Palladium-Catalyzed Synthesis and Transformation of Organoboranes

Sara Sebelius

Stockholm University
Department of Organic Chemistry
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Abstract

This thesis presents the development of new palladium-catalyzed transformations involving synthesis and application of allylborane reagents. In these reactions various palladium sources, including pincer complexes and commonly used catalysts were applied.

A new transformation for allylation of aldehyde and imine substrates was devised using allyl acetates, diboronate reagents and catalytic amounts of $Pd_2(dba)_3$. By employment of commercially available chiral diboronates enantioenriched homoallyl alcohols could be obtained.

We have also developed a palladium-catalyzed method for synthesis of functionalized allylboronic acids from vinyl cyclopropane, vinyl aziridine, allyl acetate and allyl alcohol substrates using diboronic acid as reagent. In this process a highly selective selenium based pincer-complex was used as catalyst. The resulting allylboronic acid products were converted to potassium trifluoro(allyl)borates or allylboronates.

The functionalized allylboronic acids generated in the above procedure were employed as reagents in two synthetic transformations. One of these transformations involves a palladium(0)-catalyzed coupling reaction between allylboronic acids and aryl iodides. The reaction was regioselective for the branched allylic product, typically difficult to prepare in the absence of directing groups. We also developed another transformation for allylation of aldehydes with allyl alcohols via allylboronic acid intermediate. This procedure can be performed as a simple one-pot sequence affording homoallyl alcohols with excellent stereo- and regioselectivity.

List of Publications

This thesis is based on the following papers referred to by their Roman numerals **I-VI**.

I. S. Sebelius, O. A. Wallner and K. J. Szabó, *Org. Lett.* **2003**, *5*, 3065. **Palladium-Catalyzed Coupling of Allyl Acetates with Aldehyde and Imine Electrophiles in the Presence of Bis(pinacolato)diboron.**

II. S. Sebelius and K. J. Szabó, *Eur. J. Org. Chem.* **2005**, 2539. **Allylation of Aldehyde and Imine Substrates with In Situ Generated Allylboronates. A Simple Route to Enantioenriched Homoallyl Alcohols.**

III. S. Sebelius, V. J. Olsson and K. J. Szabó, *J. Am. Chem. Soc.* **2005**, *127*, 10478. **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.**

IV. V. J. Olsson, S. Sebelius, N. Selander and K. J. Szabó, *J. Am. Chem. Soc.* **2006**, *128*, 4588. **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.**

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

VI. N. Selander, S. Sebelius, C. Estay, and K. J. Szabó, *Eur. J. Org. Chem.* **2006**, *in press.* **Highly Selective and Robust Palladium-Catalyzed Carbon-Carbon Coupling between Allyl Alcohols and Aldehydes via Transient Allylboronic Acids.**

Contents

Abbreviations

Bn	Benzyl
cat	Catalyst
COD	Cyclo-octa-1,5-diene
dba	Dibenzylidene acetone
d.r.	Diastereomeric ratio
DMSO	Dimethyl sulfoxide
E^+	Electrophile
ee	Enantiomeric excess
L	Ligand
L.A.	Lewis acid
Lg	Leaving group
M	Metal
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
OAc	Acetate
Ph	Phenyl
PTS	p-Toluenesulfonic acid
r.t.	Room temperature
THF	Tetrahydrofuran
Ts	Tosyl
TS	Transition state

1. Introduction

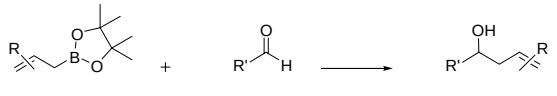
Application of palladium catalysis offers a mild and selective method for synthesis and transformation of allylic organometallic compounds.[1] Many excellent methods have been published for synthesis of allylic boranes, silanes, stannanes and other compounds, which are reactive synthetic intermediates in advanced organic chemistry and natural product synthesis.[1, 2] Allylboranes represent an important class of organic reagents because of the high stereoselectivity of the coupling reactions with electrophiles. However, these compounds are relatively unstable and therefore preparation of functionalized allylboranes is often a challenging synthetic task.

This thesis is focused on the development of palladium-catalyzed transformations involving allylboranes.[3-8] In these reactions we employed both pincer-complex[5-6] and common palladium(0)[3,4] catalysis to generate these species. The pincer-complex-catalyzed transformation proved to be a very efficient way to prepare functionalized allylboronic acids.[5-6] Thus, we have explored the possibilities to couple these allylboronic acids with aryl iodides.[7] Furthermore, we developed a new efficient one-pot reaction for coupling of allyl alcohols with aldehydes via catalytic generation of allylboronic acids.[8]

1.1 Synthesis of allylboranes from allylmetal reagents

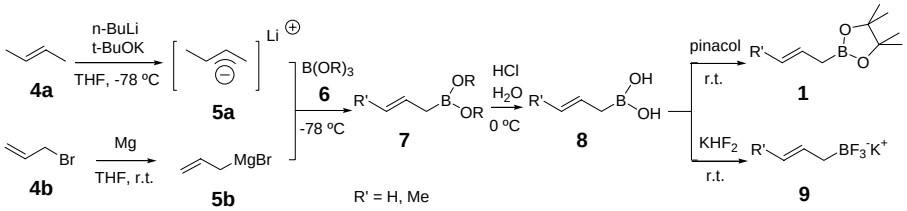
Allylborane derivatives (e.g. **1**) are highly selective reagents in organic synthesis. One of the most important reactions involves allylation of aldehydes (**2**) to afford homoallylic alcohols (**3**) (Scheme 1).[9] Allylboranes are also important alternatives to other allylating agents, such as allylsilanes and allylstannanes. For example, the stereoselectivity of the allylation reactions with allylboranes is usually different from that of the corresponding transformations with allylsilanes and allylstannanes.[9a, 10] Furthermore, allylsilanes and allylstannanes react with aldehydes only in the presence of Lewis acid

catalysts, while allylboranes usually undergo uncatalyzed coupling with these electrophiles.



Scheme 1. Allylation of aldehyde by allylboronate allylating agent.

The simplest method for synthesis of allylboranes (Scheme 2) is based on transmetalation of allyl lithium (**5a**)[2d, 11] or Grignard reagent (**5b**).[2c, 2e] In these processes, the corresponding allylmetal species are generated from **4a** or **4b** followed by addition of trialkoxy borane (**6**), affording allyl dialkoxy borane derivatives (**7**), which are usually hydrolyzed to the corresponding allylboronic acids (**8**). The allylboronic acids are known to be highly unstable;[12] however, these compounds can easily be converted to relatively stable allylboronates (**1**) or potassium trifluoro(allyl)borates[13] (**9**).



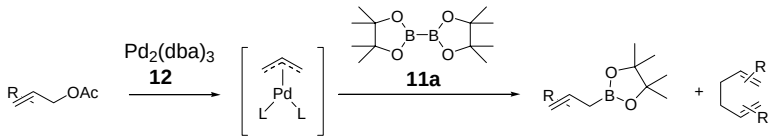
Scheme 2. Commonly used methods for allylborane preparation.

Since hydrolysis of allyl dialkoxy borane derivatives **7** requires harsh reaction conditions, it would be desirable to prepare allylboronic acids (**8**) directly, which is, however, not possible by the above described methods (Scheme 2). We have found a new procedure to prepare allylboronic acids (**8**) directly from vinyl cyclopropanes, vinyl aziridines, allyl acetates and allyl alcohols. These studies are given in Chapter 3.

1.2 Transition metal-catalyzed methods for synthesis of allylboranes

As mentioned in Section 1.1, the simplest method for synthesis of allylboranes is based on transmetalation of allyllithium or Grignard reagents. However, these methods are associated with a low functional group tolerance, and therefore functionalized allylboranes incorporating carbonyl,[14] amine, nitrile, nitro and related functionalities cannot be prepared by these processes.

On the other hand, palladium-catalyzed reaction of allyl electrophiles with appropriate boronation reagent offers a viable alternative route to functionalized allylboranes.[15, 16, 17] For example, Miyaura and co-workers[15a] synthesized various functionalized allylboronates from allyl acetates (**10**) and bis(pinacolato)diboron (**11a**) in the presence of palladium catalyst **12** (Scheme 3). Unfortunately, the allyl-allyl coupling process is an undesired side reaction in this transformation. Formation of side-product **13** can be explained by the reaction of allylboronate product **1** with mono-allylpalladium intermediate **14** to give a bis-allylpalladium complex (see Section 1.4), which undergoes allyl-allyl coupling.[18] Obviously, efficient synthesis of allylboranes requires the use of new types of highly efficient catalysts, which do not react with the allylborane products (**1**). We have found that pincer complex catalysts fulfil this requirement; these studies are given in Chapter 3 of this thesis.



10 **14** **1** **13**

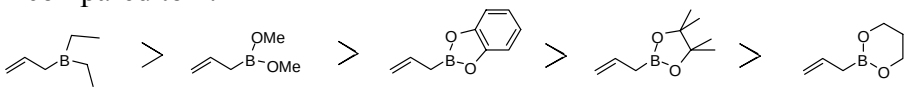
Scheme 3. Preparation of allylboronates in palladium-catalyzed reaction by Miyaura and co-workers.[15a]

1.3 Allylboranes as reagents in organic chemistry

Allylboranes are important substrates in coupling reactions. The most commonly applied reaction is the coupling with aldehyde electrophiles.[9, 19a-b, 20-25]

Reactivity of allylboranes.[2e-f, 2n] Allylboronates are relatively easy to handle, and therefore these compounds are attractive precursors in selective boronation reactions.[2e] In allylboronates (**1**) the lone-pair (n_π) electrons of oxygen conjugate to the empty p_π orbital of boron. This n_π-p_π interaction leads to decreased electrophilicity of the boron atom. Therefore when electron-withdrawing groups decrease the availability of the lone pairs of oxygen attached to boron, the boron atom becomes more electrophilic. For example, catechol allylboronate (**15**), in which the lone pairs of the boronate oxygen are delocalized by the benzene ring, is highly reactive. Dialkyl allylboranes (**16**) are even more reactive, as they lack lone pair electrons, which are present in the oxygen of boronates. Without oxygen lone pairs next to boron the n_π-p_π interaction does not apply, and the empty p_π orbital of boron is

easily accessible to nucleophiles. This makes dialkyl allylboranes (**16**) extremely electrophilic and highly unstable, and explains the wide synthetic application of the more stable allylboronates (**1**). In general, five-membered cyclic boronate derivatives (borolanes, **1**) are more reactive in allylborations than their six-membered analogues (borinanes, **17**).[2e] Furthermore, acyclic species (e.g. **7**) undergo allylboration more rapidly than cyclic ones (Scheme 4). This trend can be explained by the increased steric bulk of the substituents in **17** and **1** compared to **7**.

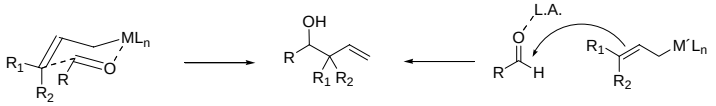


16 **7** **15** **1a** **17**

Scheme 4. Reactivity order of allylborane derivatives.

The reactivity of allylboranes is highly dependent on the substituent (*vide infra*) and solvent effects as well as the reaction temperature. Brown and co-workers[2e] concluded that noncoordinating polar solvents enhance the rate of allylboration, while low solvent polarity or a polar solvent that can coordinate to the allylboron reagent retards the reaction rate. According to Brown and co-workers,[2e] an increase in the temperature by 25 °C increased the rate of allylation by a factor of three.

Selectivity of the allylation reactions. The highly stereoselective allylation of aldehydes is one of the most important reasons for application of allylboronates in these processes. Allylboron compounds belong to the type I class of allylating reagents (**18a**)[10] (Scheme 15, $ML_n = B(OR)_2$), whose addition to aldehydes occurs via six-membered cyclic transition states characterized by internal activation of the aldehyde by the boron centre.[19b] This mechanism contrasts with the type II reagents (**18b**) exemplified by allylsilane and allylstannane analogues ($M'L_n = SiR_3$, SnR_3), which react with aldehydes generally under the activation of an external Lewis acid catalyst and proceed by way of open transition structures (Scheme 5).

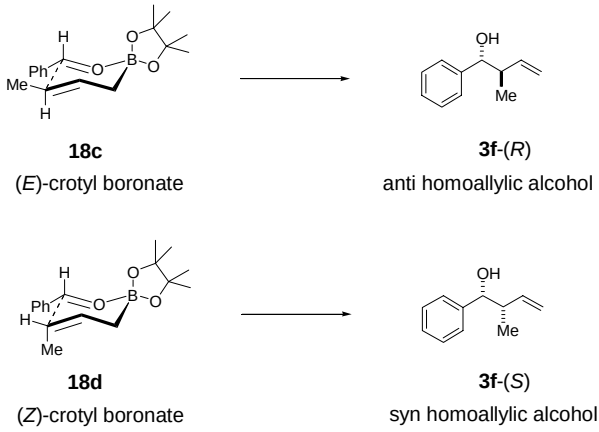


18a **3** **18b**

type I type II

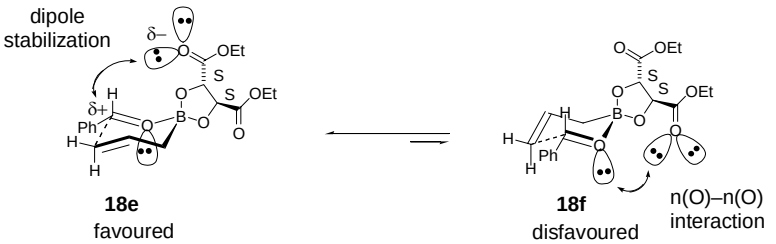
Scheme 5. Mechanism[10] for type I and type II allylation reagents.

