Catalytic Regio- and Stereoselective Reactions for the Synthesis of Allylic and Homoallylic Compounds

Rauful Alam
To my parents
Abstract

This thesis is focused on two main areas of organic synthesis, palladium-catalyzed functionalization of alkenes and allylic alcohols, as well as development of new allylboration reactions.

We have developed a palladium-catalyzed selective allylic trifluoroacetoxilation reaction based on C−H functionalization. Allylic trifluoroacetates were synthesized from functionalized olefins under oxidative conditions. The reactions proceed under mild conditions with a high level of diastereoselectivity. Mechanistic studies of the allylic C−H trifluoroacetoxilation indicate that the reaction proceeds via (η³-allyl)palladium(IV) intermediate.

Palladium-catalyzed regio- and stereoselective synthesis of allylboronic acids from allylic alcohols has been demonstrated. Diboronic acid B₂(OH)₄ was used as the boron source in this process.

The reactivity of the allylboronic acids were studied in three types of allylboration reactions: allylboration of ketones, imines and acyl hydrazones. All three processes are conducted under mild conditions without any additives. The reactions proceeded with remarkably high regio- and stereoselectivity.

An asymmetric version of the allylboration of ketones was also developed. In this process chiral BINOL derivatives were used as catalysts. The reaction using γ-disubstituted allylboronic acids and various aromatic and aliphatic ketones afforded homoallylic alcohols bearing two adjacent quaternary stereocenters with excellent regio-, diastereo- and enantioselectivity (up to 97:3 er) in high yield. The stereoselectivity in the allylboration reactions could be rationalized on the basis of the Zimmerman-Traxler TS model.
List of Publications

This thesis is based on a licentiate thesis by Rauful Alam entitled “Palladium-catalyzed Allylic C–H and C–OH Functionalization. Reactions of the Obtained Allylboronic Acids” and the following papers, referred to in text by their Roman numerals I–VI. Reprints were made with the kind permission from the publishers (Appendix A).

I. **Stereoselective Intermolecular Allylic C-H Trifluoroacetoxylolation of Functionalized Alkenes**

II. **Palladium-Catalyzed Synthesis and Isolation of Functionalized Allylboronic Acids. Facile, Direct Allylboration of Ketones**

III. **Selective Formation of Adjacent Stereocenters by Allylboration of Ketones under Mild Neutral Conditions**

IV. **Synthesis of Adjacent Quaternary Stereocenters by Catalytic Asymmetric Allylboration**

V. **Stereoselective Allylboration of Imines and Indoles under Mild Conditions. An *in situ* E/Z Isomerization of Imines by Allylboroxines**

VI. **Stereocontrol in Synthesis of Homoallylic Amines. Syn Selective Direct Allylation of Hydrazones with Allylboronic Acids**
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Abbreviations

Abbreviations are used in agreement with standards of the subject. Additional non-standard or unconventional abbreviations that appear in this thesis are listed below.

B$_2$pin$_2$  \hspace{1cm} \text{bis(pinacolato)diboron}
BINOL  \hspace{1cm} 1,1’-bi-2-naphthol
Bpin  \hspace{1cm} \text{pinacolato boron}
BQ  \hspace{1cm} 1,4-benzoquinone
dba  \hspace{1cm} \text{dibenzylideneacetone}
DFT  \hspace{1cm} \text{density functional theory}
DMC  \hspace{1cm} \text{dimethyl carbonate}
dr  \hspace{1cm} \text{diastereomeric ratio}
er  \hspace{1cm} \text{enantiomeric ratio}
L.A.  \hspace{1cm} \text{Lewis acid}
L  \hspace{1cm} \text{ligand (neutral)}
*L  \hspace{1cm} \text{chiral ligand}
MS  \hspace{1cm} \text{molecular sieves}
NOE  \hspace{1cm} \text{nuclear Overhauser effect}
PIFA  \hspace{1cm} \text{phenyliodine bis(trifluoroacetate)}
PIDA  \hspace{1cm} \text{phenyliodonium diacetate}
TFA  \hspace{1cm} \text{trifluoroacetate}
TS  \hspace{1cm} \text{transition state}
rt  \hspace{1cm} \text{room temperature}
X  \hspace{1cm} \text{ligand (charged)}
1. Introduction

The development of highly selective transformations is of fundamental importance in modern organic chemistry. Transition metal-catalysis is one of the useful synthetic approaches to achieve this goal. The allylation reaction using allylboron reagents and other allyl sources is also an important approach to develop selective syntheses.

1.1 Palladium-catalyzed allylic C–H acetoxylation

Transition metal-catalyzed substitution of allylic acetates and their analogs is one of the most utilized and studied reactions. An important method to synthesize allylic acetates is Pd-catalyzed allylic C–H functionalization. Pioneering works by McMurry and Kocovsky and Åkermark have shown that Pd(II)-catalyzed allylic acetoxylation of cyclic and acyclic olefins can be achieved in the presence of acetic acid and benzoquinone (BQ) as oxidant (Scheme 1). Mechanistic investigations by Bäckvall and co-workers indicated that a (π-allyl)palladium(II) intermediates are involved in the process and that BQ serves as both oxidant and activator ligand in the C–OAc bond formation process.

Scheme 1. Pd-catalyzed allylic C–H acetoxylation reaction.\textsuperscript{7a}

Recently the White\textsuperscript{9} and the Stahl\textsuperscript{10} group independently reported new methods for C–H acetoxylation reactions using palladium catalysis. The latter group used O\textsubscript{2} as an oxidant instead of BQ. According to the mechanistic studies by these authors, the C–H acetoxylation process take place via Pd\textsuperscript{0} and Pd\textsuperscript{II} catalytic intermediates.

Hypervalent iodine reagents were also employed as the principal component in the allylic C–H oxidation reactions.\textsuperscript{5, 11} For example, Szabó and co-workers\textsuperscript{11b} have reported the allylic C–H acyloxylation reaction with PhI(OAc)\textsubscript{2} (2a) as the oxidant and source of OAc (Scheme 2). The use of a
palladium catalysts and hypervalent iodine reagents, allowed an easy access to allylic acetoxy and benzyloxy compounds. Based on the mechanistic studies, a Pd\textsuperscript{II}/Pd\textsuperscript{IV} catalytic cycle was proposed, when PhI(OAc)\textsubscript{2} was used as the oxidant.

\[
\begin{array}{c}
\text{H} & \text{H} \\
R & \\
\end{array} \quad \xrightarrow{5 \text{ mol}\% \text{ Pd(OAc)}_2, \text{PhI(OAc)}_2} \quad \begin{array}{c}
\text{H} & \text{H} \\
R & \text{OAc} \\
\end{array} \quad \xrightarrow{\text{CH}_3\text{CN, KOAc, 40 }^\circ\text{C, 18 h}} \quad \begin{array}{c}
\text{H} & \text{H} \\
\text{Ph} & \text{OAc} \\
\end{array} \quad \xrightarrow{\text{PhI(OAc)}_2, \text{PIDA}} \quad \begin{array}{c}
\text{H} & \text{H} \\
\text{Ph} & \text{OAc} \\
\end{array}
\]

Scheme 2. Pd-catalyzed C–H acetoxylation reaction reported by Szabó and co-workers.\textsuperscript{11b}

In spite of the wide application of allylic C–H acyloxylation reactions in organic synthesis, the stereoselective transformations of substituted cyclic alkenes are limited. Particularly, the intermolecular diastereoselective C–H acyloxylation is still a challenge. A new synthetic process for such a reaction is presented in Chapter 2.

1.2 Synthesis of allylboronates

Allylboronates are efficient reagents for regio- and stereoselective allylation of carbonyl compounds and some related functionalities.\textsuperscript{3, 12} Due to the importance of allylboronates in synthetic organic chemistry there has been a large interest in the development of new methods for the synthesis of these reagents. The classical synthetic procedures involve application of allyl-Grignard and allyl-Li reagents.\textsuperscript{13} However, these methods have a limited synthetic scope because of problems with the regioselective formation of the allylboronates.

Palladium-catalyzed methods based on the substitution of allylic alcohol derivatives have proven to be a versatile and relatively simple method to obtain allylboronates. The first process was reported by Miyaura and co-workers\textsuperscript{14} (Scheme 3). In this process, B\textsubscript{2}pin\textsubscript{2} was used as the boron source. Although the regioselectivity of the reaction is excellent, a drawback of this process is the formation of varying amounts of homocoupling products.

\[
\begin{array}{c}
\text{AcO} & \text{Ph} \\
\end{array} \quad \xrightarrow{5 \text{ mol}\% \text{ Pd(dba)}_2} \quad \begin{array}{c}
\text{O} & \text{O} \\
\text{B–O} & \text{B–O} \\
\text{B}_2\text{pin}_2 & \\
\end{array} \quad \xrightarrow{\text{DMSO, 50 }^\circ\text{C, 16 h}} \quad \begin{array}{c}
\text{AcO} & \text{Ph} \\
\end{array} \quad \xrightarrow{83\%} \quad \begin{array}{c}
\text{B–O} & \text{B–O} \\
\text{Ph} & \text{Ph} \\
\end{array} \quad \xrightarrow{8\%} \quad \begin{array}{c}
\text{Ph} & \text{Ph} \\
\end{array}
\]

Scheme 3. Pd-catalyzed borylation of allylacetates.\textsuperscript{14}

The Szabó group\textsuperscript{15} has expanded the substrate scope to include allylic alcohols instead of allylic acetates (Scheme 4). It was also shown that
certain Pd(II) pincer complexes are more efficient than Pd(dba)$_2$. In depth mechanistic studies revealed that catalytic amounts of Lewis or Brønsted acids are required in the reaction to activate the allylic alcohols for Pd-catalyzed substitution.$^{16}$ The reaction is substantially accelerated in the presence of MeOH or other protic co-solvents.

\[
\text{Scheme 4. Pd-catalyzed borylation of allylic alcohols.}^{15c, 15d}
\]

The Szabó group also developed palladium-catalyzed allylic C-H borylation methods.$^{17}$ These processes allowed for the synthesis of allylboronates from readily available alkenes under oxidative conditions using BQ (1) or the hypervalent iodonium salt.

Ito, Sawamura and their co-workers reported the regio- and stereo-selective synthesis of allylboronates by Cu-catalyzed substitution of allyl carbonates.$^{18}$ This method can also be extended to asymmetric catalysis for the synthesis of enantioenriched allylboronates (Scheme 5).$^{19}$

\[
\text{Scheme 5. Cu-catalyzed asymmetric borylation of allylcarbonates.}^{19}
\]

Enantioselective synthesis of α-substituted allylboronates has been reported by Hall and co-workers (Scheme 6).$^{20}$ This method is based on copper-catalyzed substitution of allylhalide substrates. The chiral allylboronates generated in this reaction were used for further transformation without isolation.

\[
\text{Scheme 6. Cu-catalyzed borylation reported by Hall and co-workers.}^{20}
\]

Related Cu-catalyzed asymmetric synthesis of allylboronates have also been independently reported by the groups of Hoveyda$^{21}$ and McQuade.$^{22}$ Nickel-catalyzed stereospecific borylation of allylic acetates was developed by Morken and co-workers.$^{23}$ The reaction is highly selective for the termi-
nal allylboronates (Scheme 7). The Morken group also developed palladium-catalyzed enantioselective borylation methods for the synthesis of allylboronates.\textsuperscript{24}

\[ \text{Scheme 7. Ni-catalyzed selective borylation of allylic acetates.} \textsuperscript{23} \]

Very recently Aggarwal and co-workers have reported a new method for the preparation of enantioenriched allylboronates.\textsuperscript{25} This so called “lithiation-borylation method” involves homologation of vinyl boronates using alkyl carbamates and butyllithium (BuLi) in the presence of (+)-sparteine (Scheme 8).

\[ \text{Scheme 8. Synthesis of allylboronates by lithiation-borylation method.} \textsuperscript{25b} \]

As shown above, synthesis of allylboron reagents has attracted large interest in modern organic chemistry. As a contribution to this field we developed a new method for the synthesis and isolation of allylboronic acids, which is presented in Chapter 3.

