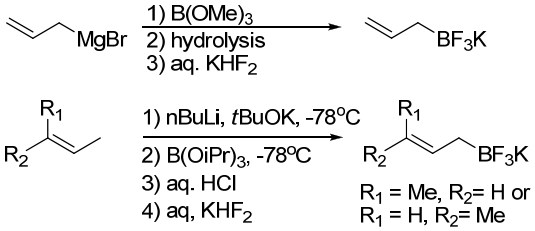
To access simple boronates such as allyl (R_1=H, R_2=H, Scheme 9) and crotyl (R_1=Me, R_2=H, Scheme 9) species, this method has the advantage of using readily available and inexpensive starting materials. However, these reactive species are known to undergo facile metallotropic rearrangements,[109-111] which may lead to scrambling of both regio- and stereoisomers in the case of substituted substrates (Scheme 9). Furthermore, the incompatibility of lithium and Grignard reagents with many functional groups, such as cyanides, ketones, esters and amines, limits the scope of this approach.

Allylboronates from palladium catalyzed allylic substitution. Since the classical methods for the synthesis of allylboronate derivatives are often associated with problems, such as low regio- and stereoselectivity as well as poor functional group tolerance, milder methods are required for obtaining functionalized derivatives. The use of transition metal catalysis has shown to be an efficient alternative route for the synthesis of various functionalized allylboronates.[114-125] An interesting approach was presented by Miyaura and co-workers, [115] where various functionalized allylboronates (**11**) were obtained by reacting allyl acetates **12** with bis(pinacolato)diboron **13** in the presence of palladium catalyst **14** (Scheme 10). Unfortunately considerable amounts of the corresponding allylic dimer **15** is also formed as a by-product in these processes. Formation of **15** can be explained by a transmetallation reaction of mono-allylpalladium intermediate **6** with the formed allylboronate product **11** resulting in a bis-allylpalladium intermediate **7** (section 1.2), which subsequently undergoes allyl-allyl coupling.



Scheme 10. Preparation of allylboronates by palladium catalyzed allylic substitution by Miyaura and co-workes.[115]

Allyltrifluoroborates: A new class of allylboron reagents. In the past decade, organotrifluoroborates have become important reagents in organoboronate chemistry, in particular for transition metal catalyzed coupling reactions.[131-132,188] These reagents are air- and thermostable species, which are usually easier to handle and purify, than other organoboronates. Recently, Batey and co-workers[133-134] described the synthesis of a new class of allylboron compounds containing a trifluoroborate functionality. This synthesis was achieved by reacting allylmagnesium bromide or crotylpotassium with trialkyl borates, followed by hydrolysis and subsequent *in situ* reaction with aqueous potassium hydrogen fluoride (Scheme 11).



Scheme 11. Synthesis of allyltrifluoroborates.

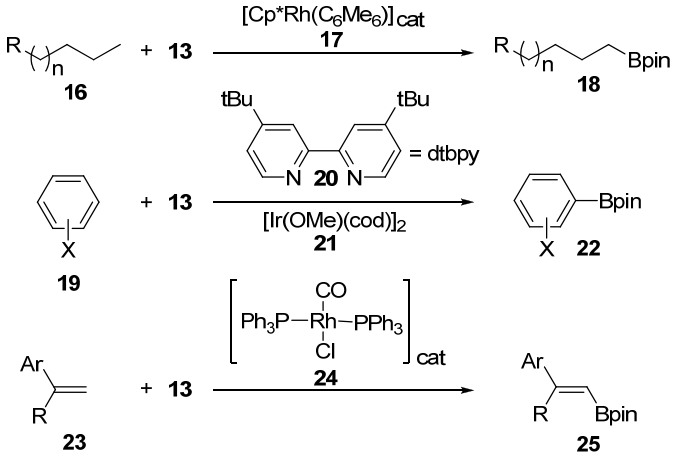
Allyltrifluoroborates are organic salts with several attractive features such as air- and water-stability, which allows their easy isolation by recrystallisation. Moreover, allyltrifluoroborates have been shown to be effective allylating reagents for aldehydes (see Scheme 1). However these processes require pre-activation of the employed allyltrifluoroborates with $BF_3{\cdot}OEt_2$[134] Alternatively, allyltrifluoroborates may also be employed as substrates for the palladium pincer-complex catalyzed allylation of sulfonylimines (Scheme 8) in the absence of Lewis acids or bases.[89-90]

1.5 Synthesis of organoboronates via metal-catalyzed carbon-hydrogen bond activation

The development of catalytic and selective functionalization of non-activated carbon-hydrogen bonds[136-137] is a research area of great interest since it allows the synthesis of functionalized substrates from inexpensive starting materials such as hydrocarbons. It has been shown that organoboronates can be directly obtained *via* catalytic CH-

activation of organic substrates such as alkanes and aromatics.[138-166] Extensive mechanistic studies have revealed metal boryl complexes[167-169] as key intermediates.

For example, Hartwig and co-workers[138] have demonstrated that alkanes (**16**) may undergo regioselective terminal functionalization by catalytic borylation in the presence of rhodium catalyst **17** affording alkylboronates **18** (Scheme 12). They also demonstrated that aromatic substrates (**19**) underwent borylation by catalytic CH-activation under mild reaction conditions with diboronate **13** in the presence of Ir catalyst **20** and ligand **21** yielding the corresponding aromatic boronates **22**.[156] The employment of alkenes as substrates in these reactions received less attention.[172-188] However, Marder and co-workers[178] have shown that arylated alkenes, such as **23** undergo dehydrogenative borylation with diboronate **13** in the presence of catalytic amounts of rhodium complex **24** yielding *trans*-vinylboronates **25** in high regio- and stereoselectivity (Scheme 12).



Scheme 12. Synthesis of organoboronates by transition metal-catalyzed C-H bond activation.[137,154,178]

Although C-H activation based borylation reactions represent a very efficient, inexpensive synthetic method for preparation of organoboronates, development of new catalytic procedures to functionalized boronates is a highly challenging task. As organic molecules contain many different types of carbon-hydrogen bonds, control of the regioselectivity is often very difficult.

1.6 Major objectives of this thesis

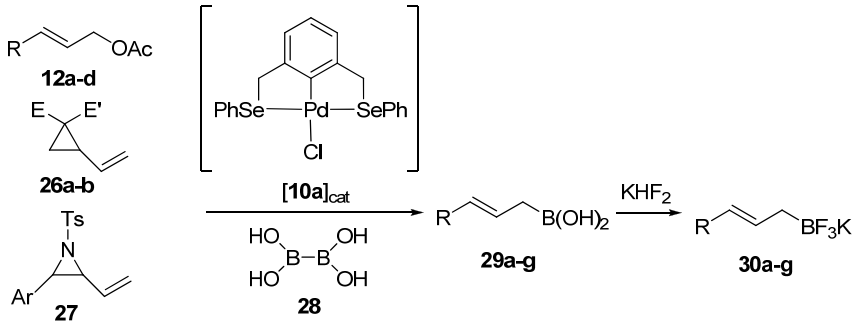
The most important goals of this thesis is to present new catalytic procedures for synthesis and transformation of functionalized boronates from unexpensive easily accessible starting materials. Accordingly, the main efforts are focused on palladium-catalyzed substitution of allylic alcohols (and other allylic substrates), and reactions based on iridium catalyzed C-H borylation. One-pot versions of such reactions would prove particularly attractive, opening new synthetic routes for the preparation of stereodefined homoallylic alcohols and functionalised butadiene derivatives. Asymmetric catalytic allylation of sulfonylimines with allylstannanes was also briefly studied.

2. Selective synthesis and transformation of allylboronic acids *via* palladium-catalyzed allylic substitution reactions (Papers I-III)

Allylboronic acids are important precursors for the synthesis of various allylboronate[37] derivatives and potassium allyltrifluoroborates.[133-134] However, known instability[99] and cumbersome synthetic methods have limited the access to functionalized allylboronic acids (Section 1.3, Scheme 11). Efficient mild methods for the synthesis of functionalized allylboronates have previously been reported.[114-130] For example, Miyaura and co-workers[115] developed a palladium(0)-catalyzed coupling of allylic acetates with diboronates (Section 1.3, Scheme 10). However, formation of the corresponding allylic dimer (Section 1.2) and low conversion of the allylic precursors usually limits the synthetic scope of these methods. Therefore, application of more selective catalysts for the carbon-boron bond formation is highly desirable. In this chapter a mild and efficient method for the synthesis of highly functionalized allylboronic acid derivatives by the application of palladium pincer-complexes[79-95] (section 1.3) as catalysts. Also, a novel coupling reaction with the *in-situ* generated allylboronic acid products and iodobenzenes is described.

2.1 Palladium pincer complex-catalyzed substitution of allylic substrates

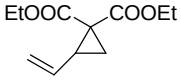
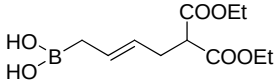
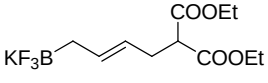
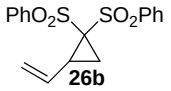
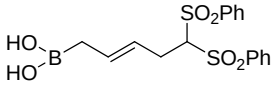
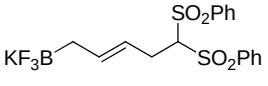
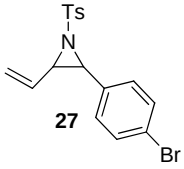
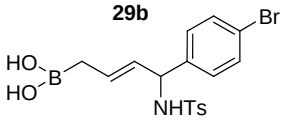
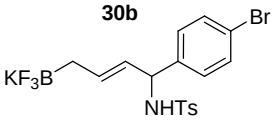
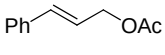
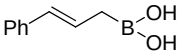
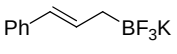
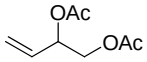
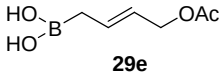
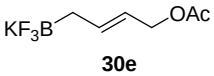
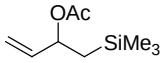
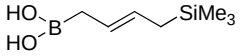
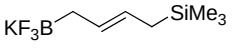
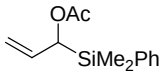
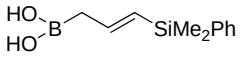
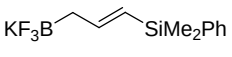
It was found that SeCSe pincer-complex **10a** readily catalyzes boronate transfer reactions (Scheme 13) from diboronic acid[187] **28** to a variety of allylic substrates such as functionalized allylic acetates (**12a-d**), vinyl cyclopropanes (**26a-b**) and vinyl aziridines (**27**). These reactions proceed readily at 40°C in DMSO yielding allylboronic acids (**29a-g**), which were subsequently converted to the corresponding potassium allyltrifluoroborates (**30a-g**) by *in situ* reaction with aqueous KHF_2 (Table 1).