Because of their compact and organized transition state structure, allylborations with γ-substituted reagents tend to demonstrate a level of diastereoselectivity superior to that of type II reagents and in a highly predictable fashion.[20] For example, (*E*) and (*Z*)-crotylboron reagents (**18c** and **18d**) provide the corresponding anti (**3f**-(*R*)) and syn (**3f**-(*S*)) addition products with very high selectivity (Scheme 4).



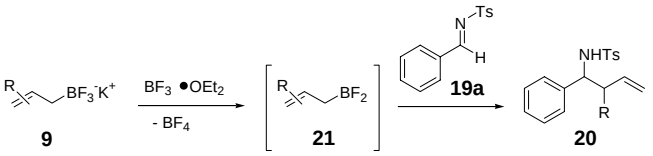
Scheme 6. Rationalization of the diastereoselectivity in the reaction of allylboranes with aldehydes.

Enantioselective allylation can also be achieved in the reactions of aldehydes with chiral allylboronates. The mechanism of the asymmetric induction was studied by Roush and co–workers (Scheme 7).[2c, 21] According to these authors, TS structure **18e** is stabilized by attractive interactions between the aldehyde carbonyl carbon (δ+) and the ester carbonyl oxygen (δ–).[21] On the other hand, **18f** is destabilized by four–electron interactions induced by the close proximity of the lone–pair electrons in the aldehyde carbonyl and in one of the ester carbonyls of the tartrate functionality. Considering these interactions, TS **18e** is favored, and therefore the allylation by allyl diethyl-(*S,S*)-tartrate glycolboronate reaction gives predominantly the (*R*)-enantiomer.[2c, 22]

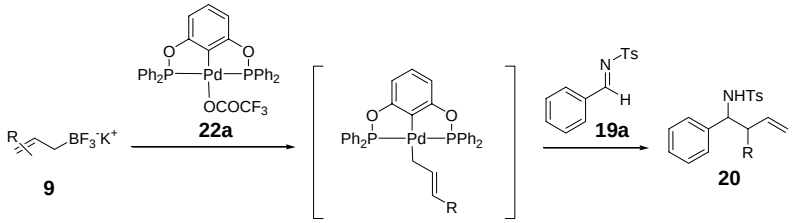


Scheme 7. Mechanism of the enantioselection in the TS of the allylation reaction.

Reactivity of potassium allyl(trifluoro)borates. Although allylboronates (such as **1a**) are easier to handle than dialkyl allylboranes (such as **16**), these compounds still suffer from a low thermal stability and a their purification is cumbersome. A few years ago Batey and co-workers,[2f, 13] described a new class of allylborane species including a potassium trifluoroborate functionality (**9**). Potassium allyl(trifluoro)borates are air and moisture stable species; and they can be easily purified by recrystallization from acetone or methanol. These species are efficient allylating reagents for aldehyde (**2**)[2f, 13] and imine (**19**)[2h, 26] substrates affording homoallyl alcohols (**3**) and homoallyl amines (**20**). In order to react with aldehydes or imines the potassium allyl(trifluoro)borates (**9**) have to be activated. This activation can be performed using $BF_3{\bullet}OEt_2$ (Scheme 8), which strips off a fluoride ion from the trifluoroborate salt affording allylic difluoroborane (**21**), generating a highly reactive allylating agent.[2f, 2h, 13] Alternatively, allyl(trifluoro)borates (**9**) can be activated by using catalytic amounts of palladium pincer-complex **22a** (see Section 1.5), followed by allylation of sulfonimines (Scheme 9).[26]



Scheme 8. Activation of allyl(trifluoro)borates (**9**) by use of $BF_3{\bullet}OEt$.

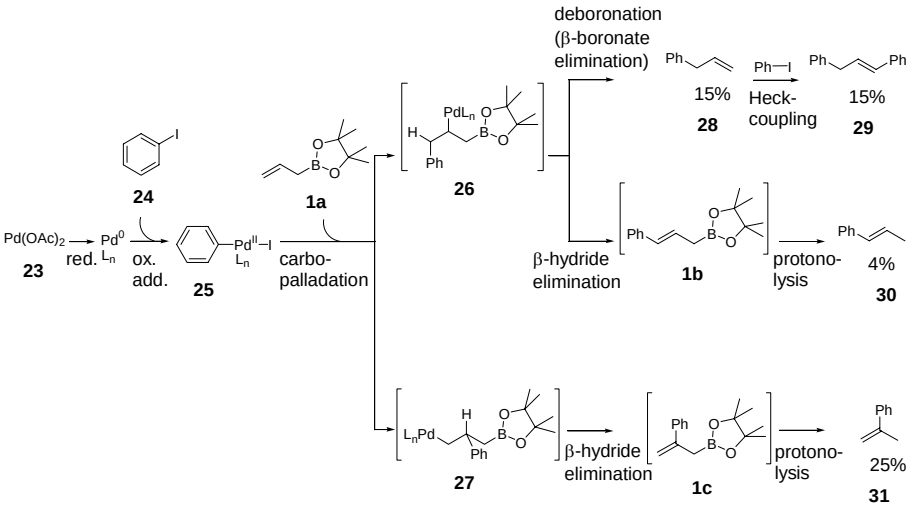


Scheme 9. Activation of **9** by palladium pincer-complex **22a**.

Palladium catalyzed coupling of allylboranes with haloarenes. Hallberg and co-workers[27] reported the first studies of arylation of allylboronates under Suzuki-Miyaura conditions. According to these studies, when iodobenzene (**24**), pinacolato allylboronate (**1a**) and catalytic amounts of palladium acetate (**23**) were reacted at 100 °C in

THF, a complex mixture of products was obtained. It was found that the expected coupling product (**28**) was formed only in trace amounts, while the major product was methyl styrene (**31**); considerable amounts of diphenyl propene (**29**) were also generated. Formation of **31** and **30** together with the results of further mechanistic studies suggested that the palladium-catalyzed coupling of **1a** to **24** does not proceed via (η^3-allyl)palladium complexes.[27] Based on the analysis of the obtained reaction mixtures, the authors concluded that the coupling reactions take place via carbopalladation of **1a** to give reaction intermediates **26** and **27**, which probably undergo either β-hydride elimination or deboronation to give **1b**-**1c** and **28**, respectively. These reaction intermediates are converted then to final products **29**-**31** (Scheme 10).

We have carried out related coupling reactions under Suzuki-Miyaura conditions using functionalized allylboronic acids in place of **1a**; these studies are described in Chapter 5.

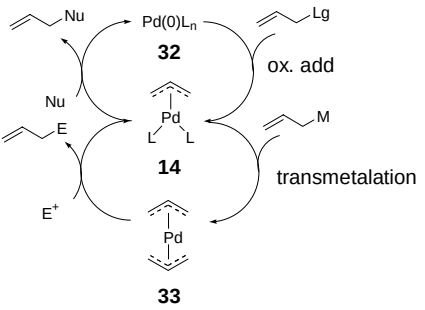


Scheme 10. Suggested mechanism for palladium-catalyzed coupling of allylboronate **1a** with iodobenzene.

1.4 Bis-allylpalladium complexes

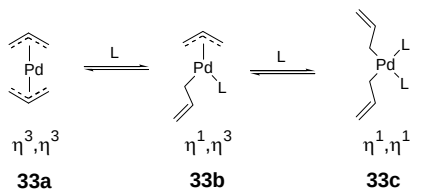
Allylic displacement of chloride, carbonate and acetate groups with nucleophilic reagents is one of the most widely applied synthetic procedures.[1] These reactions proceed via catalytically generated mono-allylpalladium complexes **14** (c.f. Scheme 3),[1a-c, 28] which are formed by oxidative addition of palladium(0) (**32**) to the allylic

substrate. Subsequent nucleophilic[29] attack on **14** provides the allylated product and regenerates the palladium(0) catalyst.[1] On the other hand, complex **14** can also be reacted with several main-group allylic organometallics to form a bis-allylpalladium complex **33** (Scheme 11).[1k, 18a] In contrast to mono-allylpalladium complexes bis-allylpalladium complexes react with elecrophiles.[30, 31g, 32, 33e]



Scheme 11. Formation and reactivity of mono-allylpalladium and bis-allylpalladium complexes.

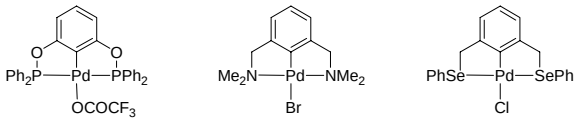
Bis-allylpalladium complexes may occur in several isomeric forms (Scheme 12). In an η^3,η^3-bis-allylpalladium complex (**33a**) the allyl moieties occupy two coordination sites each. Coordination of additional ligands changes the hapticity of the allyl moieties. In case of phosphine ligands, the η^1,η^3-allyl complex **33b** is a thermodynamically stable species, which readily reacts with electrophiles (such as aldehydes and imines) under catalytic conditions.[18b-c, 30, 34] A bis-allylpalladium complex may also isomerize to η^1,η^1-form **33c**, which is prone to undergo reductive elimination to give the allyl-allyl coupling product.[18] Formation of diene product **13** in the boronation reaction developed by Miyaura and co-workers (Scheme 3) can also be explained by the formation of η^1,η^1-bis-allylpalladium complex **33c**.



Scheme 12. η^3- η^1 isomerization of a bis-allylpalladium complex.

1.5 Palladium pincer complexes

Organometallic complexes containing a terdentate monoanionic (pincer) ligand of the general structure $[2,6\text{-}(ACH_2)_2C_6H_3]^-$ are called pincer complexes (Scheme 13).[35a] The pincer complexes are usually classified according to the heteroatoms on the side-arms of the pincer ligands. For example, complex **22a**[35b] is called a PCP complex, **22b**[32c] is designated as a NCN complex; while **22c**[35d] referred to as a SeCSe complex.



22a **22b** **22c**

Scheme 13. The palladium pincer complexes employed in this thesis.

Recently a number of catalytic applications using pincer-complex catalysts appeared.[26, 33] There are three important features that make palladium pincer complexes useful species in catalytic applications.

(1) The strong terdentate coordination of ligand leaves only a single coordination site available for external ligands. Therefore, bis-allylpalladium complexes (e.g. **33**) cannot be formed from pincer complexes.

(2) In pincer complexes the oxidation state of palladium is restricted to +2 under ambient conditions.[36] Therefore, functionalities sensitive to oxidative addition (e.g. aromatic bromides) are tolerated.

(3) The strong terdentate coordination of the ligand prevents dynamic ligand exchange processes, which ensures high catalyst stability.

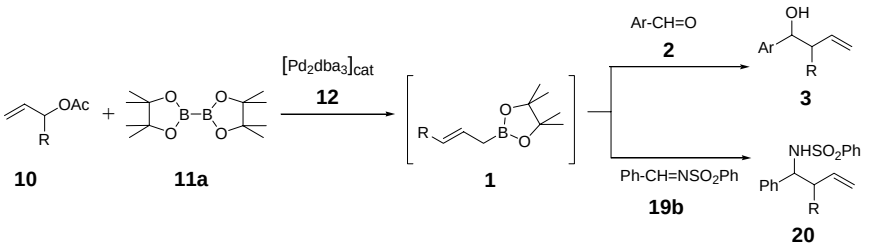
These properties of pincer-complexes can also be exploited for design of new efficient syntheses of functionalized allylboranes, as discussed in Chapter 3.

2. Allylation of Aldehyde and Imine Substrates with In Situ Generated Allylboronates (Papers I-II)

Palladium catalysis offers an attractive synthetic approach for stereo- and regioselective allylation of electrophilic substrates.[37] These reactions usually proceed in two consecutive steps. The first is a palladium-catalyzed formation of an allylmetal species from allylhalides or allyl acetates and an organometallic reagent[31, 33e] (such as $SnCl_2$, $ZnEt_2$, Et_3B, $(SnMe_3)_2$). Usually the allyl-metal intermediates are reactive enough for direct coupling with electrophiles.[31a-f] However, less reactive species, such as transient trialkyl allylstannanes, require a second palladium-catalyzed step to accomplish the allylation of the electrophile.[31g, 33e] The organometallic reagents employed in these reactions have to comply with two important requirements: 1) they must be compatible with several reactive functionalities to ensure a broad synthetic scope for the catalytic transformations; and 2) the transient allylmetal compound has to undergo highly regio- and stereoselective coupling with the electrophile.