### 1.3 Application of allylboronates in synthesis

Allylboronate reagents have been extensively used to synthesize numerous precursors for natural products and bioactive molecules.\textsuperscript{26} Addition of allylboronates to carbonyl and imine electrophiles is a well studied and documented reactions in synthetic organic chemistry.

#### 1.3.1 Stereoselective allylation of carbonyl compounds

Allylboration reactions of aldehydes have been widely applied for the stereoselective synthesis of homoallylic alcohols.\textsuperscript{3} After the discovery by Bubnov,\textsuperscript{27} the reaction was further developed by Hoffmann,\textsuperscript{28} Brown,\textsuperscript{29} Roush\textsuperscript{30} and others. Hoffmann and Brown carried out in depth mechanistic studies, which also explained the stereochemistry of the reaction. Hoffman postulated that the reaction between allylboronates and aldehydes proceeds via a six-
membered cyclic TS similar to the Zimmerman-Traxler$^{31}$ model (Scheme 9).$^{28a,32}$

The high diastereoselectivity of the allylboration reaction is attributed to an internal Lewis acid activation of the carbonyl functionality by the empty p-orbital of boron.

\[
\begin{align*}
\text{Syn} & \quad \text{with } Z\text{-allylboronate} \\
\text{Anti} & \quad \text{with } E\text{-allylboronate}
\end{align*}
\]

Scheme 9. Zimmerman-Traxler model to describe stereochemistry of allylboration reaction.

The addition of Lewis or Brønsted acids may accelerate the allylboration of carbonyl compounds.$^{33}$ Hall and co-workers proposed that Lewis acids coordinate to the lone pair of the boronate oxygen, which renders the boron atom more electron deficient (Scheme 10).$^{33b,34}$ This mechanism for L.A. and Brønsted acid activation was also confirmed by the DFT studies of Houk and co-workers.$^{35}$

\[
\begin{align*}
\text{L.A.} & \quad \text{with } \text{L.A.} \\
\text{L.A.} & \quad \text{with } \text{L.A.}
\end{align*}
\]

Scheme 10. Possible modes of Lewis acid activation for the allylboration.

Allylboronates can also react with ketones, yielding tertiary homoallylic alcohols. However the addition of allylboronates to ketones is much slower than similar reactions with aldehydes. Thus the selective allylation of ketones with allylboronates often requires the use of catalysts.$^{36}$ In addition, most of the present methods for allylboration of ketones are limited to the use of unsubstituted (parent) allylboronates or crotylboronates.

1.3.2 Enantioselective allylation of carbonyl compounds

There are basically two main approaches for the asymmetric allylboration of carbonyl compounds. The first approach is the application of enantioenriched allylboronates performing chirality transfer and the second one is
asymmetric induction by using chiral catalyst. One of the first asymmetric allylboration reactions was reported by Roush and co-workers.\textsuperscript{13b, 37} These authors employed chiral auxiliaries attached to the boron atom (Scheme 11). Diisopropyl tartrate (DIPT) proved to be a very efficient chiral auxiliary to induce enantioselectivity.

![Scheme 11](image)

**Scheme 11.** Asymmetric allylation of aldehydes using chiral allylboronate.\textsuperscript{13b}

A similar approach was reported by Soderquist and co-workers\textsuperscript{38} for the asymmetric allylboration of aldehyde and ketones. A bicyclic chiral auxiliary on the boron atom was employed for highly diastereo- and enantioselective allylboration (Scheme 12).

![Scheme 12](image)

**Scheme 12.** Diastereo- and enantioselective allylboration by chiral allylborane.\textsuperscript{38a}

Enantiomerically pure TADDOL based allylboronates were developed by Pietruszka and co-workers\textsuperscript{39}. These reagents were used for chirality transfer in allylboration of aldehydes (Scheme 13). The chiral auxiliary can be recovered after the allylation by reduction with LiAlH₄.

![Scheme 13](image)

**Scheme 13.** Asymmetric allylation of aldehyde using enantiopure allylboronate.\textsuperscript{39}

Metal-catalyzed asymmetric synthesis of heterocyclic allylboronates was described by Hall and co-workers\textsuperscript{40}. These allylboronates were used \textit{in situ} for allylboration of aldehydes. The key-step in synthesis of mefloquine was performed using this method (Scheme 14).
Scheme 14. Asymmetric allylboration by cyclic allylboronates.\textsuperscript{40}

Very recently Aggarwal and co-workers\textsuperscript{25b, 41} reported an efficient allylboration method using $\alpha$-substituted enantioenriched allylboronates (see also Scheme 8). The method is highly diastereo- and enantioselective. In addition the procedure is suitable for the synthesis of homoallylic alcohols with two adjacent quaternary stereocenters (Scheme 15).

Scheme 15. Asymmetric allylation of ketone by $\alpha$-substituted chiral allylboronate.\textsuperscript{25b}

An alternative approach for the asymmetric allylboration of carbonyl compounds involves the application of chiral catalysts. Both Lewis and Brønsted acids have been used for the asymmetric allylboration reactions. The first catalytic enantioselective allylboration reaction was reported by Miyaura and co-workers (Scheme 16).\textsuperscript{33c} This reaction proceeded with a high regio- and diastereoselectivity but the enantioselectivity was relatively low.

Scheme 16. Catalytic asymmetric allylboration of aldehyde.\textsuperscript{33c}

Hall and co-workers\textsuperscript{42} reported a Sn-catalyzed asymmetric allylboration reaction using allyl-Bpin as the allyl source. A chiral diol was used as a lig- and in this process, which was supposed to coordinate to SnCl$_4$ (Scheme 17).
Scheme 17. Tin-catalyzed asymmetric allylboration of aldehyde.\footnote{42a}

Asymmetric allylation of ketones was reported using chiral allylboronate, derived from BINOL compounds. Chong and co-workers described the allylation of ketones using 3,3-\((\text{CF}_3)_2\)-BINOL boronate \(3\alpha\) (Scheme 18).\footnote{43} The reaction gave homoallylic alcohol product with a high level of enantioselectivity.

Scheme 18. Asymmetric allylation of ketone using BINOL-boronate.\footnote{43}

Catalytic methods have also been described to control both diastereo- and enantioselectivity in the allylboration of ketones.\footnote{44} The first catalytic enantioselective allylboration of ketones was developed by Shibasaki and co-workers.\footnote{45} Brønsted acid such as BINOL derivatives\footnote{44, \footnote{46}} was found to be very efficient in the asymmetric allylboration reactions. Schaus and co-workers\footnote{44} reported a method for asymmetric allylation of ketones using isopropoxyboronate and catalytic amounts of \(\text{Br}_2\)-BINOL \(4\alpha\) (Scheme 19).

Scheme 19. Catalytic asymmetric allylboration of ketone using \(\text{Br}_2\)-BINOL.\footnote{44a}

These authors proposed a Zimmerman-Traxler type transition state to rationalize the enantioselectivity in this reaction. It has been also pointed out that the substituent in BINOL (e.g. Br or CF\(_3\)) has an important role for the enantioselectivity of these reactions.

Catalytic synthesis of homoallylic alcohols containing adjacent quaternary stereocenters has been a great challenge in synthetic organic chemistry. A new synthetic method for such reaction is presented in Section 5.2.
1.3.3 Stereoselective allylation of imines

Homoallylic amine motifs occur in many natural products and biologically relevant compounds.\(^{47}\) One of the most common strategies for homoallylic amine synthesis is the addition of allyl-metal reagents to imines.\(^{48}\) The use of allylboronate compounds for these reactions has emerged as an important synthetic approach.\(^{47}\) Allylboronates have a low toxicity, high functional group tolerance and the allylation of imines occurs with a high level of selectivity.

Stereoselective allylation of aldimines can be performed by allylboronates in the presence of Lewis acid catalysts. Batey and co-workers\(^{49}\) reported the allylboration of N-toluenesulfonylimines using crotyltrifluoroborate and BF\(_3\).OEt\(_2\) (Scheme 20). The allylation was proposed to proceed via the allyl-BF\(_3\) species which is generated from allyl-BF\(_3\)K.

\[
\text{Scheme 20. Stereoselective allylation of imine by allyltrifluoroborate.}^{49}
\]

Kobayashi and co-workers\(^{50}\) reported a three-component diastereoselective allylation reaction to synthesize homoallylic primary amines (Scheme 21). In addition, several useful methods for asymmetric allylboration of imines\(^{25b,51}\) using allylboronates can also be found in literature.

\[
\text{Scheme 21. Synthesis of homoallylic amine using multicomponent method.}^{50}
\]

Allylboration of acylhydrazones have also proven to be a very useful reaction for the synthesis of homoallylic amine derivatives. However the allylation of acylhydrazones by allylboronates requires the application of metal catalysts.\(^{52}\) An indium-catalyzed reaction for the allylation of N-acylhydrazone was reported by Kobayashi and co-workers (Scheme 22).\(^{52a}\) It has been proposed that indium undergoes a transmetallation with allyl-Bpin to form an active allyl-indium species which then added to the hydrazone.
Scheme 22. Indium-catalyzed allylation of acylhydrazone.\textsuperscript{52a}

We have developed a stereoselective method for allylation of imines and acylhydrazones using allylboronic acids. These results are summarized in Chapter 6.
2. Pd-catalyzed stereoselective allylic C–H trifluoroacetoxylation (Paper I)

As mentioned in the introduction, transition metal-catalyzed C–H bond activation methods have attracted increasing interest in organic synthesis.\textsuperscript{53} Using these methods multistep synthesis for prefuctionalization of the organic substrates is not necessary. In addition the waste production of the reaction can be reduced as the new functional group can be installed by replacement of hydrogen.\textsuperscript{54} Palladium-catalyzed allylic C–H bond activation is one of the oldest and most versatile C–H functionalization method (Section 1.1).\textsuperscript{55} In this reaction (as in C–H activation based processes in general) the greatest challenge is the control of the regio- and stereoselectivity of the process.

Steredefined allyl acetates are very important precursors for regio- and stereoselective palladium-catalyzed allylic substitution reactions.\textsuperscript{56} Although many regioselective allylic C–H functionalization methods have been reported, there are few reports on stereoselective allylic C–H acetoxylation.\textsuperscript{7a} Most of these studies are intramolecular C–H acyloxylation reactions. For example, a stereoselective allylic C–H acetoxylation method has been reported by White and co-workers (Scheme 23). Intramolecular selectivity control allowed macrocyclization\textsuperscript{57} and straightforward synthesis of \textit{anti-1,4-}
dioxan-2-ones\textsuperscript{58} from simple olefins using Pd(II)/sulfoxide catalysis. Bäckvall and co-workers\textsuperscript{59} have also developed several methods for the synthesis of allylacetoxy compounds based on palladium-catalyzed intramolecular oxidative carbocyclization.

\begin{center}
\textbf{Scheme 23.} Stereoselective intramolecular C–H oxidation reported by White and co-workers.\textsuperscript{58}
\end{center}
2.1 Development of selective intermolecular allylic C–H trifluoroacetoxylation

As our group previously developed a useful allylic C–H acetoxylation method based on using PhI(OAc)$_2$ (2a) (see Section 1.1) as oxidant and acetate source, we envisioned that PhI(OCOCF$_3$)$_2$ (2b) can also be used in this type of reaction to introduce a trifluoroacetate group at the allylic position of alkenes. Allylic trifluoroacetates are more reactive than allylic acetates in transition metal-catalyzed substitutions, and therefore an easy access to these compounds is desirable. As far as we know, selective allylic C–H trifluoroacetoxylation has not been reported in the literature.

