New Reactions with Allyl- and Allenylboron Reagents

Transition-Metal-Catalyzed and Transition-Metal-Free Carbon-Carbon Bond Formation Processes

Dong Wang

Academic dissertation for the Degree of Doctor of Philosophy in Organic Chemistry at Stockholm University to be publicly defended on Friday 7 September 2018 at 10.00 in Magnélisalen, Kemiska övningslaboratoriet, Svante Arrhenius väg 16 B.

Abstract

Organoboron compounds have been widely used in carbon-carbon bond formation reactions in organic synthesis and catalysis. This thesis is focused on cross-coupling reactions of allyl-, allenylboronic acids and their ester derivatives via transition metal catalysis or transition-metal-free processes.

The first part of the thesis describes Cu-catalyzed $C(sp^3)$-$C(sp^3)$ formation reactions involving allylboronic acids and α-diazoketones. This coupling process shows high γ-regioselectivity, resulting in branched allylic products. When stereodefined cyclic allylboronic acids were employed as the substrate, the relative facial configuration was retained in the reaction product.

The second part involves Pd-catalyzed cross-coupling of allylboronic acid and α-diazoketones. The reaction proceeds with high α-regioselectivity, affording linear allylic products. Accordingly, the palladium- and copper-catalyzed cross-coupling of allylboronic acid and α-diazoketones occurs with opposite regioselectivity.

The third part concerns a new transition-metal-free carbon-carbon bond formation between allenylboronic acids and in situ generated diazo compounds. The diazo compounds are generated from tosylhydrazones in the presence of base. The reaction is suitable for synthesis of densely substituted conjugated dienes with high *Z*-selectivity.

In the final part, the allylation of quinones with allylboronates is presented. The reaction was performed without any catalyst or additive. Various quinones can be employed as substrates, including unsubstituted, monosubstituted benzoquinones and naphthoquinones.

Keywords: *carbon-carbon bond formation, cross-coupling, organoboron compound, allylboron reagent, allylation, transition metal, metal carbene, allenylboron reagent, transition metal free, diazo compound, tosylhydrazone, quinone.*

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To my parents

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List of publications

This thesis is based on the following publications, referred to in the text by their Roman numerals I-V. Reprints were made with the kind permission of the publisher (Appendix A).

I. **Copper-Catalyzed Cross-Coupling of Allylboronic Acids with α-Diazoketones**
Das, A.; Wang, D.; Belhomme, M.-C.; Szabó, K. J.
Org. Lett. **2015**, *17*, 4754-4757.

II. **Copper-Catalyzed Stereoselective Cross-Coupling of Cyclic Allylboronic Acids with α-Diazoketones**
Wang, D.; Szabó, K. J.
Org. Lett. **2017**, *19*, 1622-1625.

III. **Formation of C(sp^3)–C(sp^3) Bonds by Palladium-Catalyzed Cross-Coupling of α-Diazoketones and Allylboronic Acids**
Belhomme, M.-C.; Wang, D.; Szabó, K. J.
Org. Lett. **2016**, *18*, 2503-2506.

IV. **Synthesis of Densely Substituted Conjugated Dienes by Transition-metal-free Reductive Coupling of Allenylboronic Acids and Tosylhydrazones**
Wang, D.; de Wit, M. J. M.; Szabó, K. J.
J. Org. Chem. **2018**, *ASAP*, DOI: 10.1021/acs.joc.8b01104.

V. **Direct Allylation of Quinones with Allylboronates**
Deng, H.-P.; Wang, D.; Szabó, K. J.,
J. Org. Chem. **2015**, *80*, 3343-3348.

Contents

Abbreviations

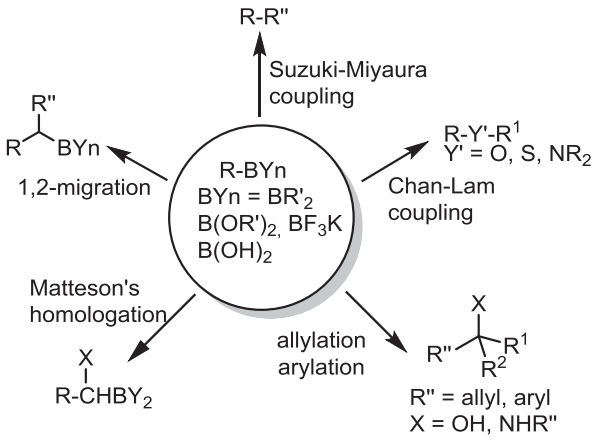
Abbreviations are used in agreement with the standards of the subject.[#] Only non-standard and unconventional abbreviations are listed here.