2.1 Boronate substitution of allyl acetates in the presence of electrophiles

We have found that bis(pinacolato)diboron (**11a**) largely satisfies the above requirements. Functionalized allyl acetates (**10**) could be reacted with aldehyde (**2**) or imine (**19**) electrophiles in the presence of **11a** and catalytic amounts of $Pd_2(dba)_3$ (**12**) affording the corresponding homoallylic alcohol (**3**) or amine (**20**) products with high regio- and stereoselectivity (Scheme 14).

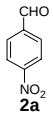
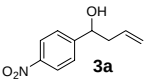
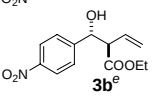
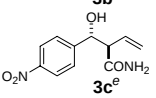
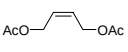
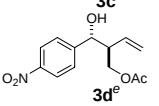
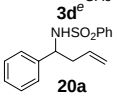
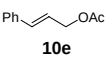
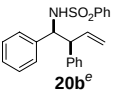
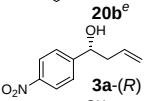
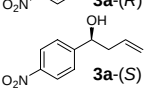
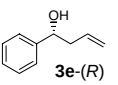
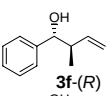
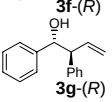
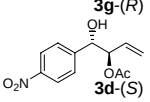
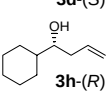
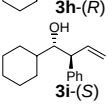


Scheme 14. Formation of homoallylic alcohols and amines by in situ formation of allylboronates.

In a typical reaction the diboronate (**11a**), the allyl acetate (**10**), the appropriate electrophile (**2** or **19**) and catalytic amounts of **12** were mixed in DMSO, and after the allotted reaction time (Table 1), the corresponding product (**3** or **20**) was isolated. Using **11a** as diboronate reagent, the typical reaction temperature was room temperature or 40°C, however the crotyl substrate (entry 2) required a somewhat higher reaction temperature (60 °C). The broad synthetic scope is a particularly important feature of this reaction as many functionalities, such as NO_2, COOEt, $CONH_2$ and OAc (entries 2-4), are tolerated. The reactions involving substituted allyl acetates provide the branched products with very high regioselectivity and diastereoselectivity. In many cases a single diastereomer was obtained (entries 4 and 6), while in the rest of the reactions one of the diastereomers was predominate. It was found that the aldehyde electrophile (**2**) reacted with anti diastereoselectivity (entries 2-4), while the imine substrate (**19**) gave exclusively or predominantly syn product (e.g. entry 6).

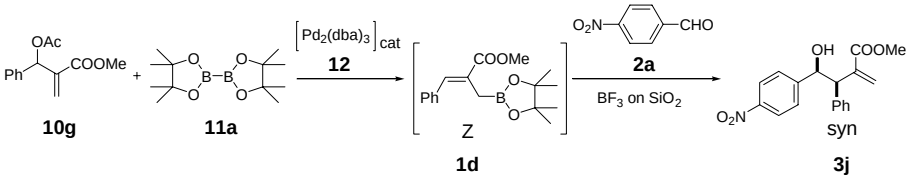
We have found that the best solvent for the reaction is DMSO. In other solvents, such as THF, acetonitrile, benzene or toluene, black palladium(0) was precipitated immediately after addition of the allyl acetate component. We were not able to stabilize the palladium(0) catalyst in these solvents by addition of phosphines (e.g. PPh_3, $P(OPh)_3$) or activated alkenes (e.g. maleic anhydride and COD), as these additives strongly inhibited the catalytic process. Other strongly coordinating ligands, such as halogenide salts, retarded or completely inhibited the catalytic formation of the transient allylboronates. Therefore employment of $Pd_2(dba)_3$ as catalyst source and DMSO as solvent or co-solvent (*vide infra*) seems to be indispensable for the catalytic generation of allylboronates from diboronate precursors.

Table 1. Selected allylation reactions of aldehyde and imine electrophiles with catalytically generated allylboronates.

entry	allyl	diboronate	electrophile	method[a]	product	d.r.[b]	ee[c]	yield[d]
1	 **10a**	**11a**	 **2a**	20/21	 **3a**	-	-	73
2	 **10b**	**11a**	**2a**	20/24	 **3b**[e]	8:1	-	75
3	 **10c**	**11a**	**2a**	20/21	 **3c**[e]	8:1	-	61
4	 **10d**	**11a**	**2a**	20/93	 **3d**[e]	ao	-	69
5	**10a**	**11a**	 **19**	60/4	 **20a**	-	-	80
6	 **10e**	**11a**	**19**	20/69	 **20b**[e]	so	-	91
7	**10a**	**11b**	**2a**	20/19	 **3a**-(*R*)	-	53	83
8	**10a**	**11c**	**2a**	20/22	 **3a**-(*S*)	-	49	92
9	**10a**	**11f**	**2a**	20/21	**3a**-(*R*)	-	1	62
10	**10a**	**11b**	 **2b**	20/63	 **3e**-(*R*)	-	45	83
11	 **10f**	**11b**	**2b**	20/96	 **3f**-(*R*)	ao	33	76
12	**10e**	**11b**	**2b**	20/21	 **3g**-(*R*)	ao	43	83
13	**10d**	**11b**	**2a**	20/21	 **3d**-(*S*)	ao	50	67
14	**10a**	**11b**	 **2c**	40/66	 **3h**-(*R*)	-	48	58
15	**10e**	**11b**	**2c**	20/69	 **3i**-(*S*)	ao	53	77
16	**10a**	**11b**	**19**	20/25	**20a**	ao	0	52

[a] The reactions with were conducted in DMSO (**11a**) or DMSO/toluene 1:1 (**11b-f**) using 6 mol% Pd_2dba_3 at given the temperature/reaction time [hours]/[°C]. [b] Diastereomer ratio (anti/syn); ao=anti isomer only; so=syn isomer only. [c] Enantiomeric excess. The major enantiomer is depicted in the product column. [d] Isolated yield. [e] The relative stereochemistry is given.

Inspired by our results, Kabalka and co-workers[16, 17] prepared homoallyl alcohols in a one-pot reaction from substituted allyl acetates. In this reaction allylboronate **1d** was prepared in situ by Pd_2dba_3 catalyzed boronation of Baylis-Hillman acetate adducts (e.g. **10g**) with bis(pinacolato)diboron (**11a**). Subsequently **1d** was reacted with activated aromatic aldehydes (such as **2a**) affording functionalized homoallyl products (**3j**) (Scheme 15).

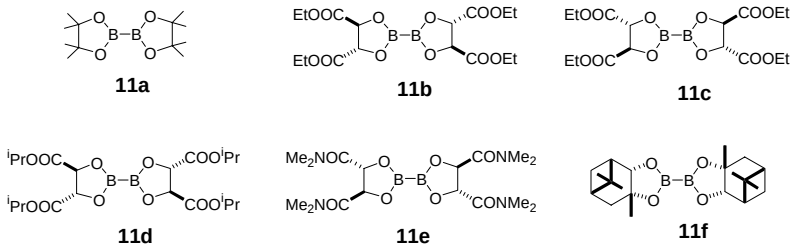


Scheme 15. Preparation of allylboronates from bis(pinacolato)diboron and disubstituted allyl acetate.

In contrast to our results (Scheme 14) this reaction proceeds with syn-stereochemistry. This stereochemistry can be ascribed to the steric effects of the large substituents in the Baylis-Hillman adducts (Ph and COOMe in **10g**). These steric interactions in the boronation reactions lead to formation of **1d** in which the double bond has cis-geometry. The subsequent allylation of cis-compound **1d** with aldehydes (see also Scheme 6) gives the syn-product (such as **3j**).[20]

2.2 Application of chiral diboronates

The high regio- and diastereoselectivity of the reaction inspired us to conduct the reaction (Scheme 14) in the presence of commercially available chiral diboronates (**11b-f** Scheme 16) in place of **11a**.

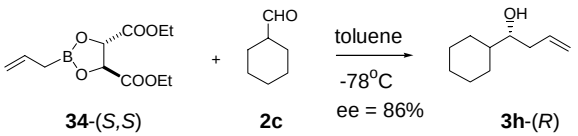


Scheme 16. Various diboronates[19c-h] employed in this study.

We have found that tartrate based diboronates **11b-d** reacted with allyl acetate (**10a**) and p-nitrobenzaldehyde (**2a**) to give homoallyl alcohol

3a with up to 53% ee (Table 1). Using D-tartrate derivatives (**11b**, entry 7) with **2a** the major product was the R-enantiomer (**3a**-(*R*)). As expected, the enantioselectivity of the reaction is reversed using L-tartrate derivative **11c** with **2a** providing **3a**-(*S*) with 48% ee (entry 8). Tartaramide derivative (**11e**) and pinane derivative (**11f**, entry 9) are ineffective in chiral induction giving a nearly racemic product. Although ethyl-ester **11b** is expected[22] to give less stable allylboronates than the isopropyl ester **11d**, we obtained somewhat higher ee with **11b** than **11d**; and moreover, **11b** is less expensive than **11d**. Therefore we employed chiral diboronate **11b** in further studies. According to Roush and co-workers[22] the highest ee with chiral allylboronates can be achieved in toluene solvent. Therefore, we conducted the asymmetric allylation reactions in the presence of toluene co-solvent (in toluene/DMSO 1:1) and found that this mixture gives higher ee and isolated yield of the products than the same process in neat DMSO.

We have found that employment of chiral tartrate derivative **11b** in place of **11a** leads to higher reactivity. Thus the allylation reactions could also be performed under mild reaction conditions using benzaldehyde (**2b**) and aliphatic aldehyde **2c**. The reaction with benzaldehyde **2b** gave predominantly **3e**-(*R*) with lower enantioselectivity (entry 10, 45% ee) than the corresponding reaction with nitro-benzaldehyde **2a** (entry 7, 53% ee). The reaction with cyclohexyl aldehyde **2c** (entry 14) requires an extended reaction time to give **3h**-(*R*) (48% ee). Roush and co-workers[22] obtained the same enantiopreference with chiral allylboronate **34**-(*S*,*S*) and **2c** (Scheme 17).



34-(*S*,*S*) **2c** **3h**-(*R*)

Scheme 17. Reaction of isolated chiral allylboronate **34**-(*S*,*S*) with **2c** reported by Roush and co-workers.[22]

We have also studied the reactions of functionalized allyl acetates **10b-f** with chiral diboronate **11b** and aldehydes **2a-c**. The high regio- and stereoselectivity of the allylation reactions is maintained for each allyl acetate, and accordingly the allylation reactions provided the corresponding branched product with anti diastereoselectivity (entries

11-13 and 15). The increased reactivity provided by the tartrate derivative **11b** allowed lowering of the reaction temperature from 60 °C to r.t. using crotyl acetate as substrate. Allylation with crotyl and cinnamyl acetate (**10f** and **10e**) proceeds with lower enantioselectivity (33-43% ee) than the corresponding process with the parent compound **10a** (53% ee). An increase in the polarity of the allylic substituent seems to improve the enantioselection. As one goes from crotyl acetate **10f** through cinnamyl acetate **10e** to diacetate **10d** the ee increases from 34% to 50%. Thus, using diacetate **10d** and **2a** the reaction provided allyl acetate **3d**-(*S*) with excellent regio- and stereochemistry and with 50% ee (entry 13). It was also found that cyclohexyl aldehyde **2c** is allylated with a higher enantioselectivity than benzaldehyde (**2a**) (c.f. entries 12 and 15).

The enantioselectivity of the allylation of aldehydes (**2a-c**) is apparently lower with in situ generated allylboronates than with isolated ones. Roush and co-workers[2c, 22] have shown that allylation of **2b** and **2c** with **34**-(*S,S*) (or its enantiomer) can be achieved with 71% and 86% ee (Scheme 17) at –78 °C in toluene. An obvious drawback of the presented reactions is that they are carried out at r.t. in presence of DMSO co-solvent. Probably the relatively high reaction temperature (required for the catalytic generation of allylboronates) is responsible for the lowering of the enantioselectivity of the process. When conducting the allylation of **2b** with isolated chiral allylboronate at r.t. (23 °C/CH_2Cl_2), the enantiomeric excess drops to 30%,[2c] which is in the same range as the analogous reaction with in situ generated allylboronate (entry 10), giving 45% ee.

As it appears above, aldehydes **2a-c** give about 35-53% ee with **11b** and various allyl acetates (**10a, 10d, 10e,** and **10f**) in the presence of catalytic amounts of palladium. However, the reaction of sulfon-imine **19** with **10a** and **11b** under the same catalytic condition gave racemic product (entry 16). The lack of the enantioselectivity in this process suggests different mechanistic features for allylation of aldehyde and imine electrophiles.