In the early stage of development and optimization, we employed carboxylated alkene 6a as our model substrate, as it gave a high yield and exhibited high selectivity in the Pd-catalyzed C–H acetoxylation with 2a.$^{11b}$ However, PhI(OCOCF$_3$)$_2$ (2b) is most likely a stronger oxidant than PhI(OAc)$_2$ (2a), and therefore we could not use oxidation sensitive solvents, such as THF or DMSO. In addition the conjugated acid of the trifluoroacetate ion (the nucleophile) is a strong acid, and therefore trifluoroacetic acid could not be used as the solvent either. After short optimization we have found that dimethyl carbonate (DMC) is an excellent solvent for all reaction components and it is not oxidized by PIFA. We have found that the isolated yields are higher when LiOCOCF$_3$ is used as additive. Under these conditions the reaction could be performed with various functionalized alkenes (Table 1).
Both Pd(OAc)$_2$ (5b) and Pd(OCOF$_3$)$_2$ (5c) were equally efficient as catalyst in the reaction. So we decided to use 5b in the present synthetic method as it is less expensive than 5c. Not only terminal (6a) but internal alkenes 6b-c could also be used for trifluoroacetoxylated groups. For compounds with long alkyl chain oxidation of the double bond occurred, while in the case of electron donating substituents, mainly oxidation of the double bond occurred together with other processes.
Table 2. Stereoselective allylic C–H trifluoroacetoxylation of cyclic alkenes.\textsuperscript{a}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & Substrate & Time (h) & Product\textsuperscript{b} & Ratio (I/II)\textsuperscript{c} & Yield (%)\textsuperscript{d} \\
\hline
1 & MeO\textsubscript{2}C & 6f & 6 & MeO\textsubscript{2}C & 95:5 & 75 \\
2 & Ph & 6g & 24 & Ph & 11:1 & 49 \\
3 & Me\textsubscript{2}N & 6h & 8 & Me\textsubscript{2}N & 3:1 & 59 \\
4 & BnO\textsubscript{2}C & 6i & 15 & BnO\textsubscript{2}C & 10:1 & 51 \\
5 & Ph & 6j & 6 & Ph & 15:1 & 49 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} Unless otherwise specified, substrate 6 (0.30 mmol) was dissolved in DMC:DCM (10:1), and 2b (0.45 mmol), Pd(OAc)\textsubscript{2} (0.015 mmol, 5 mol \%) were then added. The mixture was then stirred at 0 °C for indicated times. \textsuperscript{b} Major regioisomers are shown for clarity. \textsuperscript{c} Ratio of regioisomers was determined from \textsuperscript{1}H NMR spectrum of the crude reaction mixture. \textsuperscript{d} Isolated yields (%).

Not only acyclic alkenes but cyclic alkenes could also be employed for the trifluoroacetoxylation reaction. Monosubstituted cyclic alkenes reacted with a remarkably high selectivity (Table 2). The reaction conditions were very similar to the trifluoroacetoxylation of acyclic substrates (Table 1) but in order to get this high stereoselectivity, the reactions had to be conducted at 0 °C. This is below the freezing point of DMC, therefore the reaction medium was diluted with DCM to avoid freezing of the reaction mixture. The yields with LiOCOCF\textsubscript{3} were as high as in its absence; therefore we did not use this additive in the trifluoroacetoxylation of cyclic substrates.

Considering the number of possible regio- and stereoisomers, a mixture of six allylic trifluoroacetate products could be expected. Yet, in most cases we obtained a single diastereomer with very high regioselectivity (Table 2, entries 1-2 and 4-5). The major regioisomer in all cases was the 1,4-substituted product (7f-j) with \textit{anti} diastereoselectivity, and the minor product is the regioisomer of the same diastereomer. The stereochemistry of the major isomers was assigned based on NOE experiments.
The regioselectivity was slightly dependent on the ring size and the ring substituents. Thus, the five membered ring substrates, such as 6f gave a higher selectivity than its six-membered ring counterpart 6i. Ester- and keto-substituted substrates were also trifluoroacetoxylated with better regioselectivity than substrates with an amide substituent (c.f. entries 1 and 3). The substituent effect of the amide functionality on the selectivity was also reported in other allylic C–H acyloxylation reactions. For example, Stambuli and co-workers reported a drop in the regioselectivity of C–H acetoxylation reactions in the presence of the amide functionality.

The yields varied from fair to good. The main side reaction, lowering the yield, was the oxidation of the double bond by PIFA. Bis-trifluoroacetoxy compound 7k (Figure 1) was isolated from the reaction of 6i (entry 4).

Figure 1. Compound 7k was isolated from C-H trifluoroacetoxylation reaction of 6i.

2.2 Mechanistic proposal for the allylic C–H trifluoroacetoxylation

The stereochemical information of the above reactions with cyclic substrates (Table 2) and previous studies of our group with 2a (see Scheme 2) suggest that the reaction most likely proceeds via (η³-allyl)palladium(IV) intermediates. There are two plausible ways for the formation of an (η³-allyl)palladium(IV) species; 1) formation of an (η³-allyl)palladium(II) moiety, which is subsequently oxidized to (η³-allyl)palladium(IV) or, 2) direct oxidation of the Pd(II) catalyst prior to C–H activation and subsequent formation of an (η³-allyl)palladium(IV) intermediate. It is well-established that (η³-allyl)palladium(II) complexes can be formed from alkenes and Pd(II) precursors, and therefore, we studied the possible formation of such complexes under catalytic conditions. Kurosawa and co-workers have shown that allylic chlorides undergo stereoselective syn oxidative addition with Pd₂(dba)₃ when non-coordinating solvents (i.e., benzene) are used. Following the similar methodology, complex (5e) was prepared from product 7j (Scheme 24).
Palladium complex 5d was stable enough for purification by silica-gel chromatography. After purification, the ligand exchange was performed using AgOCOCF₃ which afforded 5e. Complex 5e is one possible reaction intermediate in the catalytic C–H trifluoroacetoxylation of 6j. We hypothesized that if the (η³-allyl)palladium(II) moiety (5e) is the key intermediate in our reaction then oxidation of 5e with PIFA (2b) would give compound 7j in a diastereoselective manner. Accordingly, 5e was treated with 2b for 1 h at 0 °C in DMC. In this process, 5e was completely consumed, resulting in a complex mixture, in which only traces of 7j was observed (Scheme 25). On the other hand, the catalytic reactions proceeded very cleanly at 0 °C. Therefore, we conclude that 5e is less likely an intermediate in the catalytic trifluoroacetoxylation with PIFA 2b (Tables 1-2).

On the basis of the above findings (Scheme 25) we assume that the initial step of the catalytic cycle (Figure 2) of the trifluoroacetoxylation reaction is oxidation of the Pd(II) catalyst by PIFA (2b) to give Pd(IV) complex 5f. Previous studies in the group have demonstrated that Pd(II) pincer complexes undergo such type of oxidation with PIFA. Coordination of the alkene to this complex 5f gives 5g, which undergoes allylic C–H cleavage, which is possibly aided by one of the OCOCF₃ ligands.

Considering the stereochemical outcome of the reaction with cyclic substrates (Table 2) the C–H bond cleavage is supposed to be stereoselective. The cleavage of the C–H bond (red colored) in 5g leads to allyl-Pd(IV) complex 5g′, in which the Pd atom and the R group are on different sides of the six-membered ring. Reductive elimination of 5g′ leads to anti-product 7j. Thus, the high regio- and stereoselectivity in the Pd-catalyzed allylic C–H trifluoroacetoxylation of the monosubstituted cycloalkenes is based on two selective steps in the catalytic cycle: stereoselective formation of 5g′ and regioselective reductive elimination of 5g′.
2.3 Conclusions for the allylic C–H trifluoroacetoxylation

We have developed a new method for the catalytic allylic C–H trifluoroacetoxylation reaction, using a palladium catalyst in the presence of an oxidant PhI(OCOCF₃)₂. This methodology is applicable for both acyclic (terminal and internal) and cyclic olefins. The reaction proceeds with remarkably high regio- and stereoselectivity for the cyclic alkenes. The described method is synthetically useful for the synthesis of stereodefined cyclic allylic trifluoroacetates from mono-substituted cyclic olefins.
3. Pd-catalyzed synthesis and isolation of allylboronic acids (Paper II)

As mentioned above (Section 1.2) there is a large interest for the development of new methods for the synthesis of allylboronates, as these compounds are useful allylating reagents for carbonyl compounds. Brown and co-workers\textsuperscript{13a} pointed out that allylboronic acids are more reactive allylating agents than traditionally used allylboronic esters, such as allyl-Bpin compounds. However, the poor stability of allylboronic acids under ambient conditions prevented their isolation and study of their reactivity.

3.1 Development of new synthetic methods for the synthesis and isolation of allylboronic acids

The palladium-catalyzed synthesis of allylboronic acids was first reported by Szabó and co-workers in 2005.\textsuperscript{64} It was also shown that allylboronic acids can be prepared from allyl alcohols and diboronic acid 9a in a palladium-catalyzed process (Scheme 26).\textsuperscript{15a} Although allylboronic acid 10 could be fully characterized on the basis of the $^1$H NMR spectrum of the crude reaction mixture, their isolation was not possible. When the solvent was removed, allylboronic acids underwent rapid decomposition. Therefore, it was appealing to develop new reaction conditions for this reaction, which allow isolation of allylboronic acids 10 in pure form.

![Scheme 26](image)

**Scheme 26.** Synthesis of allyltrifluoroborates via allylboronic acids.\textsuperscript{15a}

Diboronic acid 9a is an air-stable commercially available compound.\textsuperscript{65} Although, it was shown that 9a is an excellent boron source in many transition metal-catalyzed transformations,\textsuperscript{15c, 64, 66} it was much less used\textsuperscript{67} than its
pinacol analog B$_2$pin$_2$. One of the reasons is that the structure, solubility and handling of 9a are different from B$_2$pin$_2$. In the next section a couple of important properties of this reagent are summarized.

3.1.1 Diboronic acid B$_2$(OH)$_4$ as boron source

Commercially available diboronic acid 9a is often contaminated with traces of basic impurities, most probably HNMe$_2$. Even small traces of base may inhibit the catalyst in the synthesis of allylboronic acids. Therefore, commercially available diboronic acid was purified by washing with dioxane and water. Unlike B$_2$pin$_2$, diboronic acid 9a is insoluble in most organic solvents. The exceptions are MeOH, EtOH and DMSO in which 9a is readily soluble. Diboronic acid 9a is also fairly soluble in water, and therefore, the first choice for the reaction medium using 9a as a B(OH)$_2$ source using these solvents or their mixtures. Another important difference compared to B$_2$pin$_2$ is that 9a exist as a mixture of monomers, dimers and trimers (Scheme 27). For example, 9b and 9c were observed along with 9a in the $^1$H NMR spectrum of diboronic acid (Figure 3).