Scheme 13. Boronation of allylic acetates, vinyl cyclopropanes and vinyl aziridines catalyzed by a palladium pincer-complex.

Recrystallisation afforded the allyltrifluoroborate products **30a-g** with high purity in good to excellent yields (Table 1).

Table1. Synthesis of allylboronic acid derivatives by pincer-complex catalysis.[a]

	Substrate	t [h]	Allylboronic acid	Product	Yield[b]
1	 **26a**	3	 **29a**	 **30a**	82
2	 **26b**	3	 **29b**	 **30b**	89
3	 **27**	2	 **29c**	 **30c**	87
4	 **12a**	16	 **29d**	 **30d**	71
5	 **12b**	36	 **29e**	 **30e**	97
6	 **12c**	16	 **29f**	 **30f**	81
7	 **12d**	16	 **29g**	 **30g**	60

[a] The reactions of **28** and the corresponding substrates were conducted at 40° C in the presence of **10a (**5 mol%) in DMSO. After the indicated reaction times aqueous KHF_2 was added. [b] Isolated yield.

2.2 Reactivity and selectivity

Opening of the three-membered rings (**26a-b** and **27**) with **28** proceeds remarkably fast (in 2-5 h at 40 °C) (entries 1-3, Table 2), while boronate substitution of the allylic acetates (**12a-d**) requires much longer reaction times of 16-36 h (entries 4-7). The high reactivity of **26a-b** and **27** can be explained by ring-strain as well as the presence

of electron-withdrawing groups such as CO_2Et and SO_2Ph, which imposes further activation. The regio- and stereoselectivity of the reaction is excellent, as we have obtained only the trans-substituted linear products, even from branched allylic acetates **12b-d** (entries 5-7). The high selectivity observed in the boronation reactions can be explained by the finding that electron-rich pincer-complexes (such as **10a**) are reluctant to undergo transmetalation with allyl-metal species.[87,88] Thus, the carbon-boron bond of the allylboronic acid products **29a-g** is not cleaved by **10a**, allowing the subsequent isolation of the products (**30a-g**) in high yields (Table 1).

2.3 Synthetic scope of the reaction

As the boronation reactions (Scheme 13) proceed under mild conditions, many functionalities such as Br, COOEt, NHTs, OAc and SO_2Ph are tolerated. Surprisingly conversion of silyl substituted allylic acetates **12c** and **12d** proceeded smoothly with the silyl functionality unchanged during the boronation process and after KHF_2 treatment (entries 6-7, Table 1). Thus, useful silyl-boronate synthons **29f-g**, **30f-g** could be prepared (entries 6-7, Table 1). The obtained functionalized allylboronic acid products (**29a-c and 29e-g**) could also reacted with aldehydes affording stereodefined homoallylic alcohols containing various functionalitites such as acetates, esters, alcohols, amines and silanes. The utility of vinylsilyl-allylboronate reagents (such as **29g** and **30g**) has been shown by Roush and co-workers[106,108] in so called "double allylation" reactions. Moreover, selective substitution of one acetate group in allyl diacetate **12b** (entry 5) yields the corresponding orthogonal functionalized product (**29e**).

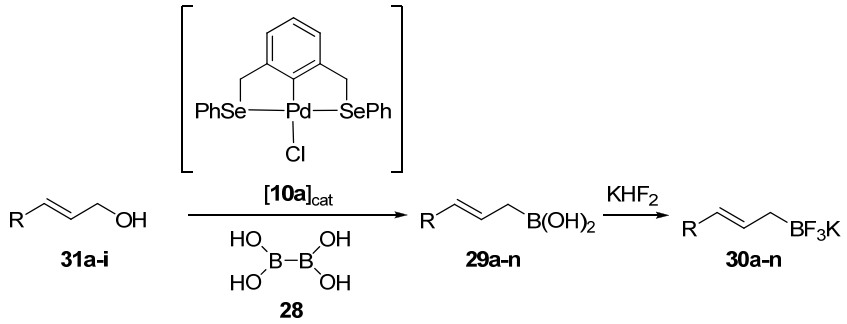
2.4 Stability of the allylboronic acid derivatives

We were not able to isolate the allylboronic acid products from the above reactions, because of their poor stability.[99] Nevertheless, the crude allylboronic acids **29a-g** were characterized by ^{1}H-NMR spectroscopy (in DMSO-d_6 and/or CD_3OD). It is known that in coordinating polar solvents such as DMSO, the reactivity of allylboronic acids toward electrophiles is lowered,[22] which increases the kinetic stability of **29a-g**. Indeed, we observed that many of these species are surprisingly stable in DMSO-solution (up to 2 days at r.t.). However upon evaporation of the solvent complete decomposition occurs. Therefore, allylboronic acids **29a-g** were converted to air-stable potassium allyltrifluoroborates[23,24] **30a-g**, which could be isolated in good to excel-

lent yields (Table 1-2). Most of the obtained allyltrifluroborates could be stored at room temperature in air after isolation. The exceptions are **30c** and **30f** (entries 3 and 6, Table 1), which underwent slow decomposition according to ^{1}H-NMR spectroscopy.

2.5 Employment of allylic alcohols as substrates in the borylation reactions

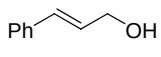
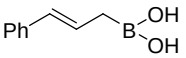
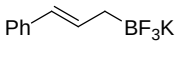
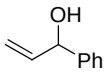
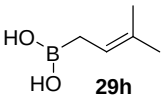
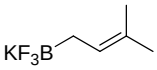
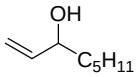
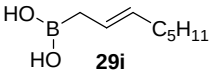
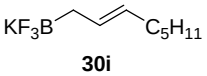
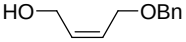
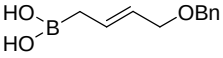
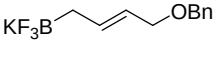
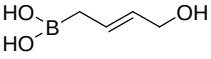
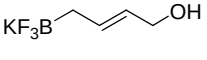
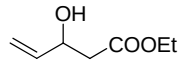
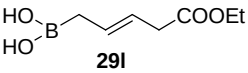
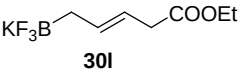
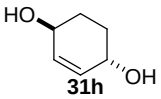
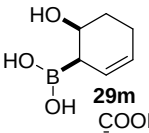
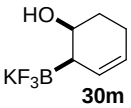
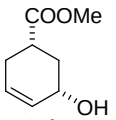
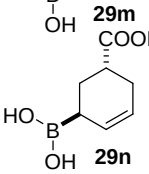
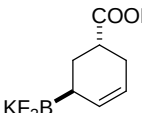
Employment of allylic alcohols in substitution reactions is a research area of great interest because of the easy availability of these substrates.[3,54,55] Unfortunately, the hydroxyl group is one of the most reluctant leaving groups in substitution reactions. Therefore, application of harsh reaction conditions and/or activation by Lewis acids are often required in these processes.[54,55]



Scheme 14. Direct boronation of allylic alcohols.

Indeed, when allylic alcohols were first tried as substrates in borylation reactions, low conversions (5-20%) were observed, even upon extended heating. However, later we found that employment of MeOH as a co-solvent dramatically accelerated the conversion of allylic alcohols to the corresponding allylboronic acids. Thus direct borylation of allylic alcohols **31a-i** could be achieved under mild reaction conditions with diboronic acid **28** in the presence of 5 mol% **10a** in a DMSO/MeOH solvent mixture (Scheme 14).

Table 2. Palladium pincer-complex catalyzed direct borylation of allylic alcohols[a]

	Substrate	cond.[°C/h]	Allylboronic acid	Product[b]	Yield[c]
1	 **31a**	40/16	 **29d**	 **30d**	92
2	 **31b**	40/7	**29d**	**30d**	86
3	 **31c**	50/16	 **29h**	 **30h**	98
4	 **31d**	50/16	 **29i**	 **30i**	90
5	 **31e**	40/21	 **29j**	 **30j**	87
6[d]	 **31f**	20/16	 **29k**	 **30k**	74
7[e]	 **31g**	40/20	 **29l**	 **30l**	77
8	 **31h**	40/16	 **29m**	 **30m**	87
9[e]	 **31i**	50/24	 **29n**	 **30n**	82

[a] Unless otherwise stated the reactions of **28** and the corresponding substrates were conducted in the presence of **10a** (5 mol%)) in a mixture of DMSO and MeOH. After the indicated reaction times aqueous KHF_2 was added. [b] Racemic. [c] Isolated yield. [d] Pure MeOH was used as solvent. e p-toluenesulfonic acid 5 mol% was used as co-catalyst.

2.6 Regio- and stereoselectivity of the catalytic process

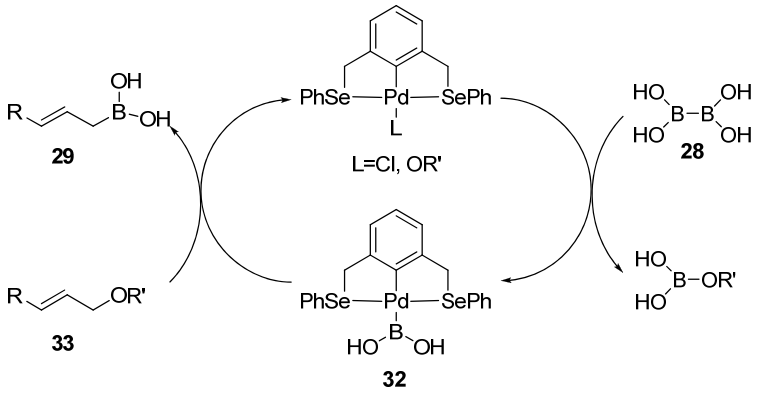
The reactions proceed with very high regio- and stereoselectivity as only the linear *trans*-substituted allylboronic acids products are obtained (Schemes 13-14, Table 1-2). Moreover, when cyclic substituted allylic alcohols such as **31h** and **31i** are employed as substrates, the corresponding products (**29m-n**, **30m-n**) are obtained as single regio- and stereoisomers (entries 8-9, Table 2).

2.7 Substituent effects on the reactivity of the allylic alcohols

It was found that in the presence of hydroxy or benzyloxy substituents the reactivity of the alcohol substrates is considerably increased (entries 5-6, Table 2). For example, boronation of **31f** proceeded at lower temperature (20 °C), than the corresponding reaction of the alkyl substituted analogs (**31c-d**) (50 °C) (entries 3-4, Table 2). The relatively low reaction temperature (20-40 ^{o}C) is also important for obtaining high isolated yields of the products, since allyl hydroxy boronates (**29j-k**) very easily undergo hydroxy-boronate 1,4-elimination to give the corresponding 1,3-diene. Accordingly, employment of more harsh reaction conditions to obtain the diboronated product from **31f** leads to extensive formation of butadiene. In contrast to hydroxy or benzyloxy substituents, the substituent effects of COOR groups in the allylic alcohols (such as **31g**) decrease the rate of borylation reactions (entry 7, Table 2). However, we found that addition of catalytic amounts (3-5 mol%) of strong acids such as p-toluenesulfonic acid (PTSA) considerably accelerated the conversion of **31g**, affording the corresponding boronated product **29l** (entry 7, Table 2).