2.3 Mechanistic studies

As indicated in the introduction, palladium-catalyzed coupling of allyl acetates with **11a** gives allylboronates.[15a] In these processes a considerable amount of 1,5-hexadiene derivatives were also formed (see Section 1.2, Scheme 3). Formation of the transient

allylboronate (**1**) is also the first step of the one-pot allylation reaction described above (Scheme 14). However, in the one-pot process we did not observe formation of hexadiene products (such as **13**), since the allylboronate formed in the palladium-catalyzed process immediately reacts with the added electrophile. We have found that in the palladium-catalyzed reaction of **11a** and **10a**, the consumption of the allyl acetate (**10a**) is faster in the presence of the electrophile (**2a**) (Figure 1). The retardation effect induced by the accumulation of the allylboronate product is even more pronounced when chiral diboronate **11b** is employed. When **10a** was treated with **11b** in the presence of palladium catalyst, only 30% of **10a** was converted in 20 hours at r.t. to **34**-(*S*,*S*) (Scheme 18). On the other hand, conducting this reaction in the presence of nitro-benzaldehyde (**2a**) under the same reaction conditions (entry 7) a full conversion of **10a** was observed. It should also be noted that formation of **34**-(*S*,*S*) in the previous reaction (Scheme 18) could be observed by ^{1}H-NMR spectroscopy, however isolation of this allylboronate was encumbered by its low stability.

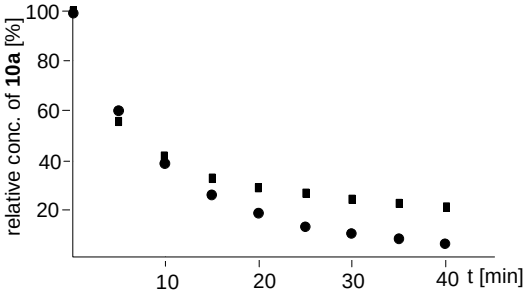
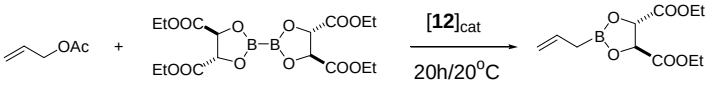


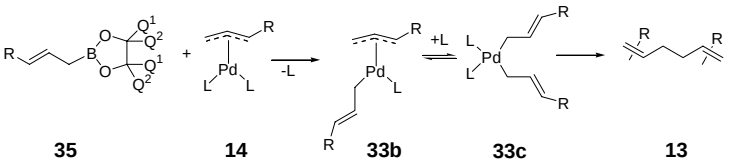
Figure 1. Palladium-catalyzed reaction of **10a** with **11a** in the presence (•) and in the absence (■) of electrophile **2a**. The reactions were performed in DMSO-d_6 using identical amounts of $Pd_2(dba)_3$ catalyst. The progress of the reaction was followed by ^{1}H-NMR spectroscopy.



10a **11b** **34**-(*S*,*S*)

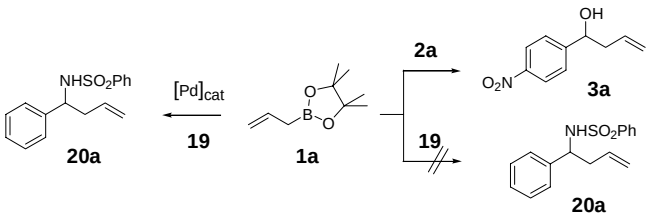
Scheme 18. Conducting the boronation reaction in the *absence* of electrophile only 30% conversion of allyl acetate **10a** could be achieved (c.f. entry 7).

The product inhibition in the above catalytic processes (Figure 1 and Scheme 18) can be explained by formation of bis-allylpalladium complex **33** (Scheme 19) from the allylboronate product (**1**) and the mono-allylpalladium intermediate of the process (**14**). Similar reactions for formation of bis-allylpalladium complexes from (η^3-allyl)palladium complexes and allylstannanes are well documented in the literature.[18a, 30, 31g, 32, 33e] As mentioned in the introduction bis-allylpalladium complexes such as **33c** are well known to undergo allyl-allyl coupling reactions to give hexadiene products,[18, 32a, 38] which also explain the formation of **13** in the palladium-catalyzed boronation reaction in the absence of electrophiles (Scheme 3, Section 1.2).



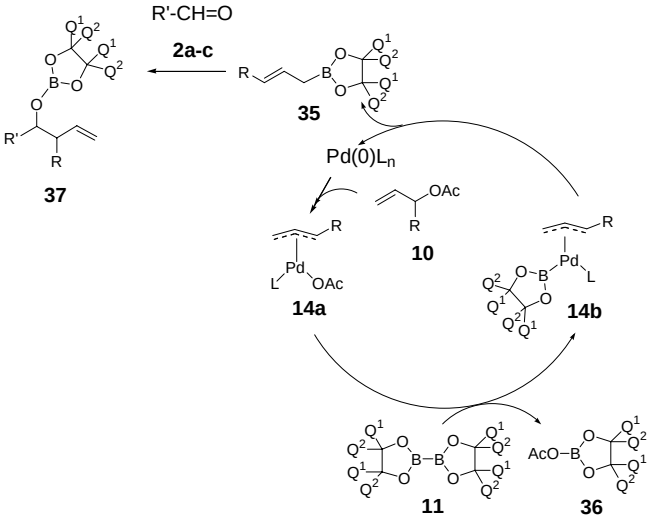
Scheme 19. Explanation of the product inhibition in the palladium-catalyzed formation of allylboronates.

On the other hand, bis-allylpalladium complexes (**33**) are also prone to react with electrophiles, such as aldehydes and imines.[18b, 30, 31g, 32b-e, 33e, 39] In order to study the involvement of palladium catalysis in the allylation step of the above reactions (Scheme 14), we reacted allylboronate **1a** with nitro-benzaldehyde **2a** and imine **19** under the usual reaction conditions but in the absence of palladium catalyst (Scheme 20). The reaction of **2a** with **1a** gave smoothly **3a**, clearly showing that the allylation of the aldehyde component does not require palladium catalysis. On the contrary, reaction of **19** with **1a** does not provide the expected product **20a** unless catalytic amount of palladium is added to the reaction mixture. This latter experiment indicates that the allylation reaction of imine **19** requires palladium catalysis, and that this reaction proceeds via bis-allylpalladium complex **33**.



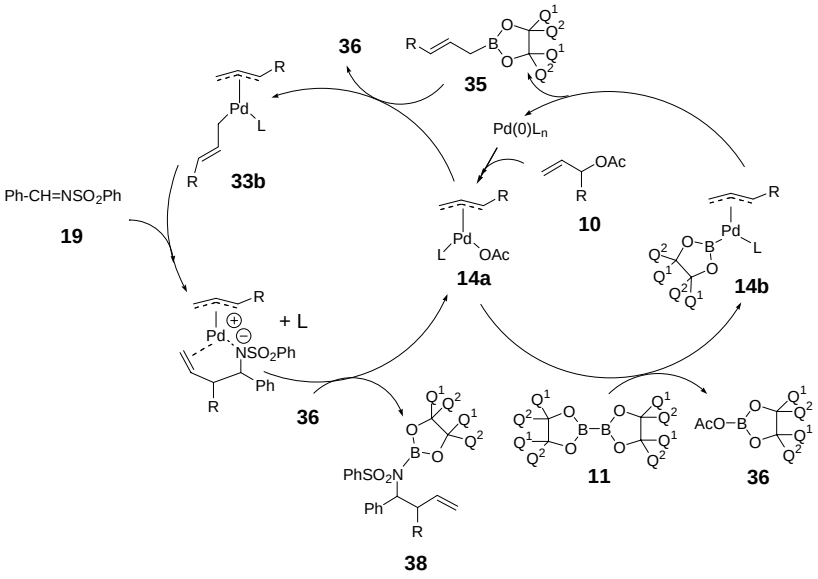
Scheme 20. Allylation of aldehyde **2a** and imine **19** in the presence and absence of palladium catalyst.

Considering the above findings two different catalytic cycles can be envisaged for the allylation of the aldehyde (**2**) and the imine substrate (**19**).



Scheme 21. Proposed catalytic cycle for the allylation of aldehydes **2a-c**.

The introducing step for allylation of aldehydes **2a-c** (Scheme 21) is oxidative addition of the palladium(0) catalyst to the corresponding allyl acetate to form (η^3-allyl)palladium complex **14a**.[1b, 40] The next step is addition of the diboron reagent to the allyl moiety of **14a** to form the transient allylboronate **35**. Considering these type of reactions with analogous dimetal reagents,[15a, 31g, 32e, 33e, 41] such as hexaalkyl/aryl disilanes (R_3Si-SiR_3) and distannanes (R_3Sn-SnR_3) the boron-carbon bond formation probably takes place via inner-sphere nucleophilic attack. Thus the nucleophilic attack is preceded by formation of complex **14b**, in which the boronate group is coordinated to palladium. Coordination of the boronate group to palladium involves ligand exchange, which is certainly hindered in the presence of strongly coordinating ligands, such as phosphines, activated alkenes or halogenides. This would explain our findings that the addition of strongly coordinating species (*vide supra*) inhibits the catalytic formation of allylboronates **35**. On the other hand, in the absence of phosphine and other ligands, DMSO is the only solvent, that is able to stabilize the palladium(0) catalyst. The final step in the catalytic cycle is the direct attack of the aldehyde electrophile on allylboronate **35** (Scheme 21) to give **37**, which subsequently hydrolyzes to give the homoallyl alcohol product.



Scheme 22. Proposed catalytic cycle for the allylation of sulfonimine **19**.

The allylation of imine (**19**) substrates also starts with palladium-catalyzed formation of allylboronate **35**. In contrast to aldehydes, imines are not able to undergo direct electrophilic substitution with **1** (Scheme 20), and therefore the allylation step requires palladium catalysis. The second catalytic cycle (Scheme 22) is assumed to start with transmetalation of **35** to **14a** providing bis-allylpalladium complex **33b**. This complex undergoes electrophilic attack with imine **19** to give product **38**. Similar reactions have been reported for palladium-catalyzed allylation of **19** with allylstannane substrates. [31g, 32e, 33e]

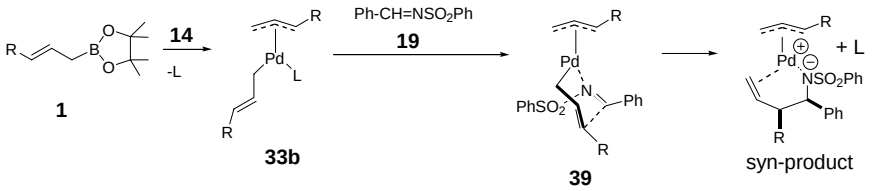
2.4 Origin of the stereo- and enantioselectivity

Probably the most important step of the catalytic process is the electrophilic attack on the metal-allyl moiety, since this step determines the selectivity of the allylation process. The stereo- and enantioselectivity of the electrophilic attack by the aldehyde (**2**) and imine (**19**) substrates is markedly different, which can be ascribed to the different reaction mechanism.

The direct allylation of the aldehyde substrate (**2**) is known to proceed with a high anti diastereoselectivity.[20] The explanation of this diastereoselectivity (Section 1.3) is based on the assumption that the

reaction takes place via six-membered cyclic TS, in which the substituents (e.g. Me and Ph in **18c,** Scheme 6) occupy equatorial positions. This arrangement of the substituents in the TS leads to formation of the anti product, which explains the anti diastereoselectivity of the allylation reactions with aldehyde electrophiles. The predominant formation of the (*R*)-enantiomer from the transient **34**-(*S*,*S*) and the corresponding aldehydes (**2a**-**c**) can be explained by the selectivity model presented by Roush and co-workers (Section 1.3, Scheme 7).[2c, 21]

The reaction of **10a**, chiral diboronate **11b** and sulfon-imine **19** leads to racemic homoallyl amine **20a** (entry 16). Formation of the racemic product is the consequence of the palladium-catalyzed allylation of imine **19** with transient allylboronate **34**-(*S*,*S*). This reaction proceeds via bis-allylpalladium complex **33b** (Scheme 22) with a complete loss of the chiral information. Another interesting feature of the allylation of **19** is that this reaction takes place with syn diastereoselectivity, while the analogous reaction with aldehydes **2a**-**c** proceeds with anti diastereoselectivity.



Scheme 23. Evolution of the stereochemistry in the allylation of sulfon-imine **19**.

Recent studies[32e] on the electrophilic substitution reactions via bis-allylpalladium complexes show that the electrophilic attack in these processes also proceed through six-membered cyclic TS. Accordingly, the development of the stereoselectivity in the reaction of sulfon-imine **19** with allyl substituted substrates **10e** (entry 6) can be discussed on the basis of a six membered TS structure model **39** (Scheme 23). The geometry of the TS structure **39** is biased by the trans geometry of the phenylsulfonyl and phenyl groups across the carbon- nitrogen double bond in **19**. Because of this trans geometry, the lone-pair on nitrogen (interacting with palladium) and the phenyl group are in a cis-arrangement. Furthermore, it is reasonable to assume that the steric interactions between the metal atom and the

bulky phenyl-sulfonyl group will be avoided. As a consequence, the preferred orientation of **19** in TS structure **39** renders the phenyl group in an axial position. Since the allylic substituent (R) is in an equatorial position, this model predicts formation of the syn diastereomer (Scheme 23). It is interesting to note that a similar syn-diastereoselectivity was reported by Lu and Chan[42] for formation of **20b** in the indium- and zinc-mediated coupling of **19** with cinnamyl bromide.