![Scheme 27. Formation of boronic acid anhydrides under drying.](image)

The oligomeric forms 9b-c easily dissociates to the monomeric form 9a in MeOH or water which was used as solvent or co-solvent.
3.1.2 Synthesis of allylboronic acids and their isolation

Our studies (see below, Section 3.2) have shown that pure, solvent-free allylboronic acid is highly oxygen sensitive. Therefore we developed a synthetic method, which allows isolation and purification of allylboronic acids under strictly oxygen free conditions. The final purification of the allylboronic acids were carried out with precipitation/crystallization of the products under inert conditions.
Table 3. Pd-catalyzed synthesis of allylboronic acids.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>5h (0.5)</td>
<td>MeOH</td>
<td>18</td>
<td>10a</td>
<td>61/65c</td>
</tr>
<tr>
<td>2</td>
<td>8b</td>
<td>5h (0.2)</td>
<td>DMSO:H$_2$O</td>
<td>14</td>
<td>10b</td>
<td>55d</td>
</tr>
<tr>
<td>3</td>
<td>8c</td>
<td>5h (2.0)</td>
<td>DMSO:H$_2$O</td>
<td>13</td>
<td>10c</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>8d</td>
<td>5h (0.2)</td>
<td>MeOH</td>
<td>1°</td>
<td>10d</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>8e</td>
<td>5h (0.5)</td>
<td>DMSO:H$_2$O</td>
<td>18</td>
<td>10e</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>8f</td>
<td>5h (5.0)</td>
<td>DMSO:H$_2$O</td>
<td>18</td>
<td>10f</td>
<td>77f</td>
</tr>
<tr>
<td>7</td>
<td>8g</td>
<td>5h (5.0)</td>
<td>DMSO:H$_2$O</td>
<td>18</td>
<td>10g</td>
<td>79f</td>
</tr>
<tr>
<td>8</td>
<td>8h</td>
<td>5i (5.0)</td>
<td>DMSO:H$_2$O</td>
<td>1</td>
<td>10h</td>
<td>25</td>
</tr>
</tbody>
</table>

*Unless otherwise specified, catalyst 5h or 5i and diboronic acid 9a (2.4 mmol) were added to allylic alcohol 8 (2.0 mmol) in the solvent (2.0-4.0 mL) mentioned above. Isolated yield applying precipitation method. Isolated yield when reaction was performed in gram scale. The reaction was performed at 0 °C. The product was isolated by extraction and the yield was determined by $^1$H NMR using naphthalene as an internal standard.

The initial method development was carried out with cinnamyl alcohol 8a as model substrate (Table 3). First we employed MeOH as solvent and Pd(MeCN)$_4$(BF$_4$)$_2$ 5i as catalyst. Catalyst 5i was particularly efficient for synthesis of the analog allyl-Bpin compounds and in depth mechanistic studies indicated that this catalyst efficiently catalyzed several key steps of the borylation (and silylation) of allyl alcohols. However, the reaction was very fast and exothermic and except the desired product 10a, a lot of by-products, such as allyl benzene was also formed. Therefore we employed a less reactive but more selective catalyst H$_2$PdCl$_4$ 5h, which can be easily prepared from PdCl$_2$ and aqueous HCl solution. Using 5h, allylboronic
Acid **10a** was readily formed from **8a** and **9a**. When the reaction was completed, Pd-black was filtered off under inert conditions, and then brine was added. Allylboric acid **10a** precipitated as a white solid, which was filtered off under inert conditions (under Ar) and the dry compound was stored and used in glove box. The above procedure is readily scalable. A four times scaling using the above described optimized conditions did not change significantly the yield (entry 1, Table 3). $^1$H NMR studies of allylboric acids in dry DMSO indicated that these compounds form allylboroxines, which are very oxygen sensitive. Characterization of cinnamyl boroxine is given below in Section 3.2.

With optimal reaction conditions in hand, we aimed to explore the synthetic scope of the reaction. Of course, we still kept the focus on the possibilities of the isolation and purification of the products under inert conditions. For sterically hindered alcohols **8b-c** and **8e** the reaction was slower than for cinnamyl alcohol **8a** and large amount of protodeborylated byproducts were formed. Changing the reaction medium to DMSO/H$_2$O we could reduce the amount of the byproducts and **10b-c** and **10e** was isolated in synthetically useful yields (entries 2-3). The products from acyclic alcohols are formed as single *trans*-isomers. The exception is **10b** with two substituents in one terminal position of the double bond. This compound was obtained as a 5:1 mixture of *E-* and *Z*-products. Geraniol (**8f**) and nerol (**8g**) could easily be borylated but **10f** and **10g** resisted to any attempts for precipitation. However, we have found that pure samples of **10f-g** can be isolated by extraction with chloroform (entries 6 and 7). Interestingly the double bond geometry of nerol and geraniol was preserved in the products **10f-g** providing interesting substrates for the studies of the stereochemistry of the allylation reactions (see Section 4.1). Cyclic boronic acid **10h** was also formed readily but it is highly soluble in water and DMSO, and therefore the isolation could only be carried out with a substantial loss of the product (entry 8).

### 3.2 Characterization of allylboroxine

The formation of boroxines from organoboronic acids is well known.$^{71}$ For example, arylboronic acids easily form arylboroxines under drying. However, in case of arylboronic acids the corresponding boroxines are usually air-stable.$^{71a}$ Allylboric acids also form boroxines under dry conditions (Scheme 28) but unlike aryl boroxines, allylboroxines are extremely air-sensitive and can easily be oxidized. We found that isolated allylboric acids (such as **10a**) decompose rapidly under air in solvent-free conditions.
Boroxines can be observed by $^1$H NMR spectroscopy in dry solvent. The $^1$H NMR spectrum of cinnamylboronic acid (10a) along with the corresponding boroxine in dry DMSO is shown in Figure 4. A doublet peak at 1.58 ppm corresponds the methylene protons (B-CH$_2$) of the boroxine of 10a. The ratio of the boroxine and the water (at 3.34 ppm) is same (1:1), since three molecules of water release during the condensation (Scheme 28). When a trace of water was added, the doublet peak (1.58 ppm) disappeared (Figure 5). This shows that formation of boroxine (under oxygen free conditions) is an equilibrium process.

\[ R\text{-C}_6\text{H}_4\text{CH}==\text{CH}_2 + \text{H}_2\text{O} \rightarrow R\text{-C}_6\text{H}_4\text{CH}==\text{CH}_2\text{B}==\text{O} + 3\text{H}_2\text{O} \]

\( \text{Boronic acid anhydride (Boroxine)} \)

Figure 4. Boroxine formation from compound 10a was identified by $^1$H NMR in dry DMSO-$d_6$. 

Scheme 28. Allylboronic acids form boroxine under drying condition.
Allylboronic acids were stored and handled in a glove box. Cinnamyl boronic acid 10a could be kept without notable decomposition in a glove box for a couple weeks at room temperature. The boroxine formation does not affect the thermal stability of the allylboronic acids. For example, heating of 10c (Table 3) in dry THF under Ar at 70 °C for 18 h did not lead to boretropic rearrangement.

3.3 Proposed mechanism for the allylic C–OH borylation

Based on the above and previous results of the Szabó group\textsuperscript{15a, 15d, 72} on the palladium catalyzed borylation and silylation of allylic alcohols, a plausible catalytic cycle is presented in Figure 6. Recent mechanistic studies of the Szabó group\textsuperscript{16} have shown that in the analogous silylation reaction with hexamethyldisilane (SiMe\textsubscript{3})\textsubscript{2}, the initial step of the reaction involves reduction of Pd(II) pro-catalyst to Pd(0). We suggest that the same happens in the presented borylation reaction as well. Complex 5h is reduced by 9a to Pd(0) catalyst 5j. Subsequently, 5j undergoes oxidative addition with the protonated allylic alcohol (8a') to give allyl-Pd complex 5k. Recent in depth mechanistic studies\textsuperscript{16} showed that coordination of Lewis acids to the OH group facilitates the C-O bond cleavage. Probably Brønsted acids (such as HCl, \textit{p}-toluene sulfonic acid etc.) have the same effect. Allyl-Pd complexes, such as 5k is known to undergo transmetallation with B\textsubscript{2}pin\textsubscript{2} \textsuperscript{16}. Therefore, we suggest that 5k undergoes transmetallation with 9a to form 5l and subsequent
reductive elimination from 5l gives allylboronic acid 10a and regenerate the catalyst 5j.

![Proposed catalytic cycle for Pd-catalyzed allylic C-OH borylation](image)

**Figure 6.** Proposed catalytic cycle for Pd-catalyzed allylic C-OH borylation.

### 3.4 Conclusions for the allylic C–OH borylation

Allylboronic acids can be prepared by Pd-catalyzed allylic substitution of allylic alcohols using diboronic acid as the boron source. The resulting allylboronic acids can form boroxines, which are very oxygen sensitive. Therefore the isolation of allylboronic acids was carried out under strictly oxygen free conditions. The method for purification and isolation is precipitation by water/brine under Ar atmosphere. The allylboronic acids can be stored and handled in a glove box.
4. Allylboration of carbonyl compounds using allylboronic acids (Paper II-III)

Stereoselective synthesis of organic molecules with contiguous stereocenters is of greatest interest in organic synthesis. As mentioned in Section 1.3, allylboration of carbonyl compounds is particularly suitable method to achieve this goal.

4.1 Allylation of ketones by allylboronic acids

The uncatalyzed reactions of allylboronates, such as allyl-Bpin derivatives, with carbonyl compounds mostly involve aldehydes as substrates. However, allylboronic esters, like allyl-Bpin, are usually unreactive towards ketones. Hoffman and co-workers\textsuperscript{73} demonstrated that very harsh conditions are required for allylboration of acetophenone. In addition, under these harsh conditions (8 Kbar pressure) the allylation is practically unselective and can afford four diastereomeric alcohols (Scheme 29). In all selective allylboration reactions Lewis-acid or other catalysts were used to activate the allylboronic esters toward reactions with ketones.\textsuperscript{36b, 44a, 45}

![Scheme 29. Addition of allylboronate to acetophenone, reported by Hoffmann and co-workers.\textsuperscript{73}]

We have found that allylboronic acids (10) readily react with various ketones (11) in the absence of any additives affording homoallylic alcohols (Scheme 30). The reactions can be performed under mild conditions at room temperature in dry solvents (typically THF) under Ar (Table 4). Addition of cinnamylboronic acid (10a) to acetophenone (11a) in THF occurred smoothly at room temperature. The reaction was accomplished within 24 h and afforded a single diastereoisomer of homoallylic alcohol 12a. The addition of compound 10a to the ketone 11b was very slow at room temperature and required elevated temperature 60 °C (entry 2). This is probably because of steric bulkiness in the compound 11b. However the diastereoselectivity of
the allylation of \textbf{11b} was very high and the compound \textbf{12b} was isolated as a single diastereoisomer. A very fast reaction was observed, when acyl cyanide \textbf{11c} was treated with boronic acid \textbf{10a} (entry 3). As far as we know, only one literature example\textsuperscript{74} is reported for the preparation of a homoallyl cyanohydrin. However, synthesis of stereodefined quaternary cyanohydrins (\textbf{12c}) by allylation of acyl cyanides was not reported before.