2.8 Proposed mechanism of the borylation reaction

The proposed mechanism is based on previous mechanistic studies on the palladium pincer-complex-catalyzed trimethyltin transfer from hexamethylditin to allylic/propargylic substrates.[87,88] In these transformations, the catalytic cycle is initiated by transmetalation of the dimetallic reagent to the pincer-complex forming a palladium-tin intermediate,[87,88] followed by transfer of the organometallic group to the allylic /propargylic substrate in an S_N2/S_N2' type reaction. Likewise, it is assumed that the first step of the present boron transfer process is formation of a boryl pincer-complex intermediate **32** followed by substitution of the substrate by the $B(OH)_2$ group (Scheme 13). The borylation reaction shows a high regioselectivity for formation of the linear product (Scheme 13-14, Table 1-2). For example, both the linear substrate **31a** and branched alcohol **31b** gave exclusively terminal substituted boronic acid **29d** (Table 2, entries 1 and 2). This can be explained by nucleophilic attack occuring at the less sterically hindered position of the allylic substrate **33**.



Scheme 13. Possible catalytic cycle of the borylation process

2.9 Investigations on the activation of allyl alcohols

In order to gain insight into the activation of the hydroxy group of allyl alcohols, we carried out competitive borylation experiments (Figure 1) monitored by ^{1}H-NMR. The reaction rates of cinnamyl acetate **12a** and cinnamyl alcohol **31a** were compared. Surprisingly, under the same reaction conditions, cinnamyl alcohol **31a** was converted significantly faster to boronic acid **29d**, than cinnamyl acetate **12a**. The NMR-experiment also showed that addition of 5 mol% PTSA had

a dramatic accelerating effect on the rate of the borylation reaction of cinnamyl alcohol **31a** (Figure 1).

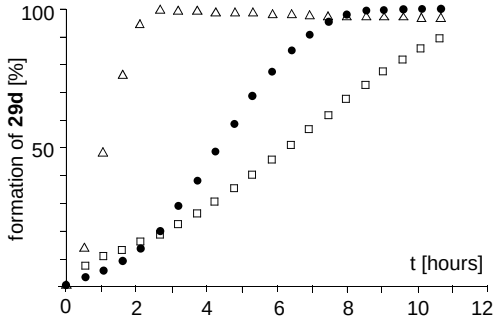
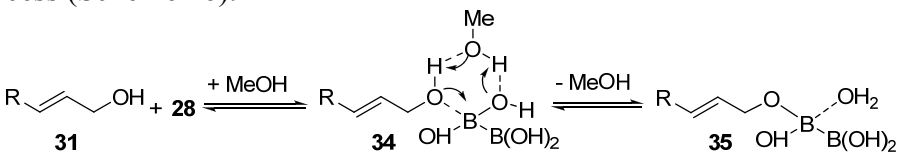


Figure 1. Formation of **29d** from **31a** (• , Δ) and cinnamyl acetate (**12a**) (□) using **28** and 5 mol% of **10a** in DMSO-d_6/MeOH-d_4 mixture at 55°C. Effects of addition of 5 mol% PTS (Δ).

The above studies clearly indicate that under the reaction conditions employed the hydroxy group of the allylic alcohol is converted to an excellent leaving group, which is easier to displace than the corresponding acetate. A possible explanation is that **28** acts as a Lewis-acid catalyst by interacting with the free electron-pairs of the oxygen of allyl alcohol **31**. A similar activation is suggested in the Tamaru reaction employing BEt_3 for activation of allyl alcohols.[54,55] On the other hand, boronic acids are far less efficient Lewis-acids than alkyl (or fluoro) boranes. Therefore, another type of activation of the hydroxy group is envisioned involving formation of allylboronic acid ester **35** (Scheme 16). This esterification may be facilitated by inclusion of a methanol molecule in the six-membered ring TS (**34**) of the process (Scheme 16).



Scheme 16. Suggested activation of the hydroxyl group by boronate ester formation.

In **35** the hydroxy group is converted to a better leaving group by, and moreover, the cleavage of the B-B bond is also facilitated by coordination of the water molecule produced in the esterification. A possible role of the PTSA (Table 2, entry 7 and 9, Figure 1) is that of catalyst for the boronate-ester formation.

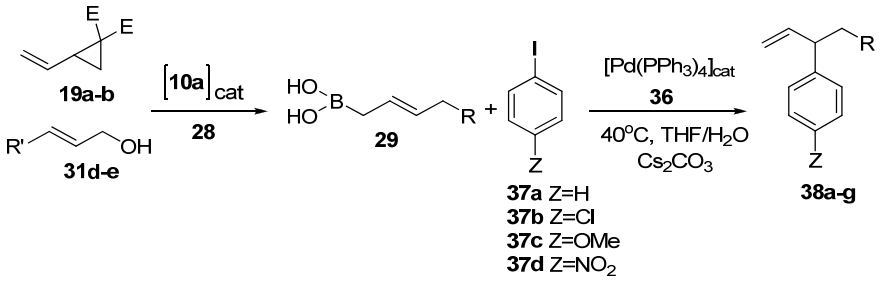
2.10 Comparisons with other palladium catalysts

Attempts were made to employ electronically altered pincer complexes, such as NCN complex **10b** and PCP complex **10c** in place of SeCSe catalyst **10a**. It was found that **10b** displayed a lower catalytic activity, than SeCSe catalyst **10a**, while **10c** proved to be completely inactive as catalyst. We have also attempted to carry out substitution reactions of allyl acetates with diboronic acid **28** in the presence of 5 mol% $Pd_2(dba)_3$ (**14**) or $Pd(PPh_3)_4$ (**36**) in place of **10a**. These transformations resulted in complex mixtures of several unsaturated products. The best result was achieved with $Pd_2(dba)_3$ (**14**) and allyl acetate **12c** giving about 20% isolated yield of **30d**. The above results clearly indicate that the catalytic activity and selectivity of pincer-complexes **10b-c** and palladium(0) catalysts $Pd_2(dba)_3$ (**14**) and $Pd(PPh_3)_4$ (**36**) are inferior to SeCSe complex **10a** in the presented boronate transfer reactions.

In conclusion, we have demonstrated that palladium pincer complex **10a** is a highly selective catalyst in the borylation reaction of various allylic substrates such as allyl acetates, vinylcyclopropanes, vinylaziridines and even allylic alcohols. The reactions proceed with high regio- and stereoselectivity to give the the linear *trans*-substituted products and tolerates many functionalities such as esters, amines, bromines and sulfonyls. Moreover, the functionalized allylboronic acid products obtained could be converted to the corresponding allyltrifluoroborates for isolation in good to excellent yields after treatment with aqueous KHF_2. The synthetic scope of the presented catalytic borylation reactions have been further expanded using commercially available reagents and catalysts.[189-190]

2.11 Palladium-catalyzed regioselective allylation of aryl iodides with functionalized allylboronic acids

One of the most common palladium-catalyzed transformations is the coupling of aryl- and vinylboronates with organohalides, known as the Suzuki-Miyaura reaction.[191-196] The high selectivity and functional group tolerance of this process has triggered many synthetic applications and is widely used in natural product synthesis.[195] The reaction is well established for the construction of biaryls through aryl-aryl coupling or in stereoselective synthesis of alkenes and alkadienes by coupling of vinyl boron derivatives.[191,196] However, reports on the application of allylboronate derivatives are surprisingly scarse.[197] As we have shown (Section 2), stereodefined functionalized allylboronic acids can readily be obtained by palladium-catalyzed borylation of vinylcyclopropanes, vinylaziridines, allylic acetates and allylic alcohols. Based on this borylation process, we also discovered a novel coupling reaction of functionalized allylboronic acids with aryl iodides selectively affording branched allylic products.

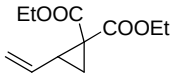
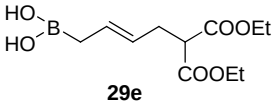
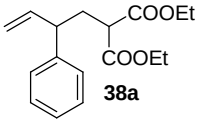
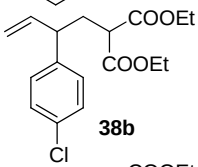
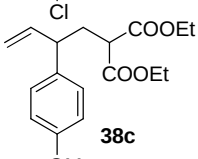
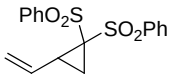
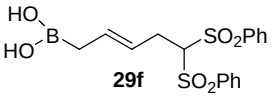
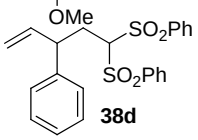
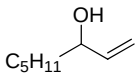
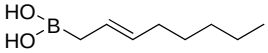
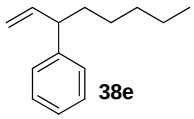
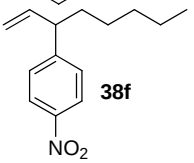
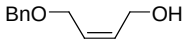
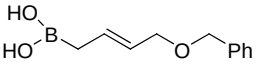
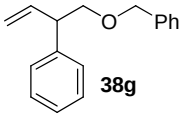


Scheme 17. Palladium catalyzed regioselective coupling of *in situ*-generated allylboronic acids with iodobenzenes.

Arylation of functionalized allylboronic acids **29** with iodobenzenes **37a-d** in the presence of catalytic amounts (5 mol%) of Pd-catalyst **36** proceeds smoothly, affording coupling products **38a-g** in high yield (Scheme 17, Table 3). The regioselectivity is suprising as the coupling reactions lead to a highly selective formation of the corresponding branched allylic coupling product **38a-g** (Scheme 17). Moreover the catalytic transformations proceed with high functional group tolerance as carbethoxy, phenylsulfonyl, aromatic chloro and nitro groups remained unchanged (Table 3, entries 2, 3 and 6,). As shown above (Section 2), the allylboronic acid precursors can easily be obtained by borylation of vinyl cyclopropanes (such as **19a-b**), and allylic alcohols

(such as **31d-e**) with diboronic acid (**28**) in the presence of catalytic amounts of pincer-complex **10a**. Unfortunately, the allylboronic acids cannot be isolated due to their low stability.[99] Thus, under solvent free conditions extensive decomposition follows and a complex mixture of degradation products is observed by ^{1}H-NMR. However, prior to the coupling reactions, sufficient purification can be achieved by ether or chloroform extraction of the crude reaction mixture followed by careful reduction of the solvent by argon-flow.