Boc	*tert*-butyloxycarbonyl
Bpin	pinacolato boron
B_2pin_2	bis(pinacolato)diboron
BQ	benzoquinone
Cp*	1,2,3,4,5-pentamethyl-cyclopentadienyl
CuTC	copper(I)-thiophene-2-carboxylate
dba	dibenzylideneacetone
D-*t*-BPF	1,1'-bis(di-*tert*-butylphosphino) ferrocene
d.r.	diastereomeric ratio
er	enantiomeric ratio
HSQC	heteronuclear single quantum correlation
L	ligand
NOEDIFF	NOE difference
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
rt	room temperature
RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
S_E2	bimolecular electrophilic substitution
Xphos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

[#]*The ACS Style Guide*, 3rd ed.; Oxford University Press: New York, 2006.

1. Introduction

Organoboron compounds are widely used in organic synthesis, catalysis, drug development, and material science.[1] Application of organoboron reagents is a fundamental tool for creation of molecular complexity. The most widely used reaction of organoboron reagents is Suzuki-Miyaura cross-coupling.[2] Other attractive methodologies include Chan-Lam coupling,[3] allylation,[4] arylation,[5] Matteson's homologation,[6] and 1,2-migration[7] (Scheme 1). This thesis is focused on the development of carbon-carbon bond formation reactions employing allylboronic acids, allylboronates and allenylboronic acids catalyzed by transition metals or under metal-free conditions.



Scheme 1. Transformations of organoboron reagents.

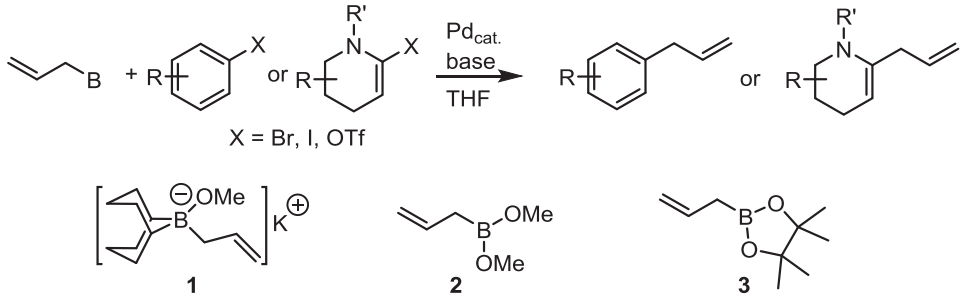
1.1 Transition-metal-catalyzed cross-couping reactions

Transition-metal-catalyzed cross-coupling reactions are powerful synthetic tools for the construction of useful organic structures by coupling different organic fragments together.[8] A well-known transition-metal-catalyzed cross-coupling reaction involving organoboron compounds is Suzuki-Miyaura cross-coupling.[9] A crucial step in this reaction is transmetalation,[10] which allows for the ligand transfer from boron to the metal catalyst. Based on relatively easy transmetallation of organoboron reagents with transition metal species,[11] many organoboron reagents have been developed for efficient carbon-

carbon bond formations via the transition-metal-catalyzed cross-coupling reaction.[2]

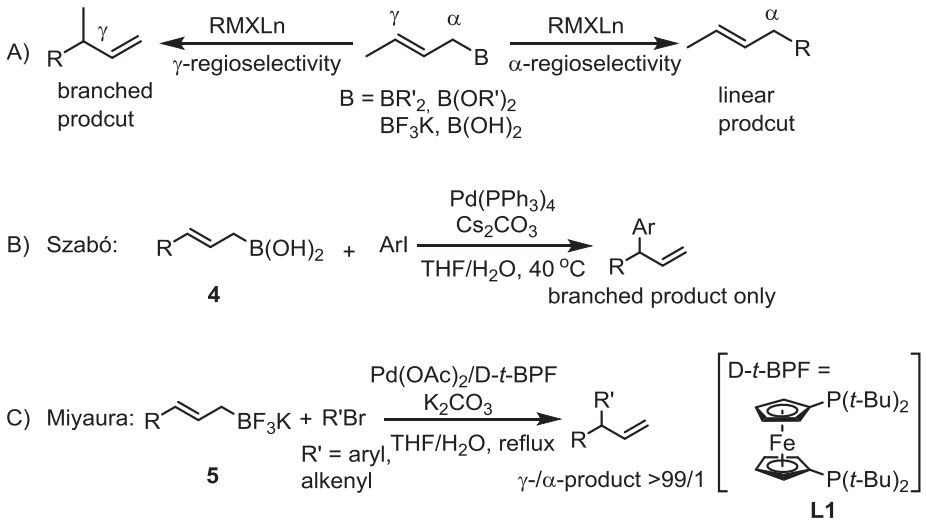
1.1.1 Reactions of allylboron compounds with C(sp^2) electrophiles

By employing allylboron compounds as the substrate, allylation of aryl and alkenyl (pseudo) halides was achieved. Initially, allylborane **1**,[12] allylboronic dimethyl ester **2**,[13] and allylboronic pinacol ester **3**[14] and aryl/alkenyl halides were applied in cross-coupling studies (Scheme 2) in the presence of Pd catalyst and a base. However, the scope of these reactions was limited since only the parent allylboron reagents without γ-substituents were used.