\textbf{Scheme 30}. General scheme for the allylation of ketones using allylboronic acids.
Table 4. Allylation of carbonyl compounds with allylboronic acids.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acid</th>
<th>Ketone</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>11a</td>
<td>THF</td>
<td>24</td>
<td>12a</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>10a</td>
<td>11b</td>
<td>THF</td>
<td>22</td>
<td>12b</td>
<td>90\textsuperscript{c}</td>
</tr>
<tr>
<td>3</td>
<td>10a</td>
<td>11c</td>
<td>THF</td>
<td>1</td>
<td>12c</td>
<td>72\textsuperscript{d, e}</td>
</tr>
<tr>
<td>4</td>
<td>10d</td>
<td>11d</td>
<td>THF</td>
<td>3</td>
<td>12d</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>10a</td>
<td>11e</td>
<td>THF</td>
<td>3</td>
<td>12e</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>10a</td>
<td>11f</td>
<td>THF</td>
<td>3</td>
<td>12f</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>10a</td>
<td>11g</td>
<td>THF</td>
<td>18</td>
<td>12g</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>10f</td>
<td>11h</td>
<td>CHCl\textsubscript{3}</td>
<td>18</td>
<td>12h</td>
<td>94\textsuperscript{f}</td>
</tr>
<tr>
<td>9</td>
<td>10g</td>
<td>11h</td>
<td>CHCl\textsubscript{3}</td>
<td>18</td>
<td>12i</td>
<td>76\textsuperscript{f}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Compound 10 (0.24-0.39 mmol) and 11 (0.2-0.3 mmol) were stirred in given solvent (0.6 mL) at rt. \textsuperscript{b} Isolated yield, unless indicated the products are single diastereomer. dr was determined from the \textsuperscript{1}H NMR spectrum of crude reaction mixture. \textsuperscript{c} Reaction at 60 °C. \textsuperscript{d} The reaction is performed at -78 °C to rt. \textsuperscript{e} dr = 90:10 \textsuperscript{f} dr = 98:2

Alkynyl ketone (ynone) 11d was reacted with 10d to give stereodefined 1,5-ynene 12d (entry 4). To the best of our knowledge, the presented reaction (entry 4) is the first example for one step synthesis of diastereoselective 1,5-ynenes with adjacent quaternary and tertiary stereocenters.\textsuperscript{20a} Derivatives of 1,5-ynenes are important substrates for the preparation of four membered
rings by ring closing metathesis.\textsuperscript{75} We have also found that α-halo ketone 11e reacts with 10a with excellent regio- and stereoselectivity (entry 5). The reaction proceeded with a clean \textit{anti} stereoselectivity and the stereochemistry of the compound 12e was confirmed by X-ray diffraction method (Figure 7). Knochel and co-workers\textsuperscript{76} have reported the allylation of α-bromo ketones with cinnamyl zinc derivatives. However, they proposed that under the basic conditions of this reaction, the bromohydrin products underwent spontaneous cyclization to give epoxides, even at low temperature (Scheme 31).

\textbf{Scheme 31}. Addition of allylzinc to α-bromo ketone reported by Knochel and co-workers.

In contrary, our method provides α-halo hydrin 12e (entry 5), as a single diastereomer. Ethyl pyruvate 11f could also be allylated in very high selectivity (entry 6). As expected, the keto group could be selectively functionalized in the presence of the ester group. The product 12f was obtained as a single diastereoisomer. Pyruvic ester analogue 11g also reacted with 10a, affording single diastereoisomer 12g. Interesting results were observed when geranyl 10f and neryl 10g boronic acids were reacted with acetophenone derivative 11h (entries 8-9). Compound 10f and 10g were added to ketone 11h at room temperature to give the epimeric products 12h and 12i, respectively. In products 12h-i two adjacent quaternary stereocenters were formed. Construction of contiguous quaternary stereocenters is one of the most challenging tasks in synthetic organic chemistry.\textsuperscript{77}

\textbf{Figure 7}. X-ray structure for the compound 12e.

Surprisingly, phenylglyoxylic acid 11i (Table 5) which is structurally very close to 11g, reacted with 10a and afforded poor stereoselectivity (dr 1:1) under our standard conditions in THF. After optimization, we found that the allylation reaction of 11i is highly selective and very fast in MeOH (instead of THF). This was a surprising finding as the allylation reactions with
other ketones, in particularly with acetophenone and its derivatives were strongly retarded or inhibited in the presence of protic solvents, such as MeOH or water. Due to this fact, we could not use one-pot conditions for the generation of allylboronates for allylation of ketones. Since we found that α-keto acid (e.g., 11i) reacts with allylboronic acid in MeOH, we could develop a sequential one pot method including borylation of allylic alcohols followed by allylation of 11i-j (Table 5). By applying this one pot procedure for allylation, the isolation step of allylboronic acids can be avoided. The optimized one pot procedure allowed us to synthesize homoallylic α-hydroxy acids (12j-n) from α-keto acids (11i-j).

Table 5. Allylboration of α-keto acids with allylboronic acids.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Conditions (First step)</th>
<th>Keto acid</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(\equiv\text{C}\equiv\text{C}\equiv\text{OH}) 8a</td>
<td>5h (1 mol %) MeOH, 18 h</td>
<td>Ph(\equiv\text{C}\equiv\text{CO}_2\text{H}) 11i</td>
<td>12j</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>8a</td>
<td>5h (1 mol %) MeOH, 18 h</td>
<td>(\text{CO}_2\text{H}) 11j</td>
<td>12k</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Ph(\equiv\text{C}\equiv\text{C}\equiv\text{OH}) 8h</td>
<td>5i (5 mol %) DMSO/H(_2)O 3 h</td>
<td>11j</td>
<td>12l</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>8i</td>
<td>5i (5 mol %) DMSO/H(_2)O 1 h</td>
<td>11j</td>
<td>12m</td>
<td>77(^c)</td>
</tr>
<tr>
<td>5</td>
<td>Ph(\equiv\text{C}\equiv\text{C}\equiv\text{OH}) 8j</td>
<td>5h (5 mol %) MeOH/DMSO 0.5 h</td>
<td>11j</td>
<td>12n</td>
<td>66</td>
</tr>
</tbody>
</table>

\(^a\) Compounds (10a, 10h-j) were generated by addition of diboronic acid 9a (0.36 mmol) to allyl alcohols 8 (0.30 mmol) in the presence of Pd-catalyst 5h-i followed by addition of 11i-j (0.24 mmol).
\(^b\) Isolated yield. \(^c\) dr = 98:2

In situ generated boronic acid 10i reacted with pyruvic acid (11j) to afford 12m with excellent diastereoselectivity (dr 98:2) (entry 4). The structure
of the compound 12m was confirmed by X-ray diffraction. The allylboronic acid formed from 8j is unstable and thus can not be isolated.

However, in situ generation of the allylboronic acid followed by the reaction with 11j gives the homoallylic alcohol 12n with excellent selectivity (entry 5).

4.2 Stereoselectivity of α-hydroxy acids

Ethyl pyruvate 11f (Table 4, entry 6) and pyruvic acid 11j (Table 5, entry 2) gave epimeric products 12f and 12k, respectively (Scheme 32). This is surprising as the two substrates 11f and 11j differ only by an ethyl group.

![Scheme 32](image)

**Scheme 32.** Different selectivity for the allylboration of pyruvic acid and its ester derivative.

We rationalized the different stereochemistries on the basis of different steric and electronic interactions in the TS of the allylation (Figure 8). The reaction with ester 11f proceeds via the expected Zimmerman-Traxler TS (TS1), in which the bulky COOEt group is equatorial and the small Me group is axial affording selectively the *anti* compound 12f. However, in TS2 the carboxyl group and the keto group form a chelate with the boron atom. The chelating geometry requires an axial COOH group and an equatorial Me substituent. Therefore, the stereochemical outcome of the reaction would be different and selectively forms the *syn* compound 12k.

![Figure 8](image)

**Figure 8.** Proposed bicyclic transition state (TS2) for syn selectivity for α-hydroxy acids (12j-n).

A similar chelation based *syn* selective allylation was reported by Kabalka for allyl-Bpin with pyruvic acid 11j. However, in that reaction Et$_3$N had
to be used for the allylation, presumably for the deprotonation of pyruvic acid.

**4.3 Conclusions for allylboration of carbonyl compounds**

Allylboronic acids react with ketones without any additives to give homoallylic alcohols. These reactions can be conducted under mild conditions, typically at room temperature in dry aprotic solvents. The reactions proceed with a high level of chemo-, regio- and diastereoselectivity. In a typical reaction, the homoallylic alcohol is formed selectively with *anti* stereoselectivity. Pyruvic acid and other α-keto acids react in MeOH with *syn* stereoselectivity. The synthesis of allylboronic acids and the allylation of α-keto acids can be performed in a sequential one-pot reaction. Since pyruvic acid reacts with *syn* stereoselectivity, while ethyl pyruvate reacts with *anti* stereoselectivity, a high level of stereocontrol can be achieved for these types of ketones.
5. Synthesis of adjacent quaternary stereocenters by catalytic asymmetric allylboration of ketones (Paper IV)

Enantioselective synthesis of acyclic molecules with quaternary stereocenters is still a challenging task in organic synthesis.\(^7^9\) Of course, selective formation of adjacent quaternary stereocenters is even more difficult. Because of the bulky (non-hydrogen) substituents, the steric repulsion between the quaternary carbons results in a weak C-C σ-bond.\(^8^0\) Such a σ-bond is difficult to form and easy to cleave. Relatively few methods are available for the asymmetric single step creation of adjacent quaternary stereocenters.\(^2^5^b\)

As mentioned in the introduction (Section 1.3.2), allyl boron reagents have proven to be very useful for the creation of quaternary stereocenters. In addition, in Chapter 4 we have shown that the allylation of ketones with allylboronic acids is highly diastereoselective. This gave the idea to develop a new method for asymmetric allylboration of ketones using γ-disubstituted allylboronic acids (such as 10f and 10g).

5.1 Method development for the asymmetric allylboration of ketones

We started to examine the BINOL based catalysts for our reactions since these compounds have been found very efficient for allylboration methods using allylboronates (see also Section 1.3.2).\(^4^3-4^4,4^6\) We screened various chiral BINOL derivatives (Figure 9). It was found that compounds 4a-b and 4f were the most efficient for the asymmetric allylboration (Table 6).

![Figure 9. Chiral BINOL derivatives.](image-url)
We have found that the allylboration between 10f and ketone 11h in the presence of 4a and 1BuOH took place with high enantioselectivity (er 97:3) and diastereoselectivity (dr >98:2). When the enantiomer of 4a, bromo-BINOL 4f was used (entry 2), the opposite enantiomer of 13a was formed in high selectivity (er 93:7). When these optimal conditions were changed, the enantioselectivity as well as in some cases the yield was depleted.

Table 6. Asymmetric allylation conditions using chiral BINOL derivatives.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>er</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>without change</td>
<td>97:3</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>using ligand 4f instead of 4a</td>
<td>93:7(^c)</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>without 1BuOH</td>
<td>86:14</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>without MS</td>
<td>85:15</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>without alcohol and MS</td>
<td>90:10</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>using 4b instead of 4a</td>
<td>95:5</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>using 4c instead of 4a</td>
<td>67:33</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>using 4e instead of 4a</td>
<td>81:19</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>using 4d instead of 4a</td>
<td>54:46</td>
<td>34</td>
</tr>
<tr>
<td>10</td>
<td>without 4a</td>
<td>50:50</td>
<td>34</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise specified 10f (0.10 mmol) was added to a mixture of 11h (0.12 mmol), 4a (0.02 mmol) and 1BuOH (0.30 mmol) and stirred at 0 °C for 24 h. \(^b\) Isolated yield. \(^c\) Opposite enantiomer of 13a

1BuOH was found to be a crucial additive to achieve a high enantiomeric ratio under the above reaction conditions. Replacing the 1BuOH by other tertiary alcohols (e.g. 1AmOH, 1-Adamantanol) leads a decrease of the selectivity. Interestingly, the reaction did not proceed at all in the presence of primary or secondary alcohols such as MeOH or 1PrOH. In the absence of tertiary alcohol (entry 3) or molecular sieves (entry 4) the selectivity dropped. When both 1BuOH and the molecular sieves were excluded (entry 5), the selectivity was somewhat higher (er 90:10) than in the presence of these additives. \(\text{L-}^2\text{BINOL 4b}\) was almost as efficient catalyst as its bromo analogue 4a (c.f. entries 6 and 1). The parent BINOL 4d (entry 9) gave very poor selectivity (er 54:46) indicating the importance of the substituent in BINOL for the enantioselectivity of the reaction. BINOL derivative 4e with the SMe substituent was more efficient than BINOL 4c (c.f. entries 7 and 8).
5.2 Stereocontrol in the asymmetric allylboration of ketone

We also examined the generality of the above asymmetric process by synthesizing all four possible enantiomers of isomeric homoallylic alcohols 13a-d (Table 7). Gratifyingly, applying the above optimal reaction conditions, we were able to synthesize all four stereoisomers with high enantioselectivity. As mentioned above (Table 6, entries 1-2) compound 10f reacted with 11h in the presence of BINOL derivatives 4a and 4f affording the enantiomeric pair 13a and 13b respectively (Table 7, entries 1-2). When the allylation of 11h was conducted with nerylboronic acid 10g in the presence of 4b, compound 13c (epimer of 13a) was formed (entry 3) with high enantioselectivity.