Table 3. Regioselective coupling of allylboronic acids with aryl iodides[a]

	Precursor	Allylboronic acid[b]	Ar-I	Product	Yield [%][c]
1	 **19a**	 **29e**	**37a**	 **38a**	91
2	**19a**	**29e**	**37b**	 **38b**	97
3	**19a**	**29e**	**37c**	 **38c**	87
4	 **19b**	 **29f**	**37a**	 **38d**	91
5	 **31d**	 **29i**	**37a**	 **38e**	97
6	**31d**	**29i**	**37d**	 **38f**	83
7	 **31e**	 **29j**	**37a**	 **38g**	99

[a] The coupling reactions of **29** and **37** were conducted in the presence of Cs_2CO_3 and $Pd(PPh_3)_4$ (5 mol%) in a THF/water mixture for 16 h at 40 °C. b The allylboronic acids prepared according to refs.[123,124]. [c] Isolated yield.

2.12 Regioselectivity of the coupling reaction

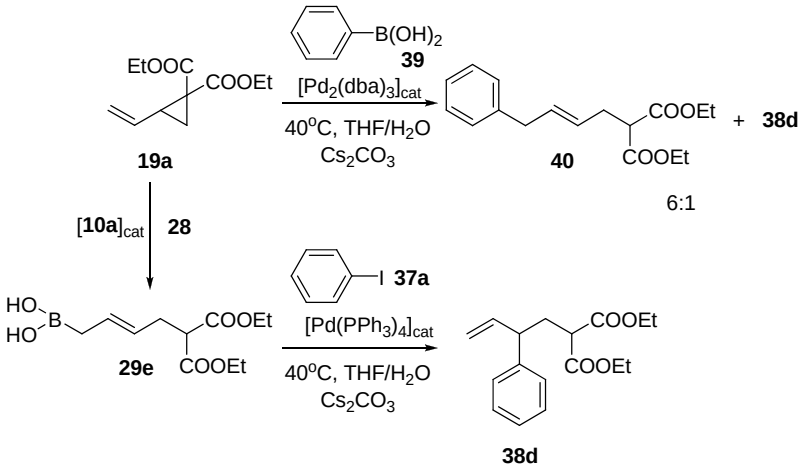
In standard palladium-catalyzed allylic substitution proceeding *via* mono allylpalladium intermediates[2] (Section 1.2), the nucleophiles preferentially attack the less hindered allylic terminus affording the linear allylic product.[10-12] There have been two main strategies for steering the nucleophilic attack towards formation of the branched allylic isomers: (i) application of directing groups in the allylic substrate;[200-204] or (ii) use of specially designed ligands that direct the nucleophilic attack on the η^3-allyl)palladium intermediates to the branched product.[205-208]

However, in the presented coupling reaction, neither the employment of directing groups in the substrates nor specially designed ligands were necessary for achieving the branched product selectively. Accordingly, alkyl-allylboronic acid **29i** readily underwent palladium(0)-catalyzed substitution reaction with iodobenzene **37a** affording the corresponding terminal alkene **38e** (Table 3, entry 5). Substituted iodobenzenes reacted similarly (entries 2, 3 and 6) indicating that the electronic effects of the aryl substituents have no significant effect on the rate of the coupling reaction. Moreover, exchange of the carbethoxy substituents in **19a** to bulky phenyl sulfonyl groups (**19b**) did not affect the regioselectivity or the rate of the reaction (entry 4). Allylboronic acids with alkyl (**29i**) and benzyloxy group (**29j**) (entries 5 and 7) reacted with the same rate and selectivity as **29e** and **29f** (entries 1 and 4), even when 4-iodo-nitrobenzene **37d** was employed as coupling component (entry 6).

Finally, allylation of ortho-chloro iodobenzene with **29e** was also attempted. However, this reaction gave only traces of the ortho-chloro analog of **38a** indicating that the coupling reaction is sensitive to the ortho- substituent on the iodobenzene component.

2.13 Comparison of the regioselectivity to common allylic substitution reactions

In order to study a possible directing effect of the COOEt group in **29e**, we carried out a classical allylic substitution reaction of **19a** with phenyl boronic acid (**39**) employing $Pd_2(dba)_3$ (**14**) as catalyst.[95] This process provided predominantly the linear product **40** and only traces of the branched allylic isomer **38d** (Scheme 18).

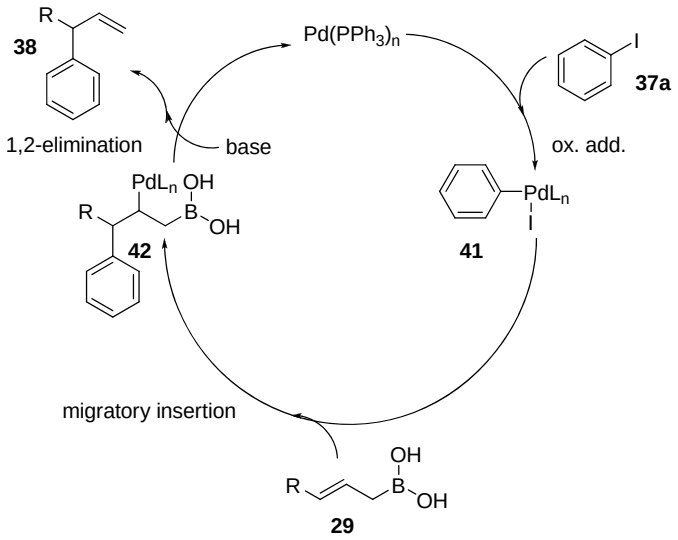


Scheme 18. Regioselectivity dependence upon the choice of reaction partners.

The observed regioselectivity is typical for the classical nucleophilic substitution[1-4] of **19a** proceeding *via* (η^3-allyl) palladium intermediate. Notably, the reaction of **19a** and **39** with $Pd(PPh_3)_4$ (**31**) in place of **14** proceeds extremely slowly giving only traces of **40**. On the other hand, when **19a** was first converted to allylboronic acid **29e** and then coupled with iodobenzene (**37a**), the regiochemistry of the process was reverted providing solely the branched product **38d** (Scheme 18). From these results it can be concluded that the COOEt group lacks any inherent directing effects for the formation of the branched coupling product **38d**.

2.13 Proposed mechanism of the coupling reaction

The above findings on the regioselectivity of the allylation reaction (Section 3.2) suggest that the coupling of allylboronic acids **29** and aryl iodides **37** does not proceed *via* (η^3-allyl) palladium intermediates. Thus, a mechanism involving transmetalation[95] of the corresponding allylboronic acids to palladium is unlikely, since this process would lead to the formation of an η^3-allylpalladium intermediate. Miayura and Suzuki have shown[198] that an alternative mechanism in the Suzuki-Miyaura cross-coupling is operating in some cases, which does not involve initial transmetalation of the corresponding organoborates. This alternative mechanism involves a migratory insertion of the palladium bound aryl ligand followed by β–boron 1,2-elimination.[198] A similar mechanistic conclusion was also reported by Hallberg and Nilsson[197] studying the palladium catalyzed Heck-type reaction of pinacolato allylboronate with iodobenzene.



Scheme 19. Catalytic cycle for the palladium-catalyzed arylation of allylboronic acids.

The described mechanism is likely to apply to the palladium-catalyzed coupling of functionalized allylboronic acids with iodobenzenes. Thus, the first step of the catalytic cycle is oxidative addition of iodobenzene **37a** to Pd(0) yielding arylpalladium intermediate **41**, which subsequently undergoes migratory insertion to give intermediate **42** (Scheme 19). Finally, a base-promoted β-boronate elimination affords product **38** and regenerates the catalyst. The last elimination step is

irreversible since it involves oxidation of the boronic acid to boric acid. Moreover, the deboronation proceeds *via* 1,2-elimination which explains the selective formation of the branched coupling product **38** (Scheme 19).

In summary, it has been shown that the palladium-catalyzed coupling of allylboronic acids with aryl iodides can be achieved under standard Suzuki-Miyaura coupling conditions.[191-192] The reactions proceed with a remarkably high regioselectivity providing the branched allylic isomers. In contrast to common palladium-catalyzed nucleophilic substitution reactions proceeding *via* (η^3-allyl)palladium intermediates,[2] this process does not require directing groups in the allyl moiety or specially designed ligands to achieve substitution at the substituted allylic terminus. Since the coupling reaction of allylboronic acids with iodobenzenes generates a new stereogenic carbon, the presented methodology creates a basis for the development of new asymmetric allylation processes.

Concomitantly to this work, similar selectivity was reported by Miyaura and co-workers[209] in a palladium catalyzed coupling reaction of allyltrifluoroborates and arylhalides. However, this method required the use of bidentate phosphines with large bite-angles to obtain the branched coupling product in high regioselectivity. Furthermore, Miyaura and co-workers[210-211] have also demonstrated that asymmetric allylation of aryl halogenides can be achived using chiral bidentate ligands.

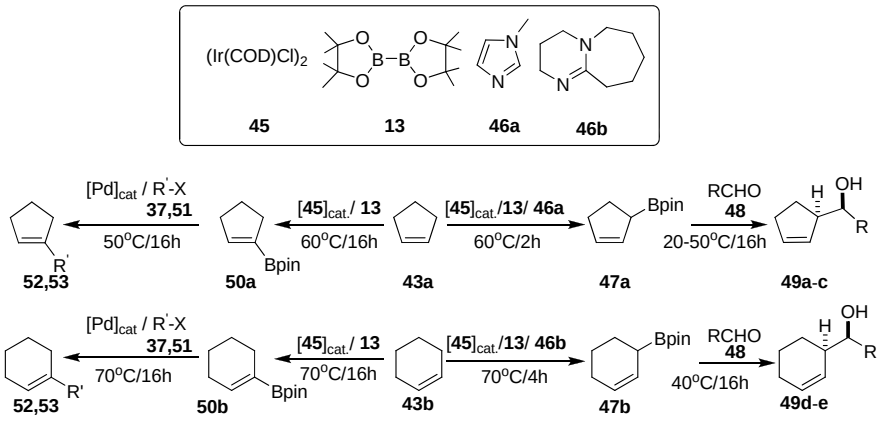
3. *In situ* generation of allylboronates and vinylboronates *via* selective catalytic carbon-hydrogen bond borylation of alkenes (Paper IV-VI)

Previous work by Hartwig, Ishiyama, Marder, Miyaura, Smith, and their co-workers[138-166] has shown that organoboronates can be directly obtained *via* CH-activation of aromatic and alkane substrates (see Section 1.5). However, application of C-H bond borylation of alkenes in these types of reactions is a much less developed area.[170-186] As alkenes contain many different types of carbon-hydrogen bonds, control of the regioselectivity is often very difficult. We envisaged that a similar approach could also be used to generate highly desirable allylboronate products. This may be done by reverting the regioselectivity of this process towards borylation of the allylic carbon-hydrogen bond.