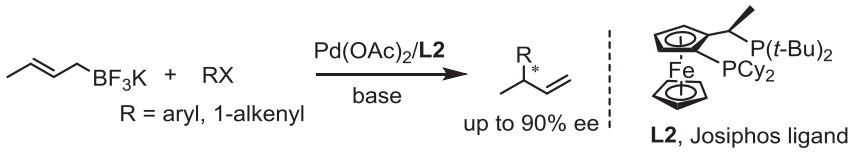
Scheme 2. Early studies of Suzuki-Miyaura coupling using allylboron reagents.

In 2006, γ-substituted allylboronic acids and allyltrifluoroborates were successfully employed in cross-coupling reactions with aryl and alkenyl halides. In these reactions, the regiochemistry emerged as an essential issue. The γ-regioselective coupling affords the branched product and α-regioselective coupling furnishes the linear product (Scheme 3A). The groups of Szabó[15] and Miyaura[16] independently reported cross-coupling reactions of the allylboron reagents leading to the branched allylic product. This is very surprising, as palladium-catalyzed allylic substitution reactions preferentially give the linear allylic product.[17] The Szabó group[15] employed $Pd(PPh_3)_4$ as the catalyst for the cross-coupling of in situ generated allylboronic acids **4** and iodobenzenes (Scheme 3B). The reactions were conducted under mild conditions and furnished only the branched product with excellent yield. Under the same reaction conditions, the allyl-Bpin analogs did not react at all. Meanwhile, Miyaura and coworkers[16] studied the regioselective cross-coupling reaction by using allyltrifluoroborates **5** and aryl bromides. They found that high γ-regioselectivity could also be achieved in the presence of a palladium/D-*t*-BPF(**L1**) complex (Scheme 3C).



Scheme 3. γ-Regioselective cross-coupling of allylboronates and aryl halides.

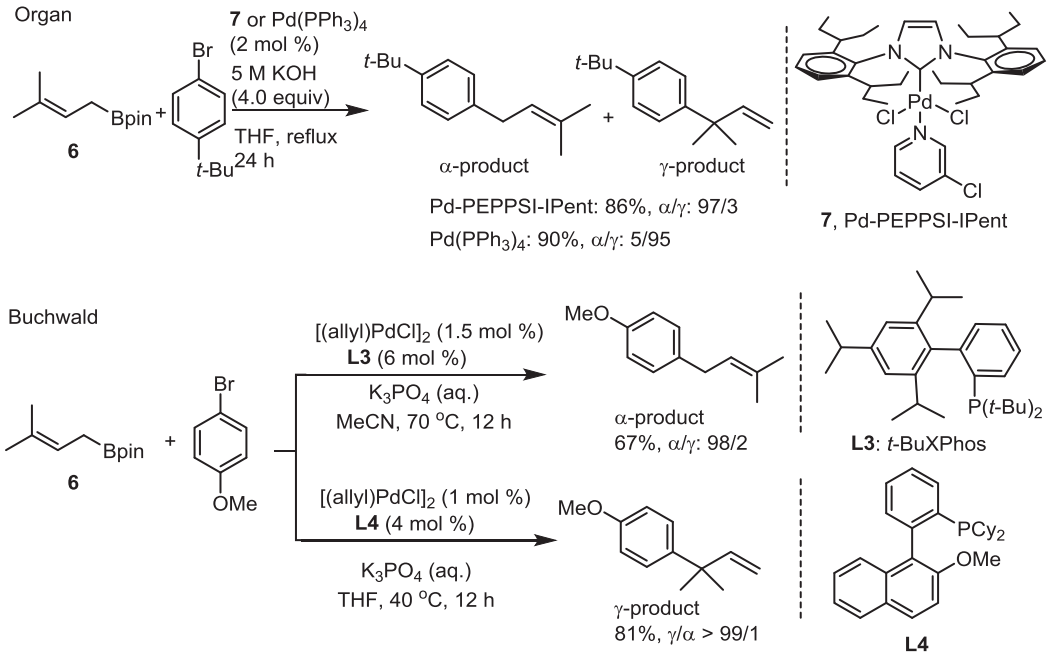
Subsequently, the Miyaura group reported an asymmetric version of this reaction using the chiral ligand Josiphos (**L2**) (Scheme 4).[18]



Scheme 4. Asymmetric cross-coupling of allyltrifluoroborates with aryl and alkenyl halides.