Table 7. Synthesis of four possible stereoisomers of 13a.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acid</th>
<th>Ketone</th>
<th>Catalyst</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10f</td>
<td>11h</td>
<td>4a(^c)</td>
<td><img src="img1" alt="Product 13a" /></td>
<td>75 er 97.3</td>
</tr>
<tr>
<td>2</td>
<td>10f</td>
<td>11h</td>
<td>4f</td>
<td><img src="img2" alt="Product 13b" /></td>
<td>89 er 95.5</td>
</tr>
<tr>
<td>3(^d)</td>
<td>10g</td>
<td>11h</td>
<td>4b</td>
<td><img src="img3" alt="Product 13c" /></td>
<td>80 er 97.3</td>
</tr>
<tr>
<td>4</td>
<td>10g</td>
<td>11h</td>
<td>4f</td>
<td><img src="img4" alt="Product 13d" /></td>
<td>83 er 96.4</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise specified 10f-g (0.10 mmol) was added to a mixture of 11h (0.12 mmol), 4b/4f (0.03 mmol) and \(^3\)BuOH (0.30 mmol) and stirred at 0 °C for 24 h. \(^b\) Isolated yield. \(^c\) 0.02 mmol of 4a was used. \(^d\) Reaction at rt.

Finally, we reacted nerylboronic acid 10g and the ketone 11h in the presence of 4f (entry 4) affording 13d (epimer of 13b) with a high selectivity. Accordingly, using allylboronic acids 10f-g and enantiomeric BINOL derivatives 4a-b and 4f, a full control of the stereoselectivity can be achieved in the asymmetric allylboration reaction of ketone 11h.
5.3 Catalytic enantioselective allylboration of ketones

After studying the reactivity of allylboronic acids under various conditions we decided to explore the scope of the reaction. Using the above described method we successfully synthesized several enantioenriched homoolylic alcohols (Table 8). We found that changing the position of the bromo substituent (11k) on the aromatic ring (entry 1) did not change the enantioselectivity. The reaction (entry 2) with methyl sulfonyl substituent in the ketone component (11l) proceeded with very high enantioselectivity (er 97:3). In addition the reaction was scaled up to five times and the selectivity of the reaction did not drop. The absolute configuration of 13f was determined by X-ray diffraction (Figure 10). When we increased the size of the ketone (entry 3) applying naphthyl derivative 11m, the enantioselectivity was slightly decreased (er 96:4). Heterocyclic ketone 11n was also subjected for allylation (entry 4) affording 13h with high enantioselectivity and yield. Not only aromatic ketones but aliphatic ketone 11o can also be employed in the selective allylboration (entry 5-6). For example cyclopropyl ketone 11o gave 13i with a er of 95:5 (entry 5). Using the R-Br₂-BINOL derivative (4f) as catalyst, homoallylic alcohol 13j was formed selectively, which is the other enantiomer of 13i.
Table 8. Asymmetric allylation of ketones with γ-disubstituted allylboronic acids.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic Acid</th>
<th>Ketone</th>
<th>Catalyst</th>
<th>Product</th>
<th>Yield(%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10f</td>
<td>11k</td>
<td>4a</td>
<td>13e</td>
<td>89 er 97:3</td>
</tr>
<tr>
<td>2</td>
<td>10f</td>
<td>11l</td>
<td>4a</td>
<td>13f</td>
<td>60/72(^d) er 97:3</td>
</tr>
<tr>
<td>3</td>
<td>10f</td>
<td>11m</td>
<td>4a</td>
<td>13g</td>
<td>65 er 96:4</td>
</tr>
<tr>
<td>4</td>
<td>10f</td>
<td>11n</td>
<td>4a</td>
<td>13h</td>
<td>81 er 95:5</td>
</tr>
<tr>
<td>5</td>
<td>10f</td>
<td>11o</td>
<td>4a</td>
<td>13i</td>
<td>62 er 95:5</td>
</tr>
<tr>
<td>6</td>
<td>10f</td>
<td>11i</td>
<td>4f</td>
<td>13j</td>
<td>54 er 95:5</td>
</tr>
<tr>
<td>7</td>
<td>10g</td>
<td>11p</td>
<td>4b</td>
<td>13k</td>
<td>76 er 95:5</td>
</tr>
<tr>
<td>8</td>
<td>10g</td>
<td>11q</td>
<td>4b</td>
<td>13l</td>
<td>81 er 96:4</td>
</tr>
<tr>
<td>9</td>
<td>10k</td>
<td>11l</td>
<td>4a</td>
<td>13m</td>
<td>69 er 95:5</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise stated, 11k-q (0.12 mmol), 10f-g/10k (0.1 mmol), catalyst 4a-b/4f (0.02 mmol), iBuOH (0.3 mmol) and MS (3 Å) were stirred at 0 °C for 24 h. \(^b\) Isolated yield affording dr >98:2. \(^c\) The reaction was performed at rt. \(^d\) Yield for 0.5 mmol scale reaction.

Switching from geraniol boronic acid (10f) to nerylboronic acid (10g) the diastereomeric alcohol derivatives 13k and 13l can be synthesized (entries 7-8). In these reactions the process is faster and more selective when the iodo-BINOL derivative 4b is used instead of the bromo-derivative 4a. Not only geranylboronic acid (10f) and nerylboronic acid 10g but also prenylboronic acid 10k could be used for allylation. The high enantioselectivity (er 95:5)
was also preserved in the prenylation reaction (entry 9). The homoprenyl alcohol 13m can easily be synthesized from the reaction between 11l and 10k. Absolute configuration of compound 13m was determined by X-ray diffraction.

Figure 10. Chem3D diagram of compound 13f from the X-ray diffraction data.

5.4 Proposed mechanism for the enantioselectivity of the allylboration of ketones with allylboronic acids

We conducted experimental studies for exploration of the mechanism of the enantioselectivity. We hypothesized that the boronic acid (such as 10f) may form the esterified species with the BINOL (4) before addition to the ketones. In order to get information on the nature of the interactions between the allylboronic acids and the chiral BINOL ligand, we monitored the mixture of 10f and F₂-BINOL 4c (Scheme 33) by \(^{19}\text{F} \text{NMR}.

Scheme 33. Reaction between geraniol boronic acid 10f and BINOL derivative 4c.

The \(^{19}\text{F} \text{NMR} \) of this reaction mixture (Figure 11b) showed two peaks, which are shifted downfield with respect to the \(^{19}\text{F} \text{NMR} \) shift of the free F₂-BINOL 4c (Figure 11a). These changes of the \(^{19}\text{F} \text{NMR} \) shifts suggest that by mixing of 10f and 4c at least two new species are formed. The first one resonating at -134.1 ppm is probably an associative complex (10f...4c) between 10f and 4c, which is kept together by electrostatic forces and/or
hydrogen bonds. The second peak at -130.7 ppm was tentatively assigned to 10l (Scheme 33), which is most likely the diester of 10f and 4c. When molecular sieves (MS) 3Å were added to this mixture, the intensity of 10l was considerably increased and the intensity of 10f...4c was decreased (Figure 11c).

![Figure 11a-e. 19F NMR spectra for the mixture of 4c and 10f under different conditions.](image)

When 'PrOH was added to the mixture of 10f, 4c (in the presence of MS), the signal for 10l was disappeared and the concentration of 10f...4c was increased (Figure 11d). As mentioned in Section 5.1, 'PrOH inhibits the allylboration reaction, probably because formation of the diester of the allylboronic acid and the BINOL derivatives (such as 10l) was inhibited.

Interestingly, when 'BuOH was added to the mixture of 10f, 4c and MS, the concentration of 10l was decreased but it was still preserved in the reaction mixture. This is in line with our observation that addition of 'BuOH did not inhibit the reaction, as the active species, such as 10l, is still available for allylboration.

Pellegrinet and co-workers81 have demonstrated that boronic acid diesters of BINOL are more reactive than the corresponding monoesters. Considering the high reactivity of BINOL diesters in allylboration and the expected easy esterification of allylboronic acids and their anhydrides (see above), it is reasonable to assume that BINOL diesters of allylboronic acids (such as 10l) are the active reaction intermediates in the above processes.
5.4.1 Proposed models for enantioselectivity

Based on the above mechanistic studies and on the absolute configuration of the products (13a-m), we provide a plausible mechanism in Figures 12-13 for the enantioselectivity of the above asymmetric reaction. We suggest that in the initial stage of the reaction, the BINOL derivative (4a-b or 4f) and boronic acid (10f-g/10k) form the BINOL-boronate (Figures 12-13). The allylboration is supposed to proceed via a Zimmerman-Traxler TSs 14a-d. The facial selectivity for a certain BINOL derivative is probably determined by the steric effect of the bromo substituent of the BINOL and the methyl group of the ketone. For example, in case of Si-face, Si-face arrangement in TS 14a (ketone in the front side, allylboronate in back side) there is no steric congestion between the bromine atom and the methyl group of the ketone. This TS provides the major enantiomer, such as 13a. In TS 14b (Figure 12) when it is Re-face, Re-face arrangement (i.e. the boronate is approaching at the front side and the ketone is in the background) the steric repulsion between the bromine atom and the methyl group of the ketone may raise a high activation barrier. Since this TS is disfavored, formation of 13b is suppressed.

![Figure 12. Propose models for the enantioselectivity using the S-BINOL 4a.](image)

When the configuration of the BINOL is switched from S (such as 4a) to R (such as 4f) the formation of 13b is favored via TS 14c, which is in Re-face Re-face arrangement (Figure 13). On the other hand formation of 13a is disfavored via TS 14d (Figure 13) since there is a steric clash between the bromine atom and the methyl group of the ketone in Si-face, Si-face arrangement.
Propose models for the enantioselectivity considering the $R$-BINOL 4f.

Similar type of transition states were also proposed by Chong and co-workers for the asymmetric allylation of ketones using BINOL based allylboronates.

5.4.2 Proposed catalytic cycle

Based on the above TS model (Figures 12-13) we propose a catalytic cycle shown in Figure 14, which is exemplified with boronic acid 10f, ketone 11h and BINOL derivative 4a.

Figure 14. Proposed catalytic cycle for the asymmetric allylation of ketones.
As mentioned above, we hypothesized that the reaction between allylboronic acid 10f and BINOL derivative 4a leads to formation allylboronic acid ester 10m. This esterification process generates water, which can be adsorbed by the MS under the reaction conditions. The active boronate species 10m then undergoes allylation with ketone 11h to give 10n. The enantioselectivity is supposed to be determined in this addition step according to the above proposed model (Figures 12-13). Catalyst 4a is captured in boric acid ester 10n. For regeneration of catalyst 4a, this ester has to be hydrolyzed. This hydrolysis may take place using water formed in the 4a→10m step. On the other hand, the solvolysis of 10n may also occur by tBuOH. If the free 4a is not available, the non-asymmetric (self-catalyzed) allylboration would take over, thus decreasing the enantioselectivity of the process.