In this chapter is presented a novel and highly selective C-H functionalization/C-C coupling process based on the *in situ* formation of both allyl- and vinylboronates from alkene substrates (Schemes 20-21). Both the synthetic scope and mechanistic aspects of the reaction are discussed.

3.1 One-pot regio- and stereoselective C-H functionalization of unactivated alkenes

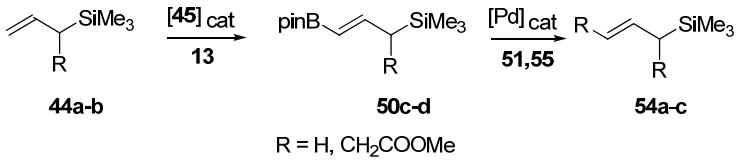
The main focus was mainly concentrated on developing C-H activation-borylation based processes of simple cycloalkenes (**43a-d**) and allylsilanes (**44a-b)**. Interesting results were obtained for cyclopentene **43a** and cyclohexene **43b**, for which the allyl and vinyl selectivity of the borylation could be controlled by appropriate choice of the reaction conditions.



Scheme 20. One-pot synthesis of homoallylic alcohols and styrene derivatives from cycloalkenes (**43a-b**) through carbon-hydrogen bond activation-borylation reactions.

Thus, cyclohexene **43b** was borylated (Scheme 20) at the allylic C-H bond using iridium catalyst **45** (2 mol%) and bis(pinacolato)diboronate **13** in the presence of DBU (**46b**) in neat **43b**. This reaction resulted in selective formation of **47b** (**47b**:**50b** 5:1) according to ^{1}H-NMR, which could be reacted *in situ* with various aldehydes (such as **48d-e**) to obtain stereodefined homoallylic alchols **49d-e** in good overall yield (Table 1, entries 4 and 5). Cyclopentene **43a** required somewhat different conditions, as the reaction with DBU (**46a**) gave the allylic product **47a** with a relatively low regioselectivity (**47a**:**50a** = 2:1). However, related N-methyl imidazole **46a** provided the desired allylic product with high selectivity under milder reaction conditions (55 °C, 2 h) than the analogous transformation of cyclohexene **43b**. The borylated product **47a** was smoothly reacted with aromatic, aliphatic or vinylic aldehydes **48a-c** to give the corresponding homoallylic alcohol products **49a-c** (entries 1-3). When the reaction was carried out at higher temperature without

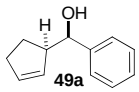
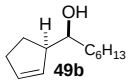
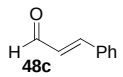
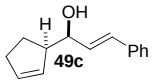
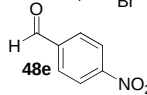
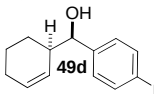
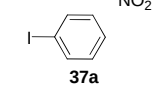
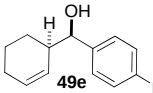
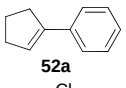
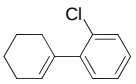
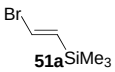
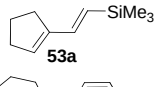
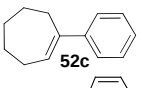
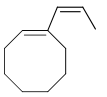
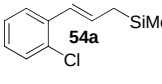
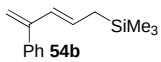
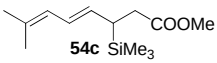
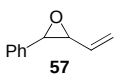
46a, vinylboronate **50a** was formed selectively, which could be reacted *in situ* with aryl iodide **37a** (entry 6) or vinyl-silyl bromide **51a** (entry 8) in the presence of palladium catalyst and base under Suzuki-Miyaura conditions.[191,192] This reaction sequence is suitable for synthesis of cyclic arylated alkenes (such as **52a**) and functionalized butadienes (such as **53a**). This approach was also successfully applied for the functionalization of cyclohexene **43b** (entry 7), cycloheptene **43c** (entry 9) and cyclooctene **43d** (entry 10). Increasing the substrate ring size from five-membered (**43a**) to eight-membered (**43d**), requires an increase in reaction temperature for the borylation from 55° C to 90° C. This indicates that the activation barrier of the C-H bond activation increases with ring-size.



Scheme 21. Synthesis of styrene and butadiene derivatives from vinylic substrates (**44a-b**) *via* catalytic borylation.

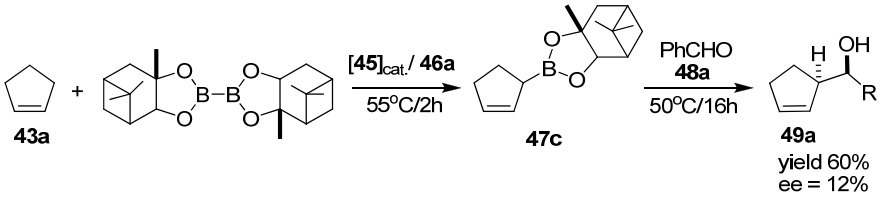
Allyl- and vinylsilanes have been widely used as useful building blocks in complex organic transformations and natural product synthesis.[212-216] The integrated borylation/Suzuki-Miyaura sequence offers an attractive synthetic route for *trans*-functionalized allylsilanes and silabutadienes from allylsilanes **44a-b** (Scheme 21).

Table 4. One-pot catalytic C-H borylation/C-C coupling of various alkenes.[a]

entry	substrates	cond.1	M	cond.2	products	yield[b]
1	 **43a** **48a**	55/2	A	20/16	 **49a**	61
2	**43a** **48b** 	55/2	A	50/16	 **49b**	60
3	**43a** **48c** 	55/2	A	40/3	 **49c**	63
4	 **43b** **48d** 	70/4	A	40/16	 **49d** 	60
5	**43b** **48e** 	70/4	A	40/3	 **49e** 	60
6	**43a** **37a**	60/16	B	50/16	 **52a**	99
7	**43b** **37e**	70/16	B	70/16	 **52b**	70
8	**43a** **51a** 	70/16	B	50/16	 **53a**	80
9	**43c** **37a**	90/4	B	60/16	 **52c**	97
10	**43d**  **51b**	100/4	B	60/18	 **53b**	52
11	**44a** **37e**	70/16	B	70/16	 **54a**	57
12	**44a**  **51c**	70/16	B	70/16	 **54b**	59
13	**44b**  **51d**	80/16	B	50/16	 **54c**	69
14	**44a**  **57**	80/16	B	50/16	**54d**	55
15	**56** **51a**	80/16	B	50/16	**58**	80

[a] Unless otherwise stated the borylation reactions were carried out in neat alkene (4-8 equiv) with diboronate **13** in the presence of 2 mol% of **45**. The reaction temperatures [°C] and times [h] are given in column cond 1. The reactions were carried out with additives **46a** or **b** [M (method)= A] or without additives [M = B]. The *in situ* generated boronates were reacted with aldehydes or aryl/vinyl halides in Suzuki-Miyaura coupling at reaction conditions given in column cond.2. [b] Isolated overall yield [%]

Allylsilane **44a** readily underwent selective borylation under similar reaction conditions (Scheme 21) to provide vinylboronate **50c**. The subsequent Suzuki-Miyaura coupling with aryl (**37e**) and vinyl (**51c**) halides affords allylsilane (**54a**) and silabutadiene (**54b**) products (entries 11-12) with a very high regio- and stereoselectivity. When the coupling reaction was performed with vinyl epoxide **57**, allylsilyl alcohol **54d** (entry 14) was formed. Our new studies show that the selective borylation and subsequent Suzuki-Miyaura coupling sequence is not restricted to the parent allyl silane, however, it can also be performed on carbethoxy-functionalized analogue **44b** (entry 13). This reaction provides a bifunctional butadiene derivative **54c** as the single product of the reaction sequence. Also other alkenes can be employed in place of allylsilanes. For example, the borylation of **56** followed by coupling with **51a** also affords silabutadiene product (**58**) in high overall yield (entry 15). In the case of acyclic substrates (**44a-b**, **56**), formation of allylboronates was not observed at all. Unlike for cyclic substrates (Scheme 20), employment of additives **46a-b** also led to the exclusive formation of vinylic boronates **50c-d** (Scheme 21).

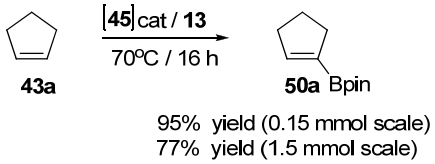


Scheme 22. Application of chiral diboronate **3b** as diboronate source.

The possibilities to replace **13** with other boronate sources was briefly studied. Application of chiral boronate bis[(-)pinanediolato]diboron was explored (Scheme 22). It was found that in the presence of **46a** as additive, the borylation reaction of **43a** proceeds as smoothly with bis[(-)pinanediolato]diboron as with **13**. As the allylic activation reaction creates a new stereocenter, this process can be potentially useful for synthesis of chiral allylboronates. Unfortunately, the level of diastereoselectivity of the above process is relatively low under the applied reaction conditions. Thus, after one-pot coupling of **47c** with benzaldehyde **48a**, homoallyl alcohol product **49a** was obtained with a poor enantioselectivity (12 %). This ee was also in accordance with the measured diastereoselectivity of the isolated allylboronate **47c**.

The successful application of the one-pot borylation-coupling sequence is attributed to the high selectivity of the reaction of allyl bo-

ronates with aldehydes (entries 1-5) and vinylboronates in Suzuki-Miyaura coupling. However, the iridium-catalyzed reaction of cyclopentene **43a** with **13** proceeds so cleanly that vinylboronate **50a** can be isolated from the reaction mixture in pure form (Scheme 23). Considering the use of inexpensive starting materials **43a** and **13** in this reaction, this is probably the simplest and the most efficient way available for the synthesis of **50a**.

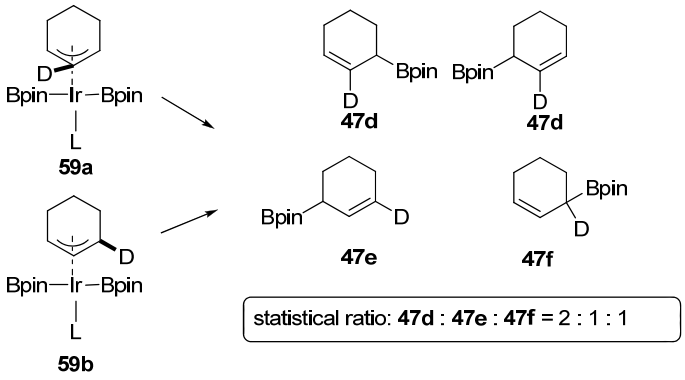


Scheme 23. Synthesis of vinylboronate **50a** by C-H bond activation borylation reaction.