In summary, homoallylic alcohols and amines could be prepared from allyl acetates via palladium-catalyzed formation of transient allylboronates. These reactions proceed with high regio- and stereoselectivity and with a high level of functional group tolerance. Using chiral diboronates, the allylation reactions can be extended to synthesis of enantioenriched homoallyl alcohols.

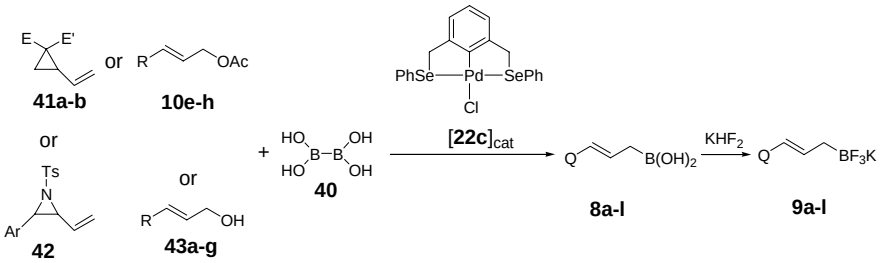
3. Palladium Pincer-Complex-Catalyzed Boronation Reactions (Papers III–IV)

As mentioned in Sections 1.2 and 2.3 the $Pd_2(dba)_3$-catalyzed method[15a] for the preparation of allylboranes suffers from two important synthetic limitations: formation of allyl-allyl coupling products (Scheme 3) and a low conversion of the allylic precursors (Scheme 18). On the other hand, application of pincer-complex catalysts[35, 36a, 43] (e.g. **22b**[35c], **22c**[35d]) offers a mild and efficient method for synthesis of functionalized organometallic compounds.[33c-d, 33f] Since commonly used palladium complexes (such as $Pd_2(dba)_3$ **12** and $Pd(PPh_3)_4$ **47**) are known to both create and cleave carbon-boron bonds (Sections 1.4 and 2.3),[1] application of highly selective pincer-complex catalysts for carbon-boron bond forming reactions is a prerequisite of a synthetically useful process.

3.1 Catalytic formation of allylboronic acids under mild conditions

Allylboronic acid derivatives are extremely useful precursors for synthesis of allylborane-based building blocks[2b-h] such as potassium trifluoroborate derivatives[2f-l] and allylboronates including chiral tartrate-based reagents.[2b-e] However, a broad access to functionalized allylboronic acids have been limited by the well known instability and the high reactivity of these species (Section 1.1, Scheme 2).[2c] We have found that SeCSe pincer-complex **22c** readily catalyzes borane transfer reactions (Scheme 24) from diboronic acid[19i] (**40**) (also referred to as tetrahydroxydiboron) to vinyl cyclopropanes (**41a-b**), vinyl aziridines (**42**), functionalized allyl acetates (**10e-h**) and allyl alcohols (**43a-g**). Thus, selective formation of allylboronic acids **8a-l** can be observed by ^{1}H-NMR spectroscopy (in DMSO-d_6) in the reaction mixture of the above processes. Many of these species are surprisingly stable in DMSO (up to 2 days at r.t.), however in concentrated solution or without solvent **8a-l** completely decompose. In coordinating polar solvents such as DMSO, the reactivity of

allylboronic acids toward electrophiles is lowered (Section 1.1) increasing the kinetic stability of **8a-l**. In order to isolate the products, the allylboronic acids **8a-l** were converted to the corresponding potassium trifluoro(allyl)borate derivatives **9a-l** or allylboronates (e.g. **46,** entry 2, Table 2).



Scheme 24. Palladium pincer-catalyzed boronation of vinyl cyclopropanes, vinyl aziridines, allyl acetates and allyl alcohols.

The reaction of vinyl cyclopropanes (**41a-b**), vinyl aziridine (**42**) and allyl acetates (**10e-h**) proceeds readily at 40 °C in DMSO. Under the same conditions allyl alcohols (**43a-g**) react very slowly giving low conversion. However, using methanol as co-solvent allyl alcohols could also be used as substrates and the corresponding allylborane products could be isolated in high yields.

3.2 Selectivity and functional group tolerance of the reactions

Opening of the strained three-membered rings (**41** and **42**) with **40** proceeds remarkably fast in 2-5 h at 40 °C (entries 1-4, Table 2), while borane substitution of the allyl acetates (**10e-h**) and allyl alcohols (**43a-g**) requires much longer reaction times of 16-36 h (entries 5-15). As the boronation reactions (Scheme 24) proceed under mild and neutral conditions many functionalities such as Br, COOEt, NHTs, OAc and $SiMe_3$ are tolerated. Therefore, the resulting products (**9a-l**) can be employed as selective organometallic reagents for synthesis of allyl or homoallyl acetates, esters, amines and silanes. For example, in diacetate **10d** only one of the acetate groups is replaced by a borane functionality (entry 7), and thus orthogonally functionalized product **9f** can be obtained. Likewise, the silyl functionality of **10h** remained unchanged under the boronation process and after KHF_2 treatment (entry 8), and thus useful silyl-borane synthon **9g** could be prepared.

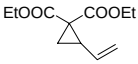
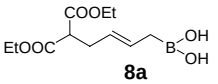
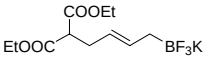
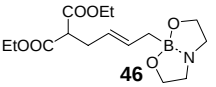
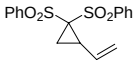
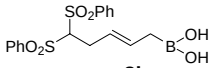
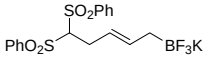
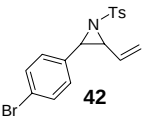
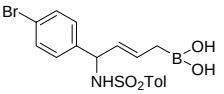
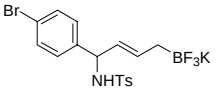
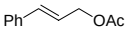
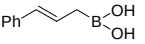
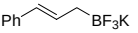
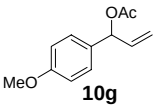
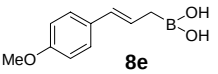
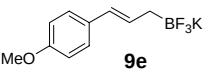
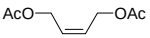
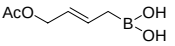
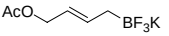
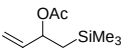
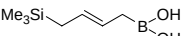
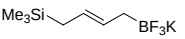
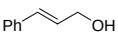
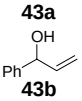
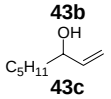
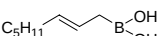
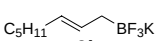
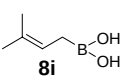
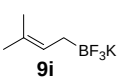
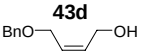
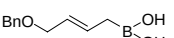
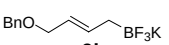
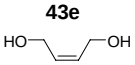
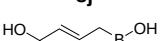
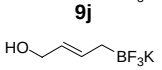
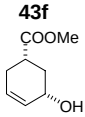
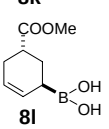
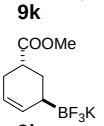
The regioselectivity of the reaction is excellent, as we obtained only the linear products, even from branched allyl acetates **10g** and **10h** (entries 6 and 8). Similarly, the boronation reactions with allyl alcohol substrates proceed with excellent regioselectivity, as isomeric allyl alcohols **43a** and **43b** give the same regioisomer **9d** (entries 9-10). Furthermore, the double bond geometry in all acyclic allylborane products (**9a-k**) was exclusively trans.

3.3 Substituent effects on the reactivity of the allyl alcohols

We have observed some interesting substituent effects on the reactivity of allyl alcohols. It was found that in the presence of hydroxy or benzyloxy substituents the reactivity of the alcohol substrates is considerably increased (entries 13-14, Table 2). For example, boronation of **43e-f** proceeded at lower temperature (20-40 °C), than the corresponding reaction of the alkyl substituted analogs **43c-d** (50 °C) (entries 11-12). In fact, the relatively low temperature is also important for the high isolated yields of the products, since allyl hydroxy boronates **8k**/**9k** very easily undergo hydroxy-boronate elimination to give the corresponding 1,3-diene. Compounds **43c-f** reacted with excellent regioselectivity to give linear products **9h-k**. Substitution of **43f** resulted in mono-boronated product **9k**, thus the reaction can be employed for desymmetrization of dialcohols too. Using harsher reaction conditions to obtain the diboronated product leads to extensive formation of butadiene.

In contrast to hydroxy or benzyloxy substituents, the substituent effects of COOR groups in the allyl alcohols (such as **43g**) decrease the rate of boronation reactions. However, we found that addition of catalytic amounts (3-5 mol%) of strong acids such as p-toluene sulfonic acid (PTS) considerably accelerated the conversion of **43g**, affording the corresponding boronated product **9l** (entry 15). Substitution of cyclic substrate **43g** provides a single diastereomer **9l** indicating that the boronation reaction is both regio- and stereo-selective (entry 15). The substitution pattern of **9l** clearly shows that the reaction proceeds with trans steroselectivity.

Table 2. A selection of pincer-complex catalyzed reactions that afford allylboranes.[a]

Entry	Substrate	[°C] / [h]	Allylboronic acids	Products[b]	Yield[c]
1	 **41a**	40/3	 **8a**	 **9a**	82
2[d]	**41a**	40/3	**8a**	 **46**	90
3	 **41b**	40/5	 **8b**	 **9b**	89
4	 **42**	40/2	 **8c**	 **9c**	87
5	 **10e**	40/16	 **8d**	 **9d**	71
6	 **10g**	40/16	 **8e**	 **9e**	75
7	 **10d**	40/36	 **8f**	 **9f**	73
8	 **10h**	40/16	 **8g**	 **9g**	81
9	 **43a**	40/16	**8d**	**9d**	92
10[e]	 **43b**	40/7	**8d**	**9d**	86
11	 **43c**	50/16	 **8h**	 **9h**	90
12	 **43d**	50/16	 **8i**	 **9i**	98
13	 **43e**	40/21	 **8j**	 **9j**	87
14[e]	 **43f**	20/16	 **8k**	 **9k**	74
15[f]	 **43g**	50/24	 **8l**	 **9l**	82

[a] Unless otherwise stated the reactions of **40** and the corresponding substrates were conducted in the presence of **22c** (5 mol%) in DMSO (entries 1-8) or in a mixture of DMSO and MeOH (entries 9-15). After the indicated reaction times aqueous KHF_2 was added. [b] Racemic. [c] Isolated yield. [d] Diethanolamine was added instead of KHF_2. [e] Pure MeOH used as solvent. [f] p-Toluenesulfonic acid 5 mol% was used as co-catalyst.

3.4 Attempts to employ other palladium catalysts and diboron reagents

We have attempted to employ NCN complex **22b** and PCP complex **22a** in place of SeCSe catalyst **22c** in the above process (Scheme 22). It was found that **22b** incorporating an NCN ligand displayed a lower catalytic activity, than SeCSe catalyst **22c**, while **22a** proved to be inactive as catalyst. The lower reactivity of these pincer complexes probably depends on their unfavourable steric and/or electronic features.[43a, 43e-f]

Miyaura and co-workers[15a, 44] have shown (Section 1.2) that allyl acetates can be converted to pinacolato allylboronates (**1**) in the presence of bis(pinacolato)diboron (**11a**) using $Pd_2(dba)_3$ catalyst (Scheme 3). Therefore we have also attempted the substitution reactions of allyl acetates with diboronic acid **40** (Scheme 24) in the presence of $Pd_2(dba)_3$ (**12**) and $Pd(PPh_3)_4$ (**47**) in place of **22c**. These transformations resulted in complex mixtures of several unsaturated products (c.f. Section 1.2). For example, the reaction of **10d** and **40** with $Pd(PPh_3)_4$ lead to full conversion of the starting material, however formation of **8f** could not be detected (c.f. entry 7). On the other hand, the reaction of $Pd_2(dba)_3$ with allyl acetates **10d** and **10h** gave traces (5-30% conversion) of the corresponding allylboronic acid products (**8f** and **8g**). However, these transformations did not proceed with full conversion of the starting materials, because of deactivation of the catalyst accompanied by precipitation of palladium-black, which was also observed for the reaction with **11a** (Section 2.3).[3] The best result with $Pd_2(dba)_3$ was achieved with **10h** giving about 20% isolated yield of **9g** (c.f. entry 8, Table 2). Interestingly, the reaction of **10d** with $Pd_2(dba)_3$ resulted in a very low conversion (5%) to **8f** (c.f. entry 7), however we observed formation of considerable amount of butadiene in the reaction mixture. This finding can be explained by formation of a β-OAc substituted allylpalladium intermediate (**14**, R = CH_2OAc), which is known[45] to easily eliminate an acetate ion providing butadiene. The above results clearly indicate that the catalytic activity and selectivity of pincer-complexes **22a-b** and palladium(0) catalysts $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ are inferior to SeCSe complex **22c** in the presented borane transfer reactions (Scheme 24).