5.5 Conclusions for the catalytic asymmetric allylboration

We have developed a catalytic enantioselective method to create adjacent quaternary stereocenters in acyclic molecules from γ-disubstituted allylboronic acids and ketones in the presence of BINOL derivatives. The reactions proceeded under mild conditions affording enantioenriched homoallylic alcohols. A full control of the diastereo- and enantioselectivity can be achieved in this process. The process could be extended to various allylboronic acids and ketones. The mechanism of the enantioselectivity could be rationalized on the basis of the Zimmer-Traxler model.
6. Allylboration of imines, indoles and hydrazones (Paper V-VI)

Allylation of imines leads to stereodefined homoallylic amines, which are synthetic intermediates, for instance in the total synthesis of alkaloids. The allylation of imines is usually considered to be more difficult than aldehydes or ketones because of the low electrophilicity of the carbon atom in the imine (C=N) compared to the carbonyl group (C=O). In addition, the imine/enamine tautomerization and E/Z isomerization of imines may complicate the outcome and the selectivity of the reaction. As mentioned in Section 1.3.3 many methods have been developed for the allylboration of imines based on catalysis. However, relatively few examples are reported in the literature for a successful reaction of allylboronic esters (such as allyl-Bpin) and imines under external catalyst free conditions.

A diastereoselective direct allylation of oximes with crotylboronates was reported by Hoffmann and co-workers (Scheme 34). Despite the harsh reaction conditions (9 Kbar pressure), the stereoselectivity of this process is high.

![Scheme 34. Direct allylboration of oxime derivatives reported by Hoffmann and co-workers](image)

Considering the selective direct allylation of ketones with allylboronic acids (Section 4.1), we decided to extend the synthetic scope of the reactions to imines.

6.1 Allylation of imines with allylboronic acids

We have found that allylboronic acids (10) readily react with imines (15) typically at room temperature, in dry DCM or CDCl₃, without any additives (Scheme 35). To ensure the dry conditions, molecular sieves (4Å) were add-
ed to the reaction mixture. In the absence of molecular sieves (MS), the imine substrates were hydrolyzed to aldehydes. Then, the aldehyde reacts with allylboronic acid to form homoallylic alcohol instead of the desired homoallylic amine product. Interestingly, the rate of hydrolysis of imines (such as 15a) was higher in the presence of allylboronic acids 10 (and absence of molecular sieves) than in pure form (i.e. without 10).

Scheme 35. Allylation of imines with allylboronic acid.

The allylboration of imines proceeds with very high regio- and stereoselectivity in most cases giving a single diastereomer as the final product (Table 9). Cinnamyl boronic acid (10a) reacted readily at room temperature with aryl and heteroaryl imines 15a-c to give homoallylic amines 16a-c as single diastereomers (entries 1-3). The relative configuration of the compound 16a was assigned on the basis of X-ray crystal structure (Figure 15).
Table 9. Direct alkylation of imines by allylboronic acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic Acid</th>
<th>Imine</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-</td>
<td>15a</td>
<td>1</td>
<td>16a</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>10a</td>
<td>15b</td>
<td>1</td>
<td>16b</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>10a</td>
<td>15c</td>
<td>3</td>
<td>16c</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>Bu-</td>
<td>15b</td>
<td>1</td>
<td>16d</td>
<td>80c</td>
</tr>
<tr>
<td>5</td>
<td>10f</td>
<td>15b</td>
<td>1</td>
<td>16e</td>
<td>66e-d</td>
</tr>
<tr>
<td>6</td>
<td>10a</td>
<td>15d</td>
<td>1</td>
<td>16f</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>10a</td>
<td>15e</td>
<td>24</td>
<td>16g</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>10a</td>
<td>15f</td>
<td>3</td>
<td>16h</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>10a</td>
<td>15g</td>
<td>1</td>
<td>16i</td>
<td>71o</td>
</tr>
</tbody>
</table>

*a* Unless otherwise specified 10 (0.28 mmol) and MS (4 Å) were stirred in DCM (0.6 mL) then 15 (0.20 mmol) was added. The mixture was stirred at rt for indicated times and isolated as single diastereomer. *b* Isolated yield. *c* dr >95:5. *d* Boronic acid solution in CDCl₃ (0.3 M) was used.

Addition of octenylboronic acid (10d) to imine 15b was also proceeded with high stereoselectivity (dr 95:5) to give 16d (entry 4). The reaction of geranylboronic acid 10f with imine 15b was surprisingly fast and resulted in 16e (entry 5) bearing adjacent quaternary and tertiary stereocenters with a
diastereomeric ratio of 95:5. It is interesting to note that compound 10f has been used by Li and co-workers\textsuperscript{85} for the synthesis of a homoallylamine-type key intermediate in the total synthesis of hapalindole-Q.

When compound 10a was added to the cyclic aldimine 15d (entry 6), an interesting feature was observed for the stereochemistry. This reaction yielded the corresponding imine 16f as single diastereoisomer. Surprisingly compound 16f has also an anti-geometry, which was confirmed by X-ray diffraction. The same, anti stereoselectivity for the allylation of both cyclic aldimine 15d (Z-geometry) and its acyclic counterpart 15a (E-geometry) was unexpected. The mechanistic aspects of the stereoselectivity of the allylation of imines are further discussed in Section 6.4.

Most of the ketimines, such as the methyl analogs of 15a, resisted to allylboration under the above reaction conditions. However, cyclic ketimine 15e reacted with excellent stereochemistry but much slower (in 24h) than the aldimines (entry 7). This indicates that allylboronic acids are able to react with ketimines as well but the reaction is sensitive to the steric factors. The reaction of 10a with imine 15e resulted in homoallylic pyrrolidine 16g with adjacent quaternary and tertiary stereocenters as single diastereomer (entry 7). Glyoxylate imine 15f also reacted readily with 10a opening a new synthetic route for stereoselective synthesis of \( \alpha \)-amino acid derivatives (entry 8). Compound 15g has both keto and aldimine functionalities (entry 9) but only the imine functionality was transformed, when 10a was added. The high chemoselectivity indicates that an aldimine reacts faster than a ketone with an allylboronic acid. Compound 16i might be useful to synthesis selective piperidine using ring closing metathesis (RCM).\textsuperscript{86}

### 6.2 Allylation of indoles with allylboronic acids

After the successful allylation reaction of imines with allylboronic acids, our interest turned towards indole compounds. Bubnov and co-workers re-
ported the allylboration of indoles by triallylborane. The reaction required harsh conditions but it proceeds with a high regio- and stereoselectivity. In addition, Batey and co-workers recently showed that indoles react with allyl-BF$_3$K derivatives in the presence of Lewis acid such as BF$_3$Et$_2$O.

We have found that allylboronic acids react readily with indoles without any additives under ambient conditions affording indolines. The reaction is highly regioselective for the C2 position of indoles as well as stereoselective (Table 10).

**Table 10: Regio- and stereoselective direct allylation of indoles.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic Acid</th>
<th>Indole</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-CH=B(OH)$_2$</td>
<td>17a</td>
<td>3</td>
<td>18a</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>10a</td>
<td></td>
<td>1</td>
<td>18b</td>
<td>96/97$^c$</td>
</tr>
<tr>
<td>3</td>
<td>Bu-CH=B(OH)$_2$</td>
<td>17a</td>
<td>3</td>
<td>18b</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$CH=B(OH)$_2$</td>
<td>17a</td>
<td>24</td>
<td>18c</td>
<td>74</td>
</tr>
<tr>
<td>5$^d$</td>
<td>10a</td>
<td>17c</td>
<td>12</td>
<td>18e</td>
<td>75</td>
</tr>
</tbody>
</table>

$^a$Unless otherwise stated, allylboronic acid 10 (0.15 mmol) was reacted with indoles 17a-c (0.1 mmol) at rt in DCM (0.4 mL).$^b$Isolated yield as single diastereomer. $^c$Reaction scale up to 0.5 mmol of indole.

Dichloromethane (DCM) proved to be the best solvent for the reactions. Polar protic solvent (e.g., MeOH) inhibits the reaction under our optimized conditions. Unlike imines, indoles react cleanly with allylboronic acids even in the absence of molecular sieves. The allylboration with 10a completed in a couple of hours using indoles 17a or 17b (entries 1 and 2) affording indolines 18a-b with high yield and high stereoselectivity. Aliphatic allylboronic acid 10d also reacted smoothly with 17a to afford single regio- and diastereomer 18c. Geranylboronic acid 10f reacted with 17a creating adjacent stereocenters (16d) including an all carbon quaternary stereocenter. This reaction is relatively slow probably because of the disubstitution at the
γ-position of 10f. Despite a methyl substituent at the 2-position 17c was also reacted (at 60 °C) with 10a affording 18e (entry 5).

6.3 Allylation of acyl hydrazones with allylboronic acids

N-Acylhydrazones have been widely used as stable imine equivalents to synthesize homoallylic amine derivatives. Kobayashi and co-workers\textsuperscript{89} reported that the allylation of acylhydrazones with allylsilanes proceeds with syn selectivity. Considering the above anti selective allylation of imines and indoles using allylboronic acids (Section 6.1 and 6.2), we sought to develop a syn selective allylation method for the synthesis of homoallylic amine compounds. Thus our attention turned towards allylboration of acylhydrazone compounds. In a previous study, Kobayashi and co-workers have shown that allylboronates (such as allyl-Bpin reagents) react with N-benzylohydrazones in the presence of indium catalyst.\textsuperscript{52} Considering the high reactivity of the allylboronic acids for the allylation of ketones and imines, we hypothesized that these species may react with hydrazones without external catalysts (such as indium) as well.

Indeed, we found that boronic acids (10) react with N-benzylohydrazone (19) under external catalyst free conditions with high regio- and stereoselectivity (Table 11). DMSO was found to be the best solvent for the reaction. Conducting the reaction in THF, MeOH or DCM at the same temperature as in DMSO resulted in either low yield or no reaction. The addition of cinnamyl boronic acid 10a to the hydrazone 19a proceeded very smoothly at room temperature affording single diastereomer 20a. The relative stereochemistry of the compound 20a was determined by X-ray diffraction. The X-ray structure of 20a clearly revealed that the allylation of hydrazones proceeds with a syn selectivity. Heteroaromatic hydrazone 19b also reacted with very high regio and stereoselectivity, giving only a single diastereomeric product (entry 2). The selectivity and reactivity with aliphatic allylboronic acid 10d was as high as with cinnamylboronic acid 10a, when aromatic hydrazone 19a was used (entry 3).
As mentioned in Section 6.1 the reaction of aliphatic imines with allylboronic acids (10) was problematic, as allylboronic acids catalyze the hydrolysis of aliphatic imines (Table 9). However alkyl hydrazones (such as 19c-e) are more stable to hydrolysis than the imine analogs. Thus isopropyl hydrazone 19c could easily be allylated with 10a, affording syn product 20d (entry 4). The stereochemistry of 20d was also determined by X-ray diffraction.

### Table 11. Stereoselective direct allylation of N-acylhydrazones.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acid</th>
<th>Hydrazone</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-CH=CHB(OH)₂ 10a</td>
<td>N⁻NHBz 19a</td>
<td>6</td>
<td>HN⁻NHBz 20a</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>10a</td>
<td>N⁻NHBz 19b</td>
<td>6</td>
<td>HN⁻NHBz 20b</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>Bu-CH=CHB(OH)₂ 10d</td>
<td>N⁻NHBz 19a</td>
<td>15</td>
<td>HN⁻NHBz 20c</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>10a</td>
<td>iPr⁻N⁻NHBz 19c</td>
<td>4</td>
<td>HN⁻NHBz 20d</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>10d</td>
<td>Ph⁻N⁻NHBz 19d</td>
<td>12</td>
<td>HN⁻NHBz 20e</td>
<td>79c</td>
</tr>
<tr>
<td>6</td>
<td>10a</td>
<td>N⁻NHBz 19e</td>
<td>10</td>
<td>HN⁻NHBz 20f</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>10f</td>
<td>N⁻NHBz 19a</td>
<td>15</td>
<td>HN⁻NHBz 20g</td>
<td>79e</td>
</tr>
<tr>
<td>8</td>
<td>10g</td>
<td>N⁻NHBz 19a</td>
<td>15</td>
<td>HN⁻NHBz 20h</td>
<td>84e</td>
</tr>
</tbody>
</table>

a Unless otherwise stated a mixture of 10 (0.20 mmol), 19 (0.30 mmol) and MS (4 Å) were stirred in DMSO (0.8 mL) at rt. b Isolated yield as single diastereomer. c dr = 4:1. d Reaction at 40 °C. e dr 97:3.