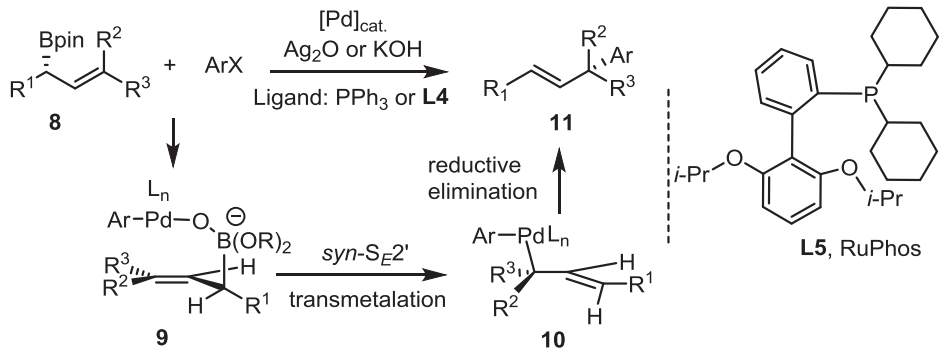
Although allyltrifluoroborates have been used as suitable cross-coupling partner, the further development of these reagents is hampered due to their relatively low reactivity and insolubility in many nonpolar solvents. In contrast, allylboronates, particularly allylboronic acid pinacol esters (allyl-Bpin), have been commonly employed in transition-metal-catalyzed cross-coupling reactions. This is owing to their relatively high stability, ease of preparation, and versatile reactivity. Based on the use of allyl-Bpin reagents, new methodologies have been established for regio- and diastereoselective carbon-carbon bond formation.

For example, the groups of Organ[19] and Buchwald[20] have studied the regioselectivity of the cross-coupling of allylboronates **6** and aryl halides (Scheme 5) independently. Their results indicated that sterically bulky ligands on Pd (**7** or **L3,** Scheme 5) preferentially gave the α-products. In contrast, with sterically less hindered ligands (PPh_3 or **L4**, Scheme 5), γ-products were formed selectively.



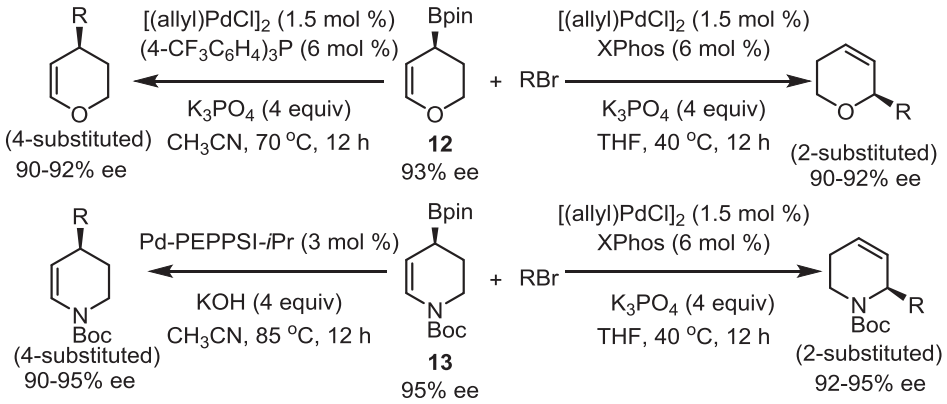
Scheme 5. Ligand effects on the regioselectivity of the cross-coupling reaction between allyl-Bpin **6** and aryl bromides.

Another example regarding the study of the regio- and diastereoselectivity is the Suzuki-Miyaura cross-coupling of secondary chiral allylboronates **8** (Scheme 6). The groups of Crudden and Aggarwal reported the reaction of enantioenriched secondary allylic boronic esters and aryl iodides proceeded with high γ-regioselectivity and retention of chirality (Scheme 6).[21] Crudden and Aggarwal proposed a mechanism involving a *syn*-S_E2' transmetalation (**9→10**) followed by rapid reductive elimination (**10→11**), to account for the regio- and stereoselectivity of the reaction. The Morken group reported the same selectivity and chirality transfer in the Pd/RuPhos (**L5**)-catalyzed cross-coupling of chiral allylboronates and electrophiles.[22] These authors also suggested that the reaction proceeded via *syn*-S_E2' transmetalation including a cyclic transition state.