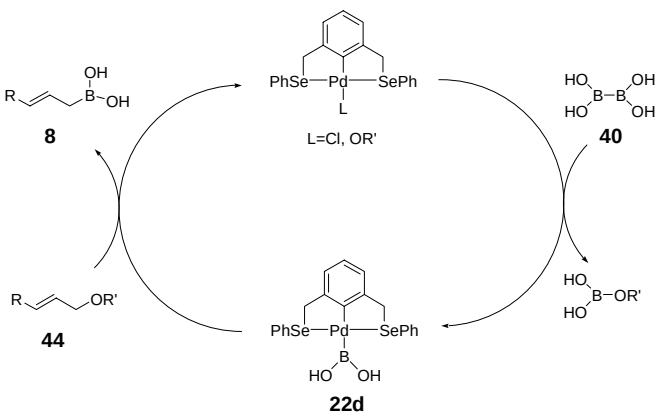
Based on the above observations, it can be concluded that **22c** has at least three advantageous features compared to that of palladium(0) catalysts, such as $Pd_2(dba)_3$ and $Pd(PPh_3)_4$: (i) reactions catalyzed by

22c proceed without formation of potentially unstable (η^3-allyl)palladium complexes (**14**); (ii) the electron rich SeCSe complex does not react with the allylborane products to give bis-allylpalladium (such as **33**) or related complexes; and (iii) the pincer-complex catalyst is not reduced to palladium(0) under the applied conditions, and therefore deactivation of the catalyst by precipitation of palladium-black can be avoided (see Section 2.1).

We have also attempted to employ bis(pinacolato)diboron **11a** as boronating reagent in place of **40** in the presence of catalytic amounts of **22c**, however, we could not observe formation of the corresponding allylboronate product. The failure of the boronation reaction with **11a** can probably be explained by the steric bulk of the pinacolato moiety, which inhibits the transmetalation with **22c**.

3.5 Mechanistic features

The catalytic cycle. Although, the exact mechanism of the pincer-complex **22c** catalyzed boronation reaction is not known, several mechanistic features are probably similar to the trimethyltin transfer reactions from hexamethylditin to allylic/propargylic substrates.[33c-d, 33f] In these transformations the catalytic cycle is initiated by transmetalation of the dimetallic reagent[33g, 33h] to the pincer-complex catalyst followed by transfer of the organometallic group to the allylic (propargylic) substrate in an S_N2/S_N2' type reaction.[33d, 33f, 46, 47]



Scheme 25. Plausible catalytic cycle for the pincer-complex-catalyzed boronation reaction.

Accordingly, we assume that the first step of the present borane transfer process is formation of a borane coordinated pincer-complex intermediate **22d** followed by substitution of the substrate by the coordinated $B(OH)_2$ group (Scheme 25). The high selectivity observed in this reaction can be explained by the finding that electron-rich pincer-complexes (such as **22c** and **22b**) are reluctant to undergo transmetalation with allyl-metal species.[33a-b] Thus, the carbon-boron bond of the allylboronic acid products **8** is not cleaved by **22c** allowing the subsequent isolation of the products (**9** and **46**). The boronation reaction has a high regiopreference for formation of the linear product. For example, both the linear substrate **43a** and branched alcohol **43b** gave exclusively terminal substituted boronic acid **9d** (entries 9 and 10). This indicates that the nucleophilic attack occurs at the less sterically hindered position of the allylic substrate, and therefore **10e** reacts with **22d** via an S_N2 mechanism,[46] while **10g** react via an S_N2' pathway.[47d]

An alternative mechanism for the pincer-complex catalyzed boronation may involve palladium(0) catalysis. It was shown[33i-j] that under harsh reaction conditions (120-180 °C) in the presence of base (such as trialkylamine or Cs_2CO_3), pincer complexes are destroyed releasing palladium(0) nano-particles. Considering the fact that we conducted the pincer-complex-catalyzed boronation reactions under mild (20-50 °C) and neutral/mildly acidic conditions formation of palladium(0) nano-particles seems to be unlikely. Furthermore, the outcome of the boronation reactions with palladium(0) reagents (such as $Pd_2(dba)_3$ or $Pd(PPh_3)_4$) and pincer-complex catalyst **22c** is markedly different (Section 3.4). Based on these facts and observations, the described pincer-complex-catalyzed boronation process probably does not involve palladium(0) species.

Activation of allyl alcohols. In order to gain insight into the activation of the hydroxy group of allyl alcohols, we carried out competitive boronation experiments (Figure 2) monitored by ^{1}H-NMR. The reaction rate of cinnamyl acetate and cinnamyl alcohol was compared. Surprisingly, under the same reaction conditions cinnamyl alcohol **43a** was converted significantly faster to boronic acid **8a**, than cinnamyl acetate. The NMR-experiment also showed that addition of 5 mol% PTS had a dramatic accelerating effect on the rate of the reaction.

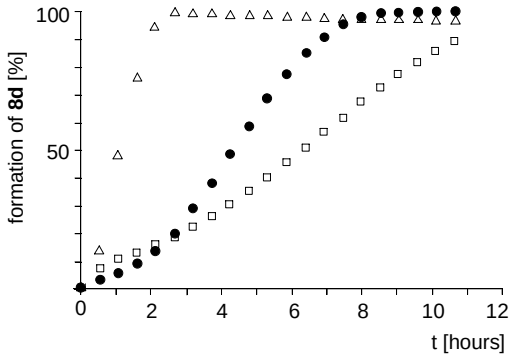
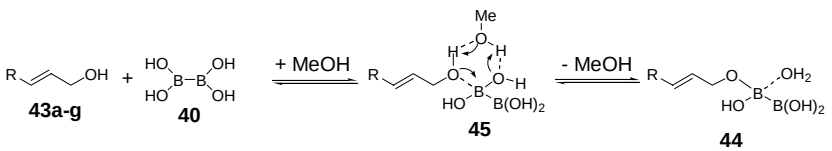


Figure 2. Formation of **8d** from **43a** (• , Δ) and cinnamyl acetate (**10e**) (□) using **40** and 5 mol% of **22c** in DMSO-d_6/MeOH-d_4 mixture at 55 °C. Effects of addition of 5 mol% PTS (Δ).

The above studies clearly indicate that under the employed reaction conditions the hydroxy group of the allyl alcohol is converted to an excellent leaving group, which is easier to displace than an acetate. A possible explanation is that **40** acts as a Lewis-acid catalyst by interacting of the free electron-pairs of the oxygen of **43a-g**. A similar activation is suggested in the Tamaru reaction employing BEt_3 for activation of allyl alcohols.[48] On the other hand, boronic acids are far less efficient Lewis-acids than alkyl (or fluoro) boranes. Therefore, we envision another type of activation of the hydroxy group involving formation of allylboronic acid ester **44** (Scheme 26). This esterification is probably facilitated by inclusion of a methanol molecule in the six-membered ring TS (**45**) of the process. In **44** the hydroxy group is converted to a better leaving group, and moreover, the cleavage of the B-B bond is also facilitated by coordination of the water molecule produced in the esterification. Application of small amounts of PTS (entry 15, Figure 2) is supposed to catalyze the ester formation.



Scheme 26. Plausible explanation for the conversion of the hydroxy group to a better leaving-group via a six-membered TS (**45**).

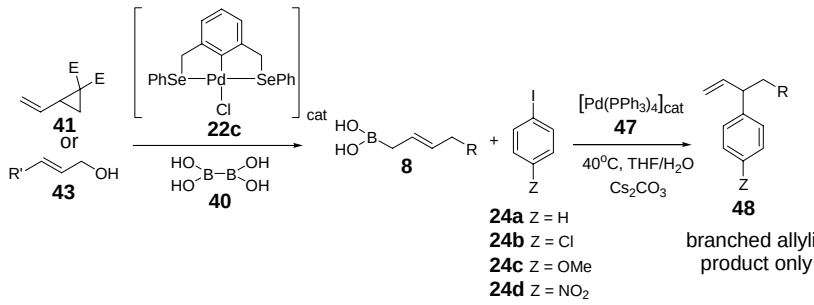
In summary, functionalized allylboronic acids could be prepared under mild reaction conditions from vinyl cyclopropanes, vinyl aziridines, allyl acetates and allyl alcohols. In these transformations diboronic acid is used as boron source and a SeCSe palladium pincer complex as catalyst. The reaction is highly regioselective, affording only the linear products with the double bond geometry trans.

4. Palladium-Catalyzed Coupling of Allylboronic Acids with Aryl Iodides (Paper V)

One of the most common palladium-catalyzed transformations of organoboranes involves coupling reaction with aryl halides and is known as the Suzuki-Miyaura reaction.[49a-b] As we have shown in Chapter 3, allylboronic acids can be easily obtained by boronation of vinyl cyclopropanes, vinyl aziridines, allyl acetates and allyl alcohols Therefore, it was appealing to attempt a coupling reaction of allylboronic acids and aryl halides. This process could be employed for aryl substitution of functionalized allylic substrates.

4.1 Allylation of aryl iodides with functionalized boronic acids

A majority of palladium-catalyzed nucleophilic allylation reactions proceed via (η^3-allyl)palladium intermediates.[1] Therefore, in case of employment of unsymmetrical allylic precursors, the control of the regioselectivity of the catalytic reactions may be problematic. In particular, when the reactions proceed through monosubstituted allyl-palladium intermediates, the nucleophiles preferentially attack the less hindered allylic terminus, affording the linear allylic product.[1h-j] As this product is achiral, there has been a considerable interest to invert the regioselectivity of this process to obtain the corresponding branched allylic isomer and thus create the basis for new palladium-catalyzed asymmetric transformations.[50] There have been two main strategies for conducting the nucleophilic attack towards formation of the branched allylic isomers: (i) application of directing groups in the allylic substrate;[50a-h] or (ii) application of specially designed ligands to bias the (η^3-allyl)palladium intermediates of the reaction.[50i-l]

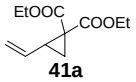
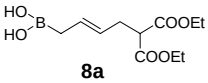
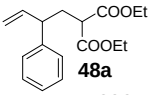
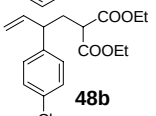
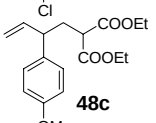
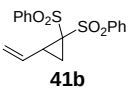
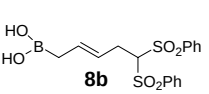
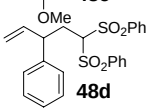
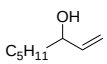
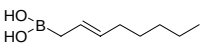
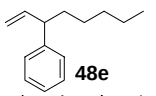
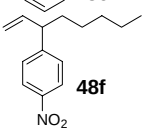
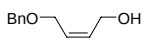
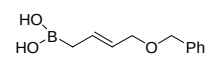
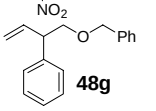


Scheme 27. Selective formation of the coupling product in the absence of directing groups.

Our studies have shown that the palladium-catalyzed arylation of functionalized allylboronic acids leads to a selective formation of the branched allylic isomers without employment of directing groups or specially designed ligands.[7] Accordingly, under standard Suzuki-Miyaura coupling conditions[49] allylboronic acids **8** readily undergo palladium(0)-catalyzed substitution reactions with aryl iodides **24a-d** affording the corresponding terminal alkenes **48a-g** (Scheme 27, Table 3). The reaction of allylboronic acid **8a** with iodobenzene proceeds smoothly at 40 °C affording coupling product **48a** in 16 h with high yield (Table 3, entry 1). Substituted iodobenzenes reacted similarly (entries 2-3) suggesting that the electronic effects of the aryl substituents have no significant effect on the rate of the coupling reaction. Exchange of the carbethoxy substituents in **41a** to bulky phenyl sulfonyl groups (**41b**) did not affect the regioselectivity or the rate of the reaction (entry 4). Furthermore, allylboronic acids with alkyl (**8h**) and benzyloxy group (**8j**) reacted with the same rate and selectivity as **8a** and **8b** (entries 5-7) even when nitro benzene derivative **24d** was employed as coupling component (entry 6).

Because of the mild reaction conditions (40 °C), the catalytic transformations proceed with high functional group tolerance as carbethoxy, phenylsulfonyl, aromatic chloro and nitro groups remained unchanged under the catalytic transformations. Allylation of ortho-chloro iodobenzene with **8a** was also attempted. However this reaction gave only traces of the ortho-chloro analog of **48b** indicating that the coupling reaction is probably sensitive to the ortho substitution of the iodobenzene component.

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

Entry	Precursor	Allylboronic acid[b]	Ar-I	Product	Yield [%][c]
1	 **41a**	 **8a**	**24a**	 **48a**	91
2	**41a**	**8a**	**24b**	 **48b**	97
3	**41a**	**8a**	**24c**	 **48c**	87
4	 **41b**	 **8b**	**24a**	 **48d**	91
5	 **43c**	 **8h**	**24a**	 **48e**	97
6	**43c**	**8h**	**24d**	 **48f**	83
7	 **43e**	 **8j**	**24a**	 **48g**	99

[a] The coupling reactions of **8** and **24** were conducted in the presence of Cs_2CO_3 and $Pd(PPh_3)_4$ (5 mol%) in a THF/water mixture for 16h at 40°C. [b] The allylboronic acids prepared according to refs.[5-6] [c] Isolated yield.