As mentioned in Section 6.1 the reaction of aliphatic imines with allylboronic acids (10) was problematic, as allylboronic acids catalyze the hydrolysis of aliphatic imines (Table 9). However alkyl hydrazones (such as 19c-e) are more stable to hydrolysis than the imine analogs. Thus isopropyl hydrazone 19c could easily be allylated with 10a, affording syn product 20d (entry 4). The stereochemistry of 20d was also determined by X-ray diffraction.
tion. Reaction of aliphatic allylboronic acids with aliphatic imine derivatives is particularly challenging. These reactions could also be easily performed (entry 5), but the stereoselectivity was dropped. While most of the other reactions afforded single diastereomer, the allylation of aliphatic boronic acid 10d with aliphatic hydrazone 19d afforded a mixture of diastereomers in a ratio of 4:1 (entry 5). Keto-hydrazones have a more limited synthetic scope than hydrazones derived from aldehydes. Yet, the hydrazone 19e was successfully allylated by 10a affording 20f.

As expected, the stereoselectivity of the above allylation is dependent on the geometry of the allylboronic acid. Therefore geranylboronic acid 10f reacted with excellent syn selectivity with 19a to give 20g. On the other hand, nerylboronic acid 10g (stereoisomer of 10f) reacted with 19a with a clean anti-selectivity, affording 20h. Both epimeric products 20g-h have two contiguous stereocenters including one all carbon quaternary stereocenter.

6.4 Mechanistic study and proposal for the allylation of aldimines

The most intriguing mechanistic aspect of the above allylboration of E and Z imines is the fast anti-selective allylation (Table 9). Since the stereochemistry is the same as for allylboration of aldehydes and ketones, we hypothesized that the reaction with imines also takes place according to the ZT model (Scheme 36) via a chair-type TS (see also Section 1.3). According to the ZT model (Scheme 36), syn-selectivity is expected for the reaction of an E-allylboronate and an E-imine. However, the above reactions (Table 9) using E-allylboronic acids with acyclic E-imines are anti-selective. In addition, the allylboration of Z-allylboronic acids and Z-imines (such as 15d, Table 9, entry 6) also proceeds with anti-selectivity. This suggests that acyclic E-imines undergo isomerization prior to the allylation process.

Scheme 36. Expected syn selectivity from E-imine following ZT model.

The thermal isomerization of aldimines has a high activation energy. For example, according to the $^1$H NMR spectrum of 15a, it exists as a stable E isomer in CDCl$_3$ even at elevated temperature (50 °C). Recently, Piers and co-workers have reported that boron-based Lewis acids, such as B(C$_6$F$_5$)$_3$.
are able to facilitate the isomerization of aldmines. Therefore, we hypothesized that allylboronic acids or allylboroxines may catalyze the E/Z isomerization of imines prior to the allylation. Since allylboronic acid 10a allylates E-aldimine (15a) rapidly, we studied the E/Z isomerization of 15a in the presence of aryl boroxine 21a (Scheme 37), which does not undergo C-C bond formation reaction with imines. Boroxine 21a was prepared from the corresponding allylboronic acid (4-fluorophenyl boronic acid). When E-imine 15a and boron compound 21a were mixed in CDCl₃ at room temperature (Scheme 37), a new species, 22a was formed. In 22a the methyl and the phenyl groups are in Z-configuration along the C=N bond, which was confirmed by NOE experiments.

Scheme 37. E/Z isomerization of 13a in the presence of aryl boroxine (Ar = 4-fluorophenyl). The significant ¹H NOEs are shown.

The Z relationship (syn geometry) of the N-methyl and phenyl groups in 22a satisfactorily explains the anti-selectivity of the allylboration via a chair TS in line with the ZT model. To further confirm this hypothesis DFT modeling studies were performed to rationalize the stereoselectivity of the allylation of imines. The results show (Figure 16) that the formation of imine-boroxine complex 22c from 15a’ (Z-imine) and allyl boroxine 21b is an exergonic process (by -4.1 kcal mol⁻¹). This assumes that facile E/Z isomerization of the imine takes place, as established above for 15a (Scheme 37). It is noteworthy that 22c, in which the N-methyl and phenyl groups are in Z-geometry, is more stable by 6.2 kcal mol⁻¹ than 22b, which has an E-geometry. Thus, the order of stability is opposite for the boroxine coordinated (22b vs. 22c) and for the free imines (15a vs. 15a’).

From 22c, the allylboration proceeds via chair TS 23a with a low activation barrier (14.9 kcal mol⁻¹) affording 24a with anti-selectivity. This is in agreement with the ZT model. The chair conformation of TS structure 23a and the TS geometry of allylboration of aldehydes 32b, 35, 92 are very similar, which is in line with the identical stereochemistry observed for the two processes. Allylation of the other imine-allyl boroxine complex (22b) or 15a, in which the N-methyl and phenyl are in E geometry, requires 5.4 kcal mol⁻¹ higher activation barriers to give the syn product 24b. The high barrier is apparently because of the axial position of the phenyl group in 23b, which is sterically unfavorable in line with the ZT model (Scheme 36). We have also calculated the activation barriers via boat TSs 84b. However, formation of the
anti product 24a via boat TS involves a much higher barrier than it’s chair TS 23a (by 7.80 kcal mol\(^{-1}\)), which is mainly because of unfavorable eclipsing strains and 1,4-diaxial strain in the boat form. These are well known by the analysis of the conformational energy surface of cyclohexane.\(^93\)

![Diagram of transition states and reaction profile]

**Figure 16.** Reaction profile for the allylboration of 15a in the presence of allylboroxine 21b. The \(\Delta G\) values are given in kcal mol\(^{-1}\).

### 6.5 Proposed mechanism for the allylboration of hydrazones

Although the allylation of imines with allylboronic acids is anti selective, the allylation of hydrazones is syn selective. Aldimine 15a and its analog compound benzoylhydrazone 19a reacted with allylboronic acid 10a under very similar conditions affording epimeric compounds 16a and 20a (Scheme 38).
As we have shown, imine 15a undergoes E to Z isomerization prior to the allylation, and it reacts with anti selectivity with 10a (Figure 16). The E to Z isomerization of 15a was even catalyzed by arylboronic acid derivatives. Conversely, our studies indicate that under similar reaction conditions 19a did not undergo E to Z isomerization.

Thus, 19a undergoes the addition to allylboronic acid (such as 10a) with an E-geometry. However, this would lead to unfavorable 1,3-diaxial repulsions involving the phenyl group of 19a in the Zimmerman-Traxler TS (27) of the reaction (Scheme 39). This thermodynamically unfavorable diaxial interaction can probably be compensated by chelation of the nitrogen and oxygen atoms of the hydrazone functional group to the B(OH)₂ group, such as in 25a. The chelation can be reinforced by water elimination to give 26. The water elimination requires the presence of a proton on one of the nitrogen atoms of 19a. When this hydrogen is replaced by a methyl group, the allylation reaction cannot be performed. The allylation via transition state 27 leads to syn selectivity affording the compound 20a. The syn selectivity in allylation of hydrazones using allylchlorosilanes was also explained by a similar chelation control.⁸⁹,⁹⁴
6.6 Proposed mechanism for the allylboration of indoles

As mentioned before (Section 6.2), the allylation of indoles by allylboronic acids proceeds with anti selectivity under additive free conditions. The anti selectivity was also observed for the allylation of ketones and imines with allylboronic acids and a Zimmerman-Traxler (ZT) model was used to describe the obtained selectivity. We also hypothesized that the anti selective allylation of indole proceeds via a ZT transition state (Scheme 40). The first step is supposed to be the coordination between the boronic acid 10a and the indole 17a to form an adduct 28a. As mentioned above Bubnov and co-workers reported allylation of indoles using triallylborane reagents. According to the mechanistic studies of these authors, a [1,3] proton shift was observed in indole prior to allylation. We also propose a similar proton shift in indole which leads to form 28b from 28a. In fact, 28b can be regarded as a complex of allylboronic acid and a cyclic imine. Subsequently, 28b may undergo allylboration via ZT TS 28b’ to give 18a. Accordingly, the same principles determine the stereochemistry of the allylation for indoles (Scheme 40) and imines (Figure 16). A similar mechanism was also proposed by Batey and co-workers for the allylation of indoles using potassium trifluoroborate salts and BF₃·Et₂O.

Scheme 40. Proposed mechanism for the allylation of indoles with allylboronic acid.
6.7 Conclusions for the allylboration of imines, indoles and hydrazones

Allylboronic acids readily react with imines, indoles and hydrazones under mild conditions. This transformation can be employed to synthesize a wide range of diastereoenriched homoallylic amines. The allylation proceeds with very high anti stereoselectivity for both E and Z imines and indoles. The experimental and theoretical studies show that boroxines catalyze the E to Z isomerization of acyclic aldimines prior to allylation. Unlike for imines, a syn selective allylation was observed for acylhydrazones. Our experiments showed that the E/Z isomerization does not occur for the hydrazones in the presence of boroxines. A chelation controlled bicyclic transition state was proposed to rationalize the syn selectivity of the allylboration of hydrazones.
7. Concluding remarks

We developed palladium-catalyzed selective allylic C–H and C–OH functionalization methods. These catalytic procedures allowed us to synthesize allylic trifluoroacetates and allylboronic acids with high regio- and stereoselectivity.

Palladium catalyzed C–H trifluoroacetoxylation can be carried out using PIFA as oxidant and trifluoroacetate source. The method is suitable for the synthesis of allylic trifluoroacetates from both cyclic and acyclic alkenes. The trifluoroacetoxylation of monosubstituted cyclic alkenes proceeds with high regio- and stereoselectivity. The reaction is suggested to proceed via a Pd(II)/Pd(IV) catalytic cycle.

A new process was developed for the synthesis and isolation of allylboronic acids. Allylboronic acids easily form boroxines, which are very oxygen sensitive species. Therefore, the purification and isolation of allylboronic acids have been done under inert conditions.

Allylboronic acids readily react with ketones and imines at room temperature without additives. The reaction proceeds with remarkably high stereoselectivity. The procedure is suitable for selective synthesis of homoallylic alcohols and amines with contiguous stereocenters. The reactions for imines proceed with anti stereoselectivity. We have found that allylboroxines catalyze the isomerization of acyclic imines prior to the allylation, which explains the observed stereoselectivity.

We have successfully developed a catalytic asymmetric allylboration process for ketones using allylboronic acids in the presence of BINOL derivatives. The method can be used for the synthesis of homoallylic alcohols with two adjacent quaternary carbon stereocenters. A high level of control of the enantioselectivity can be achieved by varying the allylboronic acid substrates and the BINOL catalyst.
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Denna avhandling fokuserar på två huvudområden inom organisk syntes, palladiumkatalyserad funktionalisering av alkener och allylalkoholer, samt utveckling av nya allylborerings-reaktioner.


En palladiumkatalyserad regio- och stereoselektiv syntes av allylborsyror från allylalkoholer har utvecklats. Diborsyra B_2(OH)_4 användes som borkälla i denna process.


10. Appendix A

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