Scheme 6. Enantiospecific, regioselective cross-coupling of secondary chiral allylboronates and aryl halides.[21]

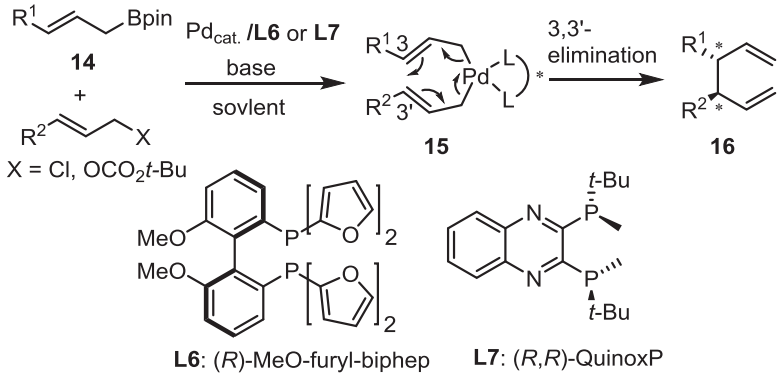
By using this chirality transfer concept of ligand-controlled regiodivergent cross-coupling, Hall and coworkers successfully synthesized 2- and 4-substituted chiral dihydropyrans and dehydropiperidines via the cross-coupling reaction of chiral cyclic allyl-Bpin **12** and **13** with aryl halides (Scheme 7).[23]



Scheme 7. Regiodivergent and enantiospecific Suzuki-Miyaura cross-coupling of allylboronates and aryl bromides.[23a]

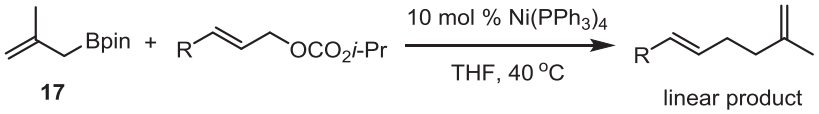
1.1.2 Reactions of allylboron compounds with C(sp^3) electrophiles

All research mentioned above have focused on the use of aryl and alkenyl halides as the coupling partners in the transition-metal-catalyzed reactions of allylboronate. On the other hand, the C(sp^3) electrophiles, such as allylic and alkyl halides can also be employed. For example, the Morken group reported the efficient palladium-catalyzed allyl-allyl cross-coupling process by using allylic halides and carbonates as the substrate (Scheme 8).[24]



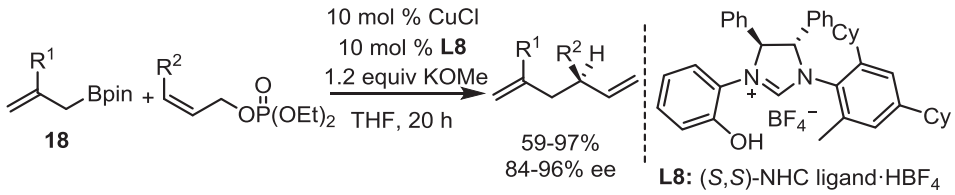
Scheme 8. Asymmetric allyl-allyl cross-coupling of allyl-Bpin and allyl halides with Pd catalyst and chiral ligands.

The authors demonstrated that the regioselectivity of the reaction could be controlled by using small-bite-angle bidentate ligands (**L6** or **L7**), which induce the γ,γ'-regioselectivity via a 3,3'-reductive elimination of bis-(η^1-allyl)palladium intermediate **15**. Moreover, enantioselective synthesis of dienes (**16**) was performed where chiral ligands were employed. Not only Pd but also Ni and Cu catalysts can be used to catalyze the allyl-allyl cross-coupling process. For example, the Kobayashi group reported their results on the $Ni(PPh_3)_4$-catalyzed cross-coupling of allylboronate **17** and allyl carbonates. The reaction proceeded with α-regioselectivity under mild conditions (Scheme 9).[25]



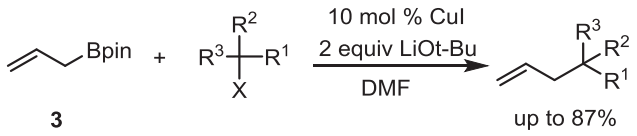
Scheme 9. Nickel-catalyzed cross-coupling reaction of allylboronate **17** and allylic carbonates.[25]

Recently, the Sawamura group studied the copper-catalyzed enantioselective cross-coupling between allylboronates **18** and allyl phosphates using a chiral *N*-heterocyclic carbene (NHC) ligand **L8** (Scheme 10).[26] They found that this reaction proceeded with γ-regioselectivities, affording chiral 1,5-dienes.