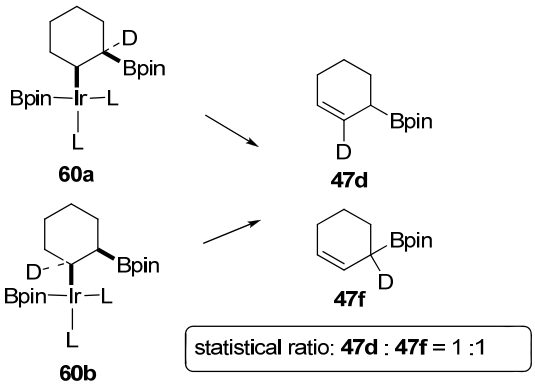
According to the above studies, when the *in situ* formation of cyclic allylboronates (such as **47a-b**) is desired, application of additives **46a-b** prove indispensible. Simple amines and phosphines cannot efficiently replace these additives. For example, application of Et_3N did not enhance the allylic selectivity of the borylation reactions. Also, the addition of coordinating ligands such as TMEDA, PPh_3, $P(OPh)_3$, DPPF or DPPB did not increase the selectivity towards the allylboronate products. Addition of catalytic amounts of 4,4'-di-tert-butyl-2,2'-bipyridine **20** (see section 1.5), which have been applied as ligand in aromatic C-H-activation/borylation processes,[154] resulted in exclusive formation of the vinylboronate product. We also attempted to replace **45** with other catalyst precursors, such as [(η^5-indenyl)Ir(cod)], [$Ir(PCy_3)(cod)(py)]PF_6$ and [$\{Rh(cod)Cl\}_2$]. However, these catalysts gave only traces or no product at all under the applied reaction conditions. The highly selective formation of acyclic boronates (such as **50a-b**) was also highly dependent of directing functionalities (such as silyl) in the alkene substrate. In the absence of directing groups, a complicated mixture of unsaturated boronates was formed. For example, 1-decene gave an isomeric mixture of decenyl boronates under the same reaction conditions.

3.2 Mechanism of the iridium-catalyzed C-H borylation

As mentioned before, catalytic C-H activation based borylation reactions of aromatics are well documented in the literature.[138-166] However, fewer studies are available for analogous reactions of alkenes. Brown and Lloyd-Jones[173] have studied the mechanism of rhodium-catalyzed vinylic functionalization of alkenes, and Marder and co-workers[178,185] have presented a useful synthetic applications of this process. Moreover, Sabo-Etienne and co-workers[180] studied the ruthenium-catalyzed hydroboration/dehydrogenative borylation of cycloalkenes. These authors have concluded that the reactions proceed by a so-called "dehydrogenative borylation mechanism". This mechanism involves initial formation of a metal-boronate complex followed by insertion of the substrate to the metal-boron bond followed by β-hydride elimination. A similar mechanism for the above described (Scheme 20) C-H bond functionalization-borylation reaction. Recently, Miyaura and co-workers[184] studied the iridium-catalyzed borylation of cyclic vinyl ethers. They concluded that the borylation of cyclic vinyl ethers proceeds by a direct C-H bond activation mechanism *via* Ir(V) intermediates, which is similar to the activation of aromatic C-H bonds.



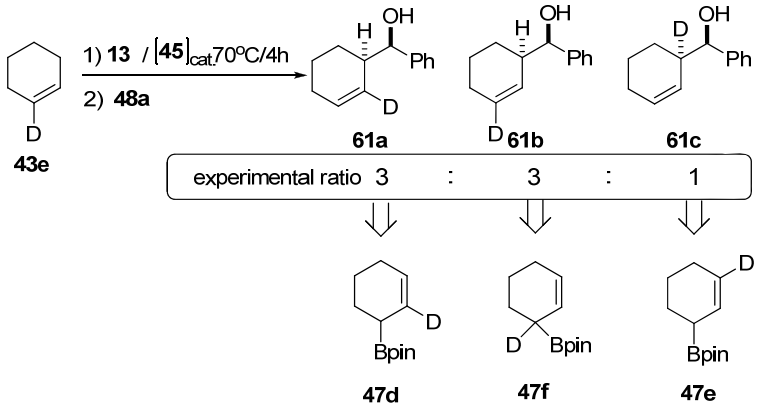
Scheme 24. Formation of allylboronates *via* (η^3-allyl)iridium complexes **59a-b**.



Scheme 25. Formation of allylboronates *via* insertion complexes **60a-b**.

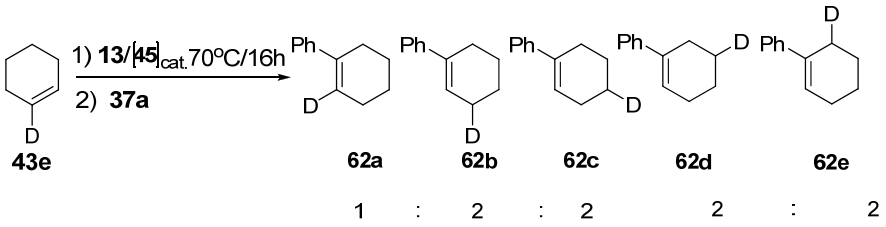
Deuterium labeling experiments. In order to clarify the mechanism of these reactions (Schemes 24-25) we have carried out a series of isotope labeling experiments and competitive borylation reactions. These studies were mainly focused on two important aspects of the reaction: (i) the mechanism of C-H bond functionalization process, which may occur by β-hydride elimination (dehydrogenative borylation mechanism) (Scheme 25) or by oxidative addition of the metal complex to the C-H bond (iridium(V) mechanism); (ii) the allyl *vs.*vinyl selectivity in borylation of cycloalkenes **43a-b**.

For the formation of allylboronates by C-H bond activation of cyclic alkenes, two basic mechanistic models were considered. The borylation may proceed *via* (η^3-allyl)iridium complexes **59** (Scheme 24) or *via* insertion complexes **60** (Scheme 25). The two mechanisms could be differentiated (Scheme 26) by reacting mono-deuterated cyclohexene **43e** with **13** using catalyst **45** at 70°C followed by addition of benzaldehyde (**48a**). The experimental ratio of the deuterated products **61a-c** was established by ^{2}H-NMR spectroscopy. It was found that the ratio of **61a** : **61b** : **61c** was 3 : 3 : 1, which shows that the corresponding allylboronates **47d** : **47e** : **47f** had been formed in formed in a ratio of to 3 : 1 : 3. If the borylation reaction had occurred *via* (η^3-allyl)iridium mechanism, the expected ratio of **47d** : **47e** : **47f** would be 2: 1: 1 (Scheme 24). On the other hand, the statistical ratio of the deuterated allylboronates *via* insertion complex **60** would be **47d** : **47e** : **47f** to 1: 0: 1 (Scheme 25). The observed ratio (Scheme 26) of **47d** : **47e** : **47f** (3 : 1 : 3) is closer to the latter, therefore we assume that the borylation reaction probably proceeds *via* insertion complex **60**. A possible explanation for the minor formation of **47e** is iridium-catalyzed partial allyl rearrangement of **43e** prior to the borylation process.



Scheme 26. Distribution of the deuturated homoallyl alcohols obtained *via* allylboronate products.

When the reaction time of the borylation step was extended to 36 h, it resulted in selective formation of the corresponding vinylboronates. This step was followed by Suzuki-Miyaura coupling with aryl-iodide **37a** affording arylated alkene isomers **62a-e** (Scheme 27). ^{2}H-NMR analysis of **62a-e** displayed a full scrambling of the deuterium labels. This scrambling can be explained by initial formation of allylboronates followed by a series of iridium-catalyzed isomerizations of the double bond.



Scheme 27. Distribution of the deuterated coupling products obtained via vinylboronate products.

Kinetic isotope effect. Further mechanistic insight was obtained by a comparison of the rate of iridium-catalyzed borylation for cyclohexene **43b** and its fully deuterated analog **63** (Figure 2) in neat **43b** and **63** respectively. Monitoring of the reaction by gas-chromatography showed that the rates of consumption of **13** with **43b** and **63** are identical. Both reactions displayed first order dependence in **13a** and the comparison of the rate constants gave a k_H/k_D value of 1.0.

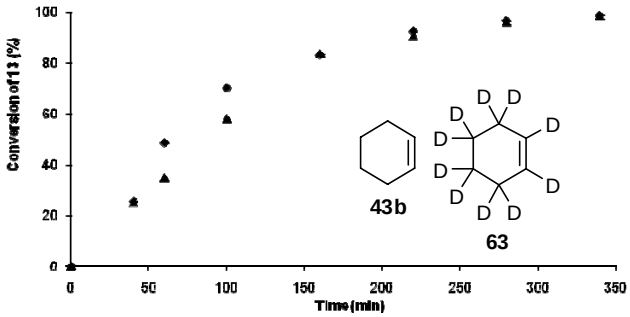


Figure 2. Competitive borylation reactions of cyclohexene (▲) *vs* cyclohexene-d_{10} (♦) monitored by GC.

Therefore, the C-H bond cleavage is not the rate-determining step of the process. It is interesting to compare these results with those of Miyaura and co-workers[184] who found that their iridium-catalyzed C-H activation-based borylation of cyclic vinyl-ethers displayed a significant deuterium isotope effect (k_H/k_D = 3.2). Based on these results, they concluded that their process occurs *via* oxidative addition of iridium to the C-H bond of the substrate. Considering the k_H/k_D value for **43b**/**63**-d_{10} is 1.0 (Scheme 28), we conclude that the reaction is unlikely to proceed *via* C-H oxidative addition, but probably according to a dehydrogenative borylation mechanism. In dehydrogenative borylation the C-H bond cleavage takes place by β-hydride elimination, which usually proceeds with a relatively low activation barrier, and therefore this process is seldom considered rate-determining in the catalytic cycle.

Regioselectivity of the C-H bond borylation. Probably one of the most useful synthetic aspects of the presented reactions is that the regioselectivity of the borylation process of **43a**-**b** could be controlled by choice of the reaction conditions. When borylation of cyclopentene **43a** was carried out using iridium catalyst **45** and **13** as the diboronate source at 55°C without any additive, formation of both allylboronate **47a** and vinylboronate **50a** was observed (Figure 3). However, after about 25 minutes the amount of vinylboronate **50a** sharply increased, while the amount of allylboronate **47a** remained constant at a relatively low level (Figure 3).

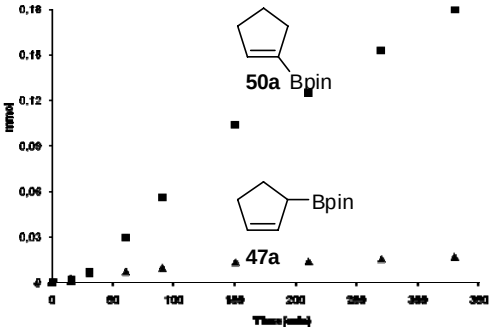


Figure 3. Monitoring of the relative concentrations of allylboronate and vinylboronate product by GC in the reaction of **43a** with **13** in the presence of catalyst **45**.