The allylboronic acid precursors can easily be obtained[5-6] by boronation reaction of vinyl cyclopropanes[5] (such as **41a-b**), and allyl alcohols[6] (such as **43c** and **43e**) with diboronic acid (**40**) in the presence of catalytic amounts of pincer-complex **22c**.[35d] Although, allylboronic acids are remarkably stable[2c, 5-6, 51] in the presence of water, air, weak bases and acids, they rapidly decompose under solvent free conditions.[2c, 5-6] Nevertheless, we have found that allylboronic acids **8** can be purified by ether or chloroform extraction of the water-diluted reaction mixture of the boronation process. As it appears in Figure 3 allylboronic acid **8a** is sufficiently pure and stable in chloroform-*d* after this extraction procedure. However, evaporation of the solvent followed by immediate dissolution of the resulting oil, severe decomposition of **8a** was observed (Figure 4). This decomposition is probably initiated by formation of a boroxine trimer,[52] which is followed by irreversible transformation of the allyl moiety.

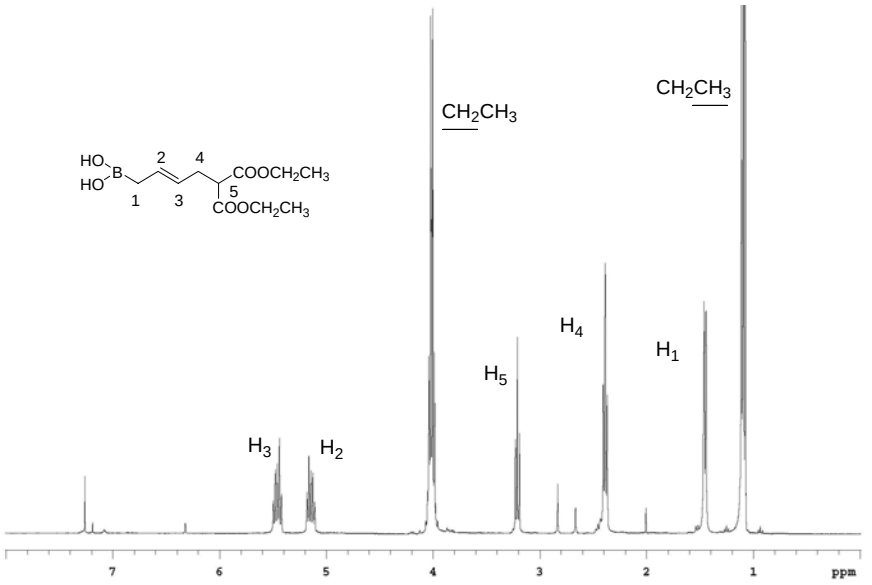


Figure 3. ^{1}H-NMR spectrum (in $CDCl_3$) of allylboronic acid **8a** after extraction from the reaction mixture of the boronation.

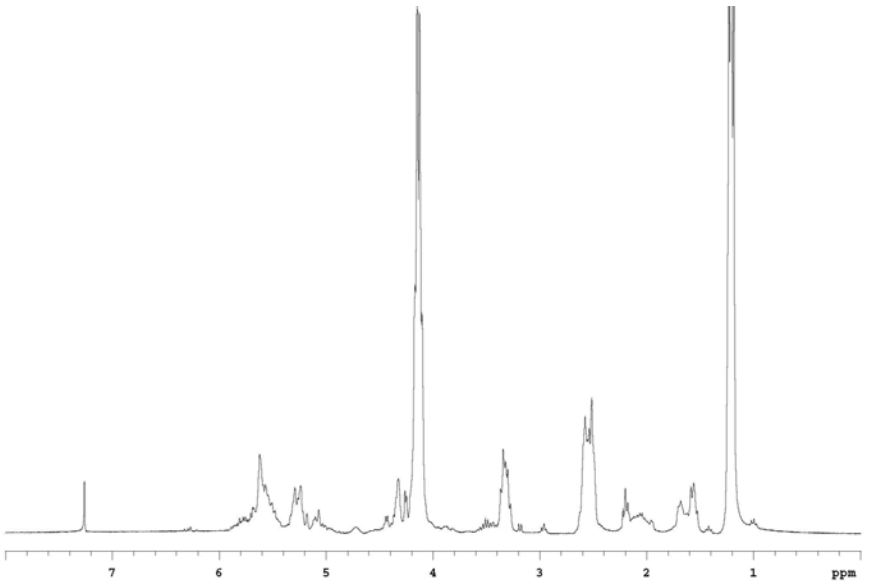


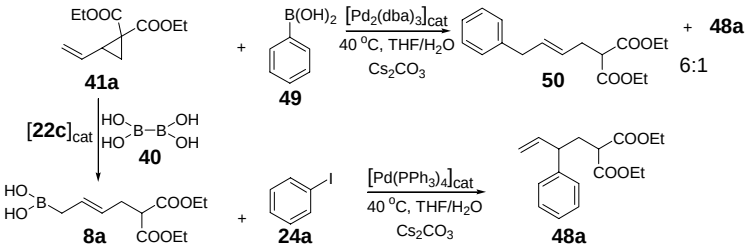
Figure 4. ^{1}H-NMR spectrum of the above sample of **8a** (Figure 3) after evaporation to dryness followed by immediate dissolution in $CDCl_3$.

Thus considering the poor stability of allylboronic acids under solvent free conditions, the coupling reactions were carried out by addition of the corresponding iodoarenes (**24a-d**), $Pd(PPh_3)_4$, Cs_2CO_3 and THF to

the wet etheral extract of **8** followed by reduction of the solvent volumes *in vacuo*. A successful coupling reaction of **8** and **24** requires the use of $Pd(PPh_3)_4$, while pincer-complex **22c** proved to be inefficient to catalyze the coupling process.

4.2 The regioselectivity of the allylation

The employed allylboronic acids do not contain any known[50] directing groups and the employed catalyst, $Pd(PPh_3)_4$, is one of the most commonly used palladium(0) sources, and the PPh_3 ligands are not expected to affect the regioselectivity. Nevertheless, the catalytic allylation process affords selectively the branched allylic product. In order to study a possible directing effect of the carbethoxy group in **8a**, we carried out a classical allylic substitution reaction of **41a** with phenyl boronic acid (**49**) in the presence of $Pd_2(dba)_3$ as catalyst (Scheme 28). This process provided predominantly the linear product **50** and only traces of the branched allylic isomer **48a**. This regioselectivity is typical of the classical nucleophilic substitution of **41a** proceeding via (η^3-allyl)palladium intermediate.[53] On the other hand, when **41a** was converted first to allylboronic acid **8a** and then coupled with iodobenzene (**24a**) the regiochemistry of the process is inverted, providing solely the branched product **48a** (entry 1, Scheme 28). Accordingly, the regioselectivity of the coupling reaction of **41a** can be fully controlled by the appropriate choice of the reaction partners. Furthermore, the above results clearly indicate that the carbethoxy groups lack any intrinsic directing effects for the formation of the branched allylic isomer **48a**. Obviously, the alkyl group of **8h** also lacks the directing effect on the regioselection of the arylation reaction (entries 5 and 6). Furthermore, the polar benzyloxy group in **8j** is expected to direct the nucleophilic attack to the less substituted allylic terminus, if (η^3-allyl)palladium intermediates were involved in the catalytic process.[1i-j] Hence, the reaction proceeds with an excellent regioselectivity providing the branched product.

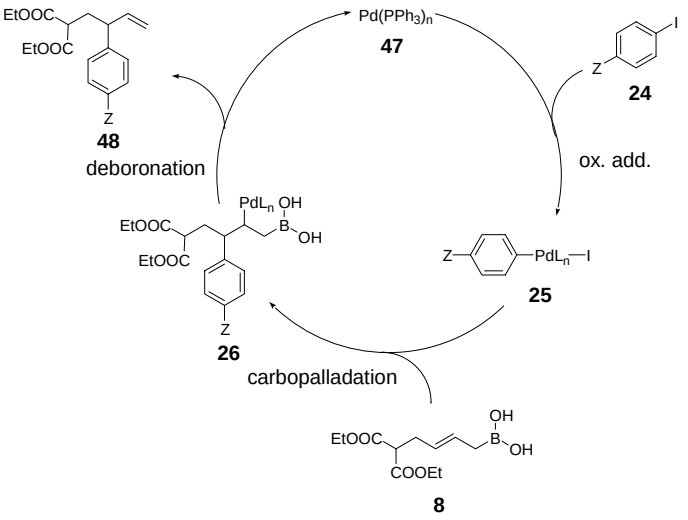


Scheme 28. The regioselectivity of the coupling reaction can be fully controlled by the appropriate choice of the reaction partners.

4.3 Mechanistic considerations

The above findings on the regioselectivity of the allylation reaction (Section 4.4) suggest that the coupling of allylboronic acids **8** and aryl iodides **24a-d** does not proceed via (η^3-allyl)palladium intermediates. A similar mechanistic conclusion was reported by Hallberg and Nilsson,[27] studying the palladium-catalyzed coupling reaction of the parent pinacolato allylboronate (**1a**) with iodobenzene **24a** (see Section 1.3, Scheme 10). These authors[27] concluded that the reaction is initiated by oxidative addition of **24a** to the palladium(0) catalyst followed by carbopalladation of the allylboronate and subsequent elimination of the palladium boronate (c.f. Scheme 10).

We believe that a similar mechanism applies for the palladium-catalyzed coupling of functionalized allylboronic acids with iodobenzenes (Scheme 29) as well. This mechanism (Scheme 29) would explain the selective coupling of **8** with **24**, involving a highly regioselective carbopalladation to form **26**, followed by β-boronate elimination by palladium affording product **48**.



Scheme 29. Plausible catalytic cycle for the arylation of allylboronic acids.

In summary, we have shown that the palladium-catalyzed coupling of allylboronic acids with aryl iodides can be achieved under standard Suzuki-Miyaura coupling conditions. These reactions proceed with a

remarkably high regioselectivity providing the branched allylic isomers. In contrast to palladium-catalyzed nucleophilic substitution reactions proceeding via (η^3-allyl)palladium intermediates, this process does not require directing groups in the allyl moiety to achieve substitution at the substituted allylic terminus. As the coupling reaction of allylboronic acids with iodobenzenes generates a new stereogenic carbon, the presented method creates the basis for development of a new asymmetric allylation processes.

5. Allylation of Aldehyde Substrates with in situ Generated Allylboronic Acids (Paper VI)

As discussed in the introduction (Section 1.3), allylation of aldehydes with allylboranes is one of the most important selective carbon-carbon bond formation reactions. Inspired by our previous results (Chapter 3) on the simple and robust method for generation of allylboronic acids, we decided to develop a new allylation method of aldehydes with in situ generated allylboronic acids (c.f. Chapter 2). As allyl alcohols are the most easily accessible substrates in the boronation reactions[6] (Chapter 3), we concentrated on development of a new one-pot process based on allylation of aldehydes with allyl alcohols via transient allylboronic acids.

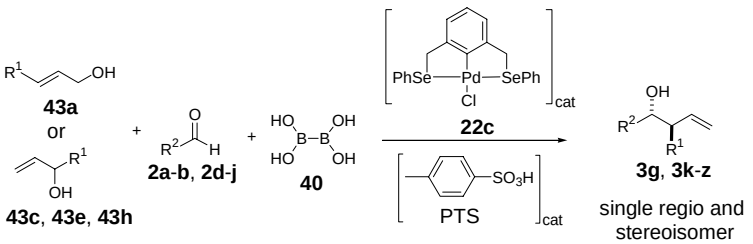
5.1 Application of allyl alcohols for allylation of aldehydes

Catalytic allylation of the carbonyl carbon of aldehydes with allyl alcohols is one of the most attractive transformations in palladium chemistry.[31d, 48a, 54, 55] In practical implementations the allylation reaction is initiated by a palladium-catalyzed conversion of the allyl alcohols to allylmetal species mediated by $SnCl_2$,[31d] BEt_3,[55a] Et_2Zn[55b] and indium salts.[55c] Subsequently, the allylmetal species undergo electrophilic allylation with the aldehyde substrate. As these transformations involve a two-step procedure using Lewis acidic and/or reductive organometallic reagents, the functional group tolerance of the reaction may be problematic. Using functionalized allyl alcohols, a further issue is the control of the stereoselectivity of the process, which is highly dependent on the applied organometallic reagent and on the steric bulk of the allylic substituent. Although, there are many excellent procedures described in the literature,[31d, 48a, 54, 55] it is still a challenging task to find highly selective and robust methods for palladium-catalyzed coupling of various allyl alcohols (including both cyclic and acyclic ones) with aliphatic and aromatic aldehydes.