Scheme 10. Copper-catalyzed enantioselective allyl-allyl coupling between allyl-Bpin and phosphates with a chiral NHC ligand.[26]

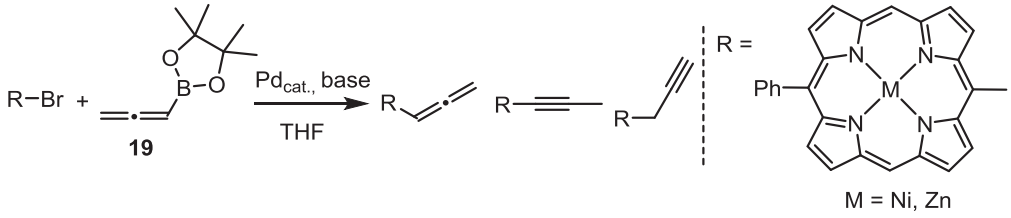
In addition to the use of allylic electrophiles, alkyl halides have also been proved to be suitable coupling partners for transition-metal-catalyzed C(sp^3)-C(sp^3) bond formation reactions. The Xu and Fu group[27] recently applied primary, secondary, and tertiary halides in the copper-catalyzed cross-coupling with allylboronate **3** (Scheme 11). The authors proposed that the reaction undergoes formation of an allylcopper species via transmetalation of CuI and the allylboronate, followed by the reaction of the allylcopper species with the corresponding halides.



Scheme 11. Copper-catalyzed cross-coupling reaction of allyl-Bpin with 1°/2°/3°-halogenated alkanes.[27]

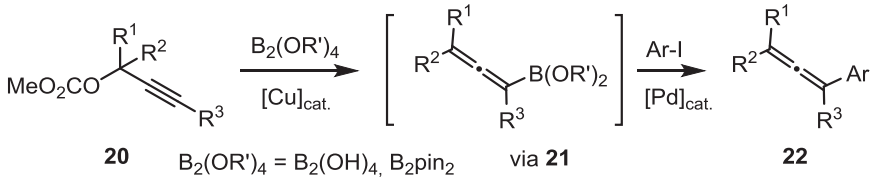
1.1.3 Reactions of allenylboronates

Allenylboronates have been employed for selective propargylation and allenylation of carbonyl compounds and imines for a long time.[28] Another attractive application is Suzuki-Miyaura cross-coupling reactions based on allenylboronates.[29] For example, synthesis of allenyl- and propargyl porphyrin using a commercially available allylboronic pinacol ester **19** and bromoporphyrin (Scheme 12) was reported by Senge.[29a] The regioselectivity was primarily affected by the porphyrin substrates, catalyst, and base.



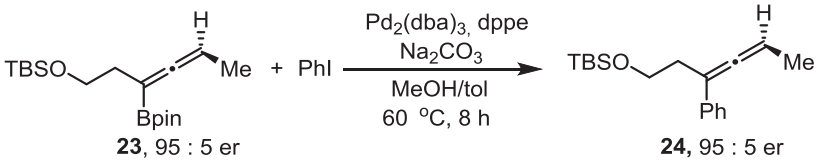
Scheme 12. Suzuki-Miyaura cross-coupling of allenyl-Bpin and bromoporphyrin.[29a]

The Szabó group reported a multicomponent reaction of propargyl carbonates **20** and aryl iodides in the presence of diboron compounds (Scheme 13).[29b] Allenylboronate species **21** was suggested to be generated in situ and couple with a variety of aryl iodides. The reaction gave allenes **22** as the sole product, showing high regioselectivity.



Scheme 13. Cross-coupling of in situ generated allenylboron species and aryl iodide.[29b]

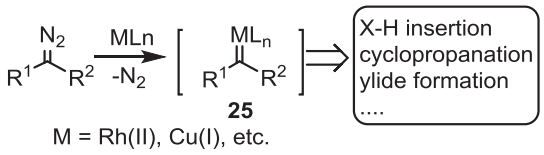
In a recent work by Hoveyda and coworkers,[29c] the cross-coupling of a chiral trisubstituted allenylboronate **23** and iodobenzene was carried out in the presence of a Pd catalyst and a base. The reaction gave the allene product **24** without loss of the enantiopurity of **23** (Scheme 14).



Scheme 14. Cross-coupling of chiral allenylboronate **23** and aryl iodide.[29c]

1.1.4 Diazo compounds as cross-coupling partners

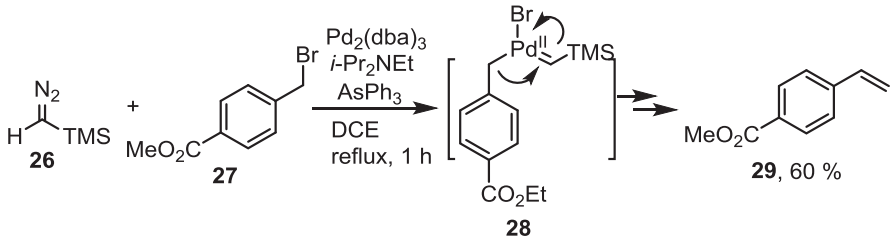
Diazo compounds readily react in many transition-metal (e.g., Rh, Cu, and Pd)-catalyzed reactions via formation of metal-carbene species (**25**, Scheme 15).[30] These metal-carbene species have been suggested to be the key intermediates in X-H (X = C, O, S, N) insertion,[31] cyclopropanation,[32] and ylide formation reaction[33] (Scheme 15).[34] Recently, transition-metal-catalyzed cross-coupling reaction of diazo compounds with organic halides, and organoboron species attracted considerable attention. Pioneering work in this research field has been done by groups of Van Vranken,[35] Barluenga,[36] and Wang[30a, 37]