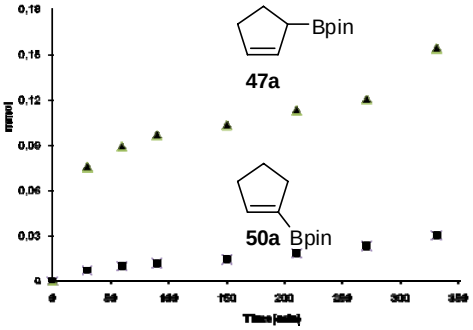
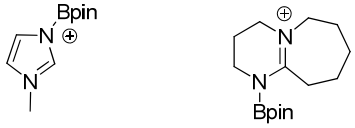


Figure 4. Monitoring of the relative concentrations of allylboronate and vinylboronate product by GC in the reaction of **43a** with **13** in the presence of catalyst **45** and **46a** as additives.

However, when the reaction is performed under the same conditions, except that **46a** (0.5 equiv) was added to the reaction mixture, the selectivity is reversed and the concentration of allylboronate **47a** increased considerably, while the amount of vinylboronate **50a** appeared as the minor product of the process (Figure 4). Obviously, imidazole derivative **46a** has an important role in changing the regioselectivity of the process, providing access to the allylic product in borylation of cyclopentene **43a**. A similar effect arises from the use of DBU **46b**, for selective synthesis of allylboronate **47b**.

Isolation and identifiction of byproducts. We attempted to explore the fate of **46a-b** in the presented allylic C-H borylation process. Thus after the described borylation reaction of **43a-b** in the presence of additives **46a-b**, boronated species **64a** and **64b** (Scheme 28) could be isolated by precipitation. Formation of a nitrogen-boron bond could be established by ^{11}B-NMR spectroscopy. Unfortunately, the counter-ion of cations **64a-b** could not be established, however may be a hydride during the catalytic process.

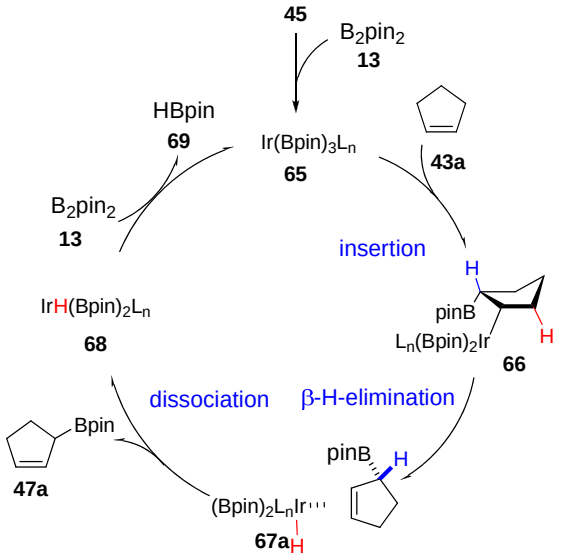


64a **64b**

Scheme 28. Species formed from the additives **46a-b** after the borylation process

Proposed catalytic cycle. Based on the above synthetic and mechanistic results, as well as the literature data available for related processes,[173,185] a catalytic cycle can be constructed for the presented C-H functionalization based borylation reaction. Extensive studies by Hartwig, Miyaura, Marder and co-workers[154,167] have shown that Ir(I) complexes readily react with **13** and other diboronates, affording tris(boryl)Ir(III) complexes. We expect that this is the initial step in the present reaction. Thus catalyst **45** reacts with **13** to provide complex **65** (Scheme 29), which is followed by coordination of the corresponding cycloalkene (such as **43a**). The next step is insertion of the iridium-boron bond to the double bond to give insertion complex **66**. Formation of this complex is the initial step of the dehydrogenative borylation mechanism.[178,180] Our deuterium labelling experiments (c.f. Schemes 24 and 25) confirmed that the reaction proceeds *via* these type of (η^1-alkyl) iridium complexes (**60**) instead of (η^3-allyl)iridium complexes (**59**). Results (Figure 2) from the measurement of the deuterium isotope effect (k_H/k_D = 1.0) also confirms a dehydrogenative

borylation mechanism, as σ-bond metathesis would have a high activation energy and, thus generate a significant deuterium isotope effect.[184,154]



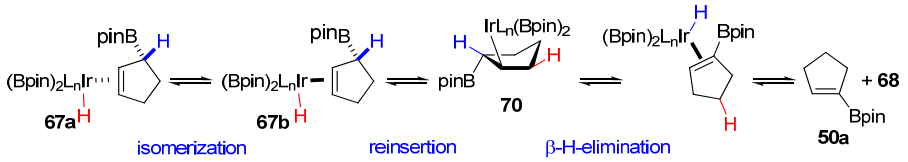
Scheme 29. Catalytic cycle for the borylation of cyclic alkenes leading to allylic C-H functionalization.

Formation of **66** proceeds *via* a stereoselective *syn* addition mechanism, and therefore the iridium-carbon and boron-carbon bonds are on the same side of the cycloalkyl ring. Accordingly, the *syn* elimination of iridium-hydride provides the allylboronate product **47a**. Elimination of the *trans*-hydride of the boronated carbon is not allowed because of steric reasons, and therefore vinylboronate product cannot be obtained as the *primary* product of the β-hydride elimination. The next step can be decomplexation of the allylic product **47a** and formation of iridium-hydride **68**. Subsequently complex **68** reacts with **13** by regenerating the active catalyst **65** and producing pinacolborane **69**.

Pinacolborane **69** is known to undergo iridium-catalyzed hydroboration[217,218] with alkenes to form alkylboronates. Fortunately, alkyl boronates are inert to aldehyde substrates and also under the applied Suzuki-Miyaura reaction conditions, and therefore they do not interfere in the above one-pot sequence. Since one of the boron atoms of **13** is sacrificed to form **69**, only one of the boronate groups of **13** may be used for C-H borylation.

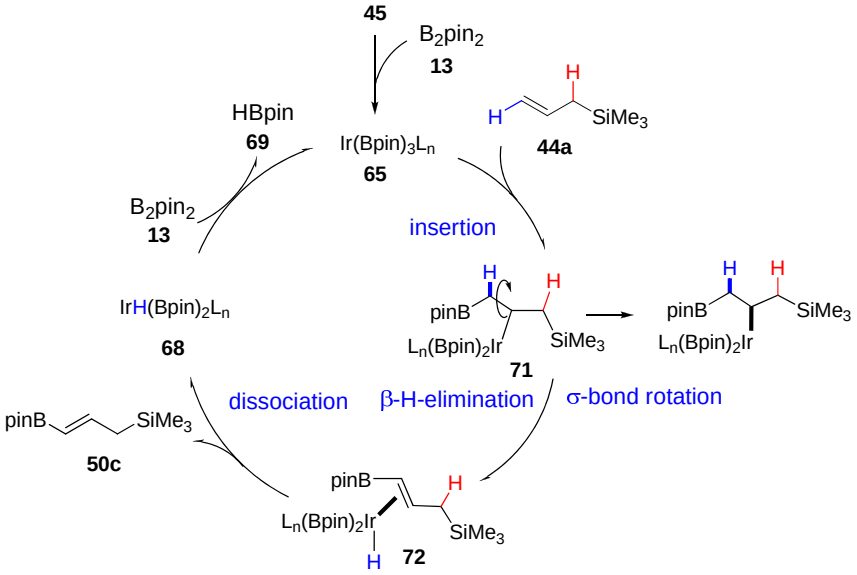
As it appears from Figure 3, when the reaction is conducted without **46a** as an additive, allylboronate **47a** could be observed only in a low

concentration in the reaction mixture, while the major product is vinyl boronate **50a**. The most probable explanation is double bond isomerization of the primary allylboronate to vinylboronate (Scheme 30)



Scheme 30. Proposed mechanism of the allylic rearrangement of the cyclic allyl boronates.

Complex **67a,** formed from β-hydride elimination of **66**, may undergo isomerization to **67b** (Scheme 30). In this isomerization process iridium switches from one side of the cyclopenetene ring to the other. Hydride insertion from intermediate (**67b**) gives complex **70.** In complex **70** the C-H bond of the boronated carbon and the Ir-C bond may enter to an eclipsed conformation, and therefore stereoelectronic requirements of the *syn* β-hydride elimination are satisfied. This process ultimately leads to formation of vinylboronate **50a**, which is probably the thermodynamic product. Application of additives **46a-b** probably inhibits this isomerization process. Detection of **64a-b** in the reaction mixture (Scheme 28) indicates that **46a-b** possibly acts as hydride scavengers on (**67**), and thus hinder the re-addition of the iridium-hydride to the double bond.



Scheme 31. Catalytic cycle of the borylation of acyclic substrates with vinylic C-H bond functionalization.

From the above mechanistic model, selective formation of the vinylic product from acyclic alkenes can also be explained (Scheme 31). Insertion of **65** to allylsilane **44a** leads to formation of insertion complex **71**. This reaction also proceeds by a *syn* mechanism (Scheme 29), however **71** may easily undergo C-C σ-bond rotation, and thus the hydrogen atom of the boronated carbon can be eliminated to give **72**, which after dissociation provides vinylboronate **50c** as the primary product.

3.3 Synthetic relevance of the C-H activation-based borylation of alkenes

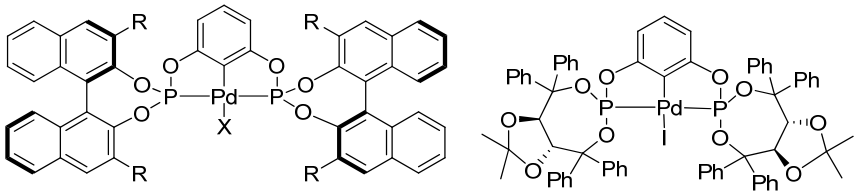
Using the above one-pot procedure, selective carbon-carbon bond formation can be carried out by carbon-hydrogen bond functionalization of unactivated alkenes. The key step is iridium-catalyzed borylation of the C-H bond followed by *in-situ* coupling reactions. For cyclic alkenes such as cyclopentene and cyclohexene, the regioselectivity of the C-H bond activation can be controlled by proper choice of the reaction conditions. In the presence of **46a-b** the reaction is selective for the formation of the allylboronate product. This allylboronate product readily reacts with aldehydes affording stereodefined allylic alcohols.

In the absence of additives, as well as for acyclic substrates vinylic, C-H bond functionalization can be carried out. The in situ formed vinylboronates readily react with aryl halides in Suzuki-Miyaura reaction. These processes can be exploited for synthesis of stereodefined allyl- and vinyl-silylbutadienes. The overall reaction, coupling of a cycloalkene with an aryl halide could in principle be performed by a standard Heck-coupling reaction.[219] However, the disadvantage of the corresponding Heck-coupling is that it gives intractable mixtures of isomeric cycloalkene derivatives,[220] while our procedure affords affords the styrene and butadiene derivatives with excellent regio- and stereoselectivity.