According to our studies, allyl alcohols (**43**) react readily with aldehydes (**2**) in the presence of diboronic acid (**40**), catalytic amounts (5 mol%) of pincer-complex catalyst **22c**[35d] and p-toluenesulfonic acid (PTS) (Scheme 30, 31 and 33 and Table 4-5). These reactions can be performed as an operationally simple one-pot sequence under mild conditions (typically 40-50 °C) in a DMSO/MeOH mixture. Allylation of the aldehyde substrates occurs via formation of allylboronic acids from allyl alcohols and **40** (Scheme 32). When the reaction is carried out without application of the aldehyde component, the allylboronic acids (**8**) can be observed and isolated after conversion to allylborates (Section 3.1).[5, 6] Since the transient allylboronic acids (**8**)[5, 6] and the other reactants, including catalyst **22c**, are stable in the presence of air, moisture, weak acids and bases the reactions can be carried out without inert atmosphere and in standard quality solvents.

5.2 Regio- and stereoselectivity of the allylation

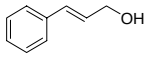
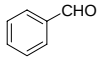
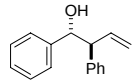
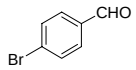
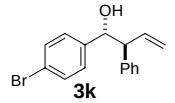
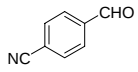
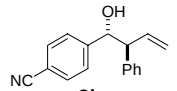
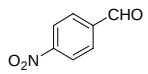
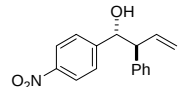
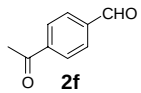
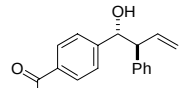
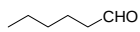
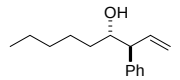
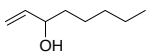
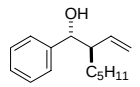
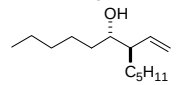
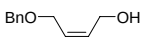
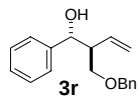
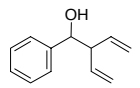
The regioselectivity[20] of the presented reactions (Scheme 30) is excellent as both linear (**43a**) and branched (**43c, 43e** and **43h**) allyl alcohols give the branched allylic product (**3g** and **3k-s**).



Scheme 30. Homoallylic alcohols prepared from allyl alcohols.

In the described processes (Scheme 30, 31 and 33) the homoallylic alcohol products **3g**, **3k-r** and **3t-z** were obtained as single diastereomers. The reactions from acyclic allyl alcohols **43a**, **43c** and **43e** give the anti products, as the transformations proceed via allylboronic acids (**8d**, **8h** and **8j**)[5, 6] in which the geometry of the double bond is trans.[20] The reaction proceeds readily and with high diastereoselectivity even for cyclic allyl alcohols **43g** and **43j**. In these reactions the double bond in the cyclic allylboronic acid (**8l** and **8m**) intermediate has a cis geometry,[5, 6] and thus the new carbon-carbon bond forms with syn diastereoselectivity.[20]

Table 4. Allylation of aldehydes with acyclic allyl alcohols (Scheme 30) (selected reactions).[a]

entry	alcohol	aldehyde	cond[b]	product[c]	yield[d]
1	 **43a**	 **2b**	40/16	 **3g**	84
2[e]	**43a**	**2b**	40/48	**3g**	96
3	**43a**	 **2d**	40/16	 **3k**	93
4	**43a**	 **2e**	40/16	 **3l**	72
5	**43a**	 **2a**	40/16	 **3m**	78
6	**43a**	 **2f**	40/16	 **3n**	75
7	**43a**	 **2g**	50/16	 **3o**	70
8	 **43c**	**2b**	50/16	 **3p**	86
9	**43c**	**2g**	50/16	 **3q**	76
10	 **43e**	**2b**	40/16	 **3r**	96
11	 **43h**	**2b**	60/16	 **3s**	82

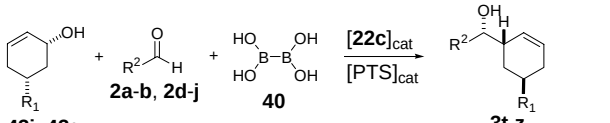
[a] Unless otherwise stated, the reactions of **43**, **2** and **40** were conducted in the presence of catalytic amounts of **22c** and PTS (both 5 mol%) in a DMSO/MeOH mixture. [b] Reaction conditions: temperature [°C]/time [h]. [c] Racemic. [d] Isolated yield. [e] PTS was not applied.

It is remarkable that starting from **43g**, a selective tandem stereoinduction can be achieved providing the product as only one of the four possible diastereomers (Table 5, entries 2-7). The excellent stereoselectivity is a consequence of the highly stereoselective formation of the allylboronic acid intermediate[5, 6] and the subsequent selective coupling with the aldehyde substrate.[3, 9a, 20, 51, 56]

5.3 Synthetic scope of the reaction

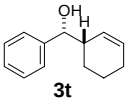
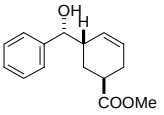
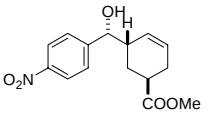
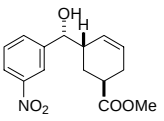
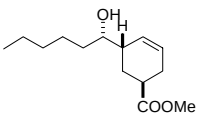
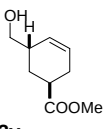
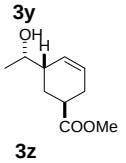
Diboronic acid **40** is a non-reductive reagent with very weak (if any) Lewis acid character, and therefore many functionalities including carbethoxy/methoxy (Scheme 33 and Table 5, entries 2-7), nitro (Table 4, entry 5, Table 5, entries 3 and 4) and cyano groups (Table 4, entry 4) are tolerated. The palladium catalyst **22c** is compatible with all these groups and aromatic bromides as well (Table 4, entry 3). Allylation of **2f** (Table 4, entry 6) represents a particularly good example for the functional group tolerance, as the aldehyde functionality of **2f** could be converted without affecting its keto functionality.

The presented reactions work smoothly with both aromatic and aliphatic aldehydes. As aliphatic aldehydes (such as **2g**) are somewhat less reactive than their aromatic counterparts (**2a-b** and **2d-f**), a higher reaction temperature (50 °C) was required for allylation of **2g** than for aromatic substrates **2a-b** and **2d-f** (40 °C). Remarkably, even paraformaldehyde (**2i**) and paracetaldehyde (**2j**) could be used as aldehyde sources (Table 5, entries 6-7); and thus, the presented one-pot sequence can be employed for homologization of allyl alcohols.



Scheme 31. High stereoselectivity is obtained.

Table 5. Coupling of cyclic allyl alcohols with aldehydes (Scheme 31) (selected reactions).[a]

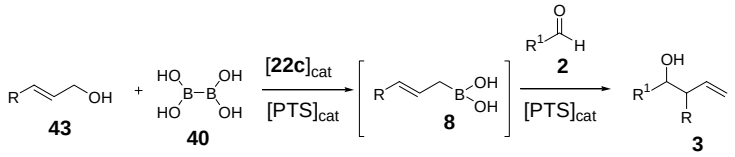
entry	alcohol	aldehyde	cond.[b]	product[c]	yield[d]
1	 **43j**	**2b**	60/16	 **3t**	98
2	 **43g**	**2b**	50/36	 **3u**	93
3	**43g**	**2a**	50/36	 **3v**	73
4	**43g**	 **2h**	50/36	 **3w**	73
5	**43g**	**2g**	50/36	 **3x**	71
6	**43g**	 **2i**	50/36	 **3y**	78
7	**43g**	 **2j**	50/36	 **3z**	72

[a] See caption *a* of Table 4 for the reaction conditions. [b] [°C]/[h]. [c] Racemic. [d] Isolated yield.

5.4 Effects of addition of catalytic amounts of acids

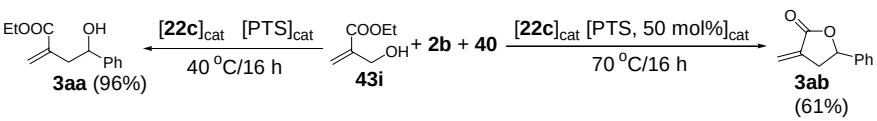
The reactions were performed in the presence of catalytic amounts of p-toluenesulfonic acid (PTS). We have previously shown (Section 3.3 and Figure 2)[6] that under the applied reaction conditions the formation of allylboronic acids (**8**) is considerably accelerated by PTS, particularly in case of carboxy substituents in the allyl alcohol substrates (**43i** and **43g**). Furthermore, Hall and co-workers[51, 56] have shown that Brønsted acids catalyze the coupling reaction of allylboronates and aldehydes. Thus, PTS catalyzes both crucial steps (Scheme 32) of the coupling reactions. Nevertheless, certain reactions

proceed even in the absence of acid catalyst PTS, as for example coupling of **43a** with **2b** (Table 4, entry 2). However, this process (entry 2) is completed in much longer time (48 h) than the corresponding reaction (entry 1) in the presence of PTS (16 h). On the other hand, in the presence of allylic carboxy substituents (**43i** and **43g**) or nitro substituent in the aldehyde component (**2a**) only traces of the coupling products formed without application of PTS.



Scheme 32. Both the crucial steps of the coupling reaction are catalyzed by PTS.

Another interesting effect of the added PTS was observed in the boronation reaction of allyl alcohol **43i**. Under mild reaction conditions (40°C) employing catalytic amounts PTS (5 mol%) the expected homoallyl alcohol **3aa** is formed, which could be isolated in excellent yield. However, at elevated temperature using 50 mol% of PTS, product **3aa** undergoes lactonization[51] affording **3ab** as the final product of the one-pot sequence (Scheme 33).



Scheme 33. The acyclic (**3aa**) or the lactonized (**3ab**) product can be obtained in a one-pot reaction by the appropriate choice of reaction conditions.

5.5 Comparison of the application of allyl acetates and allyl alcohols for allylation of aldehydes

In this Chapter we have demonstrated that aldehydes (**2**), can be efficiently allylated by allyl alcohols (**43**) via catalytically generated allylboronic acids (**8**) (Scheme 32). Previously, (in Chapter 2) we have shown a similar concept based on application of allyl acetates (**10**) and bis(pinacolato)diboron **11a**, which were converted to allylboronates (**1**) using $Pd_2(dba)_3$ as catalyst (Scheme 14). Subsequently, the transient allylboronates were reacted with aldehydes (**2**) affording

homallyl alcohol products (**3**). It is interesting to compare these two one-pot procedures (c.f. Schemes 14 and 32) for synthesis of homoallyl alcohols. In our experience, the palladium pincer-complex-catalyzed method (Scheme 32) has several advantageous features compared to the $Pd_2(dba)_3$ catalyzed method:

(1) Allyl alcohols are much more easily accessible and less expensive starting materials than allyl acetates.

(2) Pincer-complex catalyst **22** is a much more robust catalyst than $Pd_2(dba)_3$. As was pointed out in Section 2.1 the $Pd_2(dba)_3$-catalyzed reaction was accompanied by massive precipitation of black amorphous palladium(0).

(3) As the pincer-complex-catalyzed reaction does not involve palladium(0) species, substrates sensitive to oxidative addition (e.g. aromatic bromides) are compatible with the catalyst (Table 4 entry 3).

(4) The transient allylboronic acids (**8**) are more reactive in electrophilic substitution than allylboronates **1**. Therefore, the reaction proceeding via allylboronic acid (**8**) has a much broader synthetic scope (including non-activated and acyclic aliphatic aldehydes) than the alternative process via allylboronates **1**.

In summary, we have developed a versatile one-pot reaction for selective allylation of aldehydes with allyl alcohols, which can be carried out under mild conditions without using inert atmosphere. The described procedure is environmentally benign and economical: the by-product is non-toxic boronic acid and inexpensive allyl alcohols are employed as reagents.

Conclusions

In this thesis it was shown that branched homoallylic alcohols and amines can be prepared by allylation of aldehyde and sulfon-imine electrophiles with allyl acetates in the presence of diboronates and a catalytic amount of $Pd_2(dba)_3$ with excellent regio- and stereoselectivity. By employing chiral diboronates, enantiomerically enriched homoallyl alcohols could be obtained using aldehyde electrophiles. This procedure could be further developed by employment of allyl alcohols as allylating agents. In these procedures a SeCSe palladium pincer-complex catalyst was used instead of $Pd_2(dba)_3$, and diboronic acid was used as boron source.

We have also presented a new method for the synthesis of functionalized allylboronic acids. Palladium-catalyzed boronation of vinyl cyclopropane, vinyl aziridine, allyl acetate and allyl alcohol substrates could be accomplished using diboronic acid reagent in the presence of a SeCSe palladium pincer complex catalyst. These reactions result in allylboronic acids, which were converted to synthetically useful trifluoro(allyl)borates or allylboronates. The selectivity of the presented processes is very high, affording linear products that incorporate a trans double bond.

An alternative application of the allylboronic acids generated in the above pincer-complex-catalyzed reaction is palladium-catalyzed coupling with aryl iodides under Suzuki-Miyaura conditions. In these reactions functionalized allylboronic acids could be arylated with high regioselectivity. Interestingly, in these transformations the branched allylic products were formed; this is an unusual and desirable regioselectivity in palladium-catalyzed allylation reactions.

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