Scheme 15. Transition metal carbene reactions.[30a]

Van Vranken and coworkers reported the first catalytic cross-coupling reaction using a diazo compound as the precursor of the carbene in 2001.[35a] The authors reacted $TMSCHN_2$ (**26**) with benzyl bromide **27** under palladium catalysis, furnishing styrenes **29** as the coupling product (Scheme 16). The

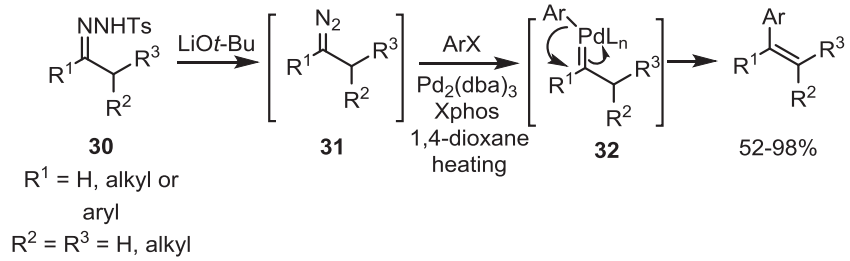
reactive palladium carbene complex **28** was proposed to be the critical intermediate in this reaction. This intermediate can undergoes migratory insertion and β-hydride elimination to afford a β-silylstyrene. De-silylation of the β-silylstyrene provided **29** as the product.



Scheme 16. Palladium-catalyzed cross-coupling of $TMSCHN_2$ and benzyl bromide.[35a]

In recent studies, diazo compounds have been extensively explored as coupling partners with various substrates, including aryl,[37b] vinyl,[38] benzyl,[37l] allyl,[37a] and alkynyl[37p] compounds by Wang's group.[30a] The scope of the transition metal catalysts has been extended to Cu,[37g, k, 39] Ni,[40] Co,[40] and Rh[37q]. Moreover, many cascade processes have been developed based on these coupling reactions.[30a, c]

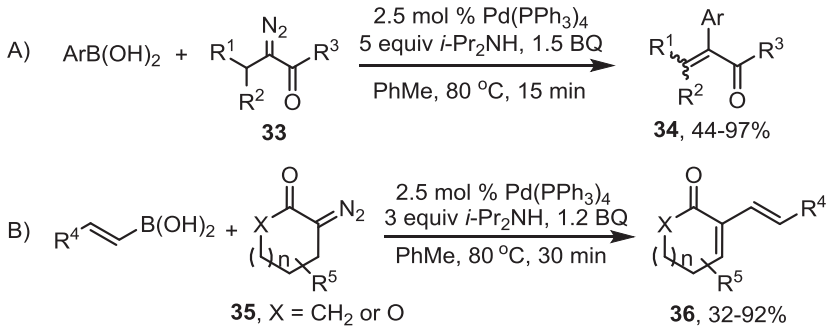
Another development involves in situ generation of diazo compounds from, for example, tosylhydrazones. Barluenga first demonstrated the ability of *N*-tosylhydrazones **30** to couple with aryl halides in the presence of Pd and a base.[36a] During this process, tosylhydrazones decomposed into the corresponding diazo compounds **31** in situ, affording the actual substrate of the coupling reaction. The following step is the formation of palladium carbene complex **32** followed by migratory insertion and β-hydride elimination to provide the product (Scheme 17).



Scheme 17. Pd-catalyzed cross-coupling reaction employing *N*-tosylhydrazones as coupling partners.[36a]

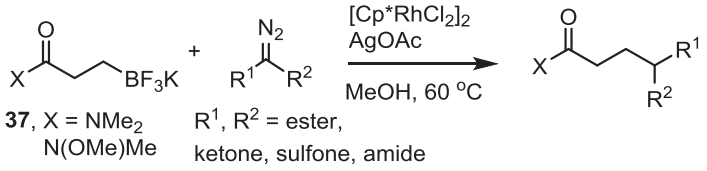
In 2008, the Wang group described the first example of palladium-catalyzed cross-coupling of α-diazoketones **33** with arylboronic acids (Scheme 18A).[37b] This reaction requires the addition of an oxidant (benzoquinone) and

a base (*i*-Pr_2NH) to create a new $C(sp^2)$-$C(sp^2)$ bond in the product **34**. In another study by the same group, vinylboronic acids were successfully applied to react with cyclic α-diazoketones **35** under similar conditions (Scheme 18B).[38]



Scheme 18. Palladium-catalyzed cross-coupling of α-diazocarbonyl compounds with arylboronic acids.[37b, 38]

Recently, the Yu group employed alkylboron species **37** and diazomalonates as coupling components.[41] The reaction was catalyzed by a $[Cp^*RhCl_2]_2$ complex in the presence of AgOAc and resulted in the formation of a $C(sp^3)$-$C(sp^3)$ bond (Scheme 19).