The presented C-H borylation/C-C coupling process offers new simple routes to densely functionalized butadiene derivatives, which are useful building blocks in natural product synthesis and drug intermediates.[212-216] By use of appropriate ligands or additives the process also has a potential for asymmetric synthesis. In this respect, two strategies could be employed: (i) application of chiral diboronates for diastereoselective boronation of cycloalkenes; or (ii) formation of allylboronates using chiral ligands on iridium.

4. Development of novel chiral palladium pincer-complex for asymmetric allylation of sulfonimines (Paper VII)

As mentioned in Section 1.3, phosphorus based palladium pincer-complexes such as PCP complex **10c**[81] can be utilized as highly selective catalysts for the allylation of sulfonimines (Scheme 8).[85,86,89] As the reaction generates a new chiral center, the development of an enantioselective version is appealing. Although reports on asymmetric allylation of imines are rather scarce,[60,61,66-68,221] Yamamoto and coworkers[60,61] have published a useful method based on chiral bisallylpalladium complexes. Unfortunately, this methodology is restricted to the use of alkylated imines as substrates, which limits the scope of this method. Our recent studies involved the synthesis of novel chiral PCP palladium pincer-complexes, which were applied as catalysts for catalytic asymmetric allylation of sulfonimines. A particular advantage of this approach is that the resulting homoallylic sulfonylamine products may easily be deprotected, preserving the alkene functionality.



73a R = H, X=**I**
73b R = Me, X=I
73c R = Cl, X=I
73d R = H, X=TFA

74

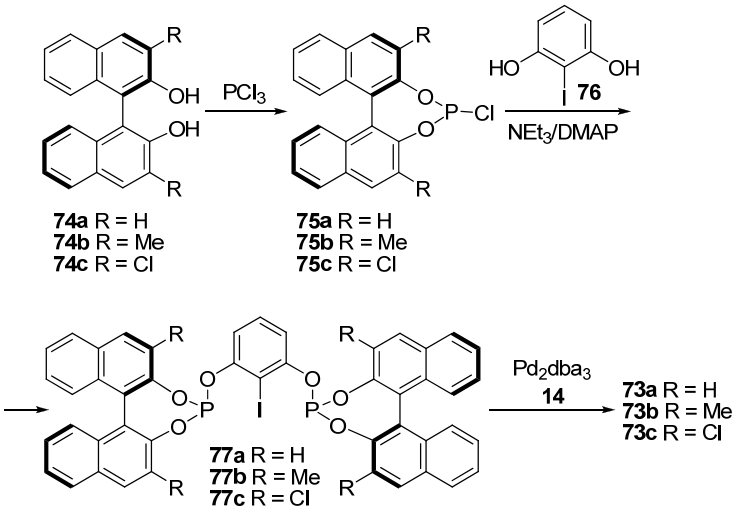
Scheme 32. Novel PCP type chiral palladium pincer-complexes employed in this study.

Two different types of chiral C_2-symmetric PCP-palladium pincer complexes based on BINOL- (**73a-d**) or TADDOL (**74**) -moieties were synthesized (Scheme 32). Application of these ligand systems is motivated by two important features: (i) possibility of modular synthesis of phosphate-based pincer-complexes and thus tuning the steric and electronic features of the chiral catalyst and; (ii) there is a large

number of BINOL and TADDOL derivatives described in the literature,[224,225] which can be employed as chiral backbones in the pincer complexes.

4.1 Synthesis of BINOL- and TADDOL-based chiral pincer-complexes

The synthesis of BINOL-based palladium complexes **73a-c** was started from BINOL-derivatives **74a-c** (Scheme 33). Treatment of **74a-c** with PCl_3 afforded the corresponding phosphorochloridites (**75a-c**). Removal of the excess PCl_3 followed by direct coupling with iodoresorcinol **76** in the presence of triethylamine and DMAP provided the corresponding proligands (**77a-c**), which were reacted with $Pd_2(dba)_3$ yielding BINOL-based complexes **73a-c**. Synthesis of pincer-complex **73a** was achieved in 89% overall yield, while preparation of γ-substituted analogues **73b** and **73c** accomplished in lower yields 18% and 26% respectively. The synthesis of TADDOL-based pincer-complex **74** was achieved similarly to the BINOL-analogues (**73a-c**), (Scheme 33) starting from TADDOL to yield the corresponding complex **74** in 34% yield. Moreover, the TFA analog (**73d**) complex **73a** (Scheme 32) was prepared in quantitative yield with AgTFA.



Scheme 33. Synthetic route for the preparation of chiral BINOL-based PCP palladium pincer-complexes.

4.2 Structural and catalytic properties of the synthesized complexes

The X-ray structure of **73a** clearly reveals short Pd-P (2.25 Å) and Pd-C (1.99 Å) bond distances indicative of a tightly bound complex with a typical pincer-type architecture (Figure 5). Moreover the presence of C_2-symmetry around a well defined chiral pocket is noted. Notably the γ-hydrogens on each BINOL sidearm are in close proximity to the open ligand site. This observation is particularly important as it suggests that fine-tuning of the chiral environment may be accomplished by substitution of the γ-posistion on the BINOL-moieties.

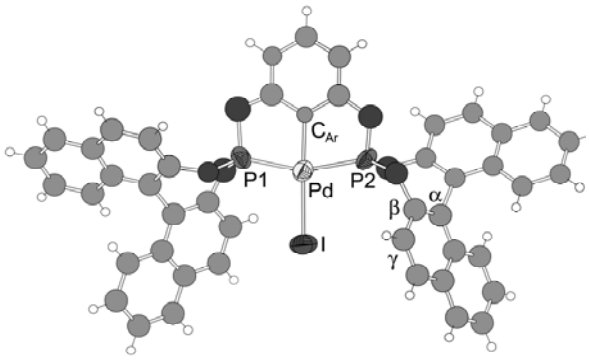
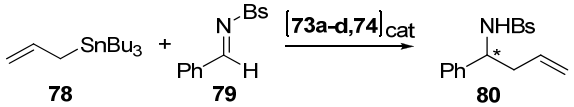


Figure 5. X-ray structure of **73a**.

BINOL-based pincer-complex **73a** readily catalyzes the allylation of sulfonimine **78** with allyltributylstannane **79** affording homoallylic amine **80** (Scheme 35) in 70% yield, however with a low enantioselectivity (20% ee) (Table 5, entry 1) in a very slow reaction (72 h at 20 ^{o}C).



Scheme 35. Employment of chiral PCP-complexes in catalytic asymmetric allylation.

On the other hand, employment of analogous Pd-TFA complex **73d** gave a much higher catalytic activity, in line with earlier results[85-86] from the palladium pincer catalyzed allylation of sulfonimines and aldehydes, affording product **80** in 90% yield after 17 h, though, unfortunately the enantioselectivity was very low (5% ee) (entry 4). In contrast to **73a** employment of γ–substituted BINOL-complex analogues **73b** and **73c** leads to a significantly improved enantioselectivity (59% ee and 34% ee respectively), (entries 2-3). The TADDOL-based catalyst **74** showed a low catalytic activity (entry 5) and enantioselectivity was low (5% ee) as well.

Table 5. Asymmetric allylation of **79** with **78**.[a]

Entry	Cat.	Time[h]	ee[b][%]	Yield[c][%]
1	**73a**	72	20	70
2	**73b**	90	59	74
3	**73c**	72	34	65
4	**73d**	16	5	90
5	**74**	72	5	60

[a]All reactions were conducted in DMF at 20°C.[b] Determined by chiral-phase HPLC.
[c] Isolated yield.

In summary, we shown that various BINOL- and TADDOL-based palladium pincer-complexes could easily be synthesized in a three step procedure. Moreover, the synthesized BINOL-based complexes showed to be promising catalysts for the asymmetric allylation of sulfonimines. Recent results from the Szabó group[226] have shown that the enantioselectivity of the allylation process could be further increased (up to 85% ee) by modification on the BINOL-moieties. Catalysts **73a-c** and their analogs were later also employed by the Szabó group[226-227] and others[228-229] in several other asymmetric applications.

5. General conclusions and outlook

We have shown that palladium pincer-complexes may be employed in palladium-catalyzed borylation reactions for the synthesis of regio- and stereodefined, densely functionalized allylboronic acid derivatives. These reactions have a broad synthetic scope since a wide variety of allylic substrates may be employed as substrates. Moreover, these novel allylboronic acids are useful reagents in the palladium catalyzed coupling reactions with haloarenes, providing selectively the corresponding branched allylic isomer. Furthermore, a novel synthetic pathway for the preparation of allyl- and vinylboronates *via* catalytic carbon-hydrogen bond activation/boronation of cyclic alkenes has been developed. This reaction can be combined with other processes in a one-pot sequence, and thus stereodefined homoallylic alcohols and functionalized butadiene derivatives can be obtained. Finally, it has been shown that novel synthesized chiral-pincer complexes are promising catalysts for the asymmetric electrophilic allylation of imines.

The developed methods have a particulary great importance in allylboronate chemistry. At present, our boronation procedure based on allylic alcohol substrates is one of the most efficient methods for obtaining functionalized allylboronates. The presented catalytic C-H borylation reaction opens a new route for selective synthesis of vinyl- and allylboronates. This method offers the opportunity for applying carbon-hydrogen bond functionalization of alkenes as the initial step in regio- and stereoselective one-pot carbon-carbon bond formations.

Acknowledgements

Jag vill tacka:
Min handledare prof. Kálmán Szabó för utmärkt handledning och stort engagemang
Prof Jan-Erling Bäckwall för visat intresse av denna avhandling
Extra tack till Luke Pilarski, Nicklas Selander, Johanna Larssonoch Ian Cumpstey för korrekturläsning
Mina medarbetare Nicklas Selander, Sara Sebeliusoch Olle Wallner
Szabó gruppen: Juhanes Aydin, Nicklas Selander, Johanna Larsson, Petter Österberg, Friedrich Böse och Luke Pilarski; för en härlig stämning
även gamla medlemmar som Olle Wallner, Niclas Solin, Sara Sebelius och Johan Kjellgren för alla goda minnen
Gamla Post docs Perumal och Senthil
Gamla exjobbare Andreas, Mahmoud, Ceasar, Kipke och Cathrin.
Nicklas för all teknisk hjälp
Alla på avdelningen på organisk kemi för en trevlig atmosfär
Juhanes och Nicklas och alla andra för alla trevliga konferensresor
Generösa resebidrag från Knut Alice Wallenbergs stiftelse, Kemistsamfundet, AstraZeneca – Nils Löfgren och Hilda Rietz
Kamilla min käresta
Mina vänner
Min familj

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