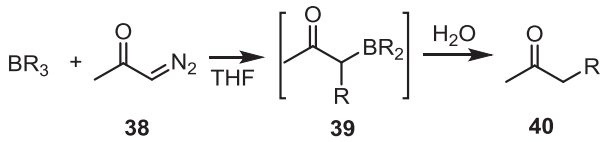


Scheme 19. Cp*Rh(III)-catalyzed cross-coupling of alkyltrifluoroborate with α-diazomalonates.[41]

1.2 Transition-metal-free cross-coupling with organoboron reagents

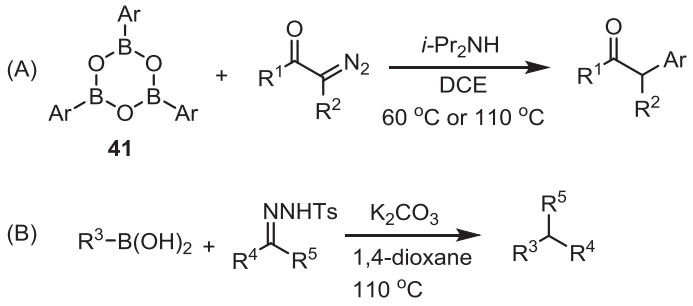
The above-described (Section 1.1) transition-metal-catalyzed cross-coupling reactions with organoboron reagents are considered as a reliable and efficient method for carbon-carbon bond formation. On the other hand, the coupling reactions without the mediation of transition metals have become an attractive alternative.[26, 42]

Hooz and Linke[43] reported one of the first metal-free coupling of an organoborane reagent with a diazo compound (**38**, Scheme 20). In this reaction a transient organoboron product **39** was proposed to form, which undergoes protodeboronation, yielding the final ketone product **40.**



Scheme 20. Transition-metal-free cross-coupling reactions of α-diazoketone **38** and organoboranes.

Wang and coworkers reported the reaction of aryl boroxine **41** and various α-diazoketones under basic conditions to access a wide range of α-substituted ketones (Scheme 21A).[44] In the same year, the Barluenga group also published a study (Scheme 21B) on the transition-metal-free cross-coupling reaction of boronic acids and tosylhydrazones (precursors for diazo compound).[45]



Scheme 21. Recent developments of the transition-metal-free coupling reactions of organoboron and diazo compounds.

Recent advances in this field includes the extension of substrate from aryl- and alkylboronic acids to alkenylboronic acids;[46] multi-component[47] and cascade[48] reactions using boronic acids and tosylhydrazones; replacement of the diazo compounds with other diazo sources, for example, from diazotisation of amines;[37m] application of flow chemistry for generation of the diazo compound[49].

1.3 The objectives of this thesis

Aryl and vinylboronic acids have been widely used to create new carbon-carbon bonds via both transition-metal-catalyzed and transition-metal-free cross-coupling reactions. This thesis is mainly focused on the development of new

coupling reactions of allyl- and allenylboronic acids with diazo compounds under transition metal catalyzed and metal-free conditions. In addition, the metal-free allylation of benzoquinones using allylboronates was also studied.

2. Copper-catalyzed cross-coupling of α-diazoketones with allylboronic acids (Paper I-II)

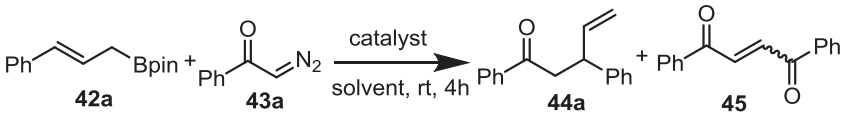
Allylboronates are versatile reagents which have been widely used in the synthesis of homoallylic alcohols and amines.[4, 50] The applications of these compounds in cross-coupling reactions are also attractive since various organic compounds can be directly allylated (Section 1.1.1 and 1.1.2). On the other hand, allylboronic acids have shown an increased reactivity compared to allylboronates,[51] and have been proved to be very useful in transition-metal-catalyzed cross-coupling reactions by the Szabó group.[15] As our group has been focusing on the synthesis and application of allylboronates and allylboronic acids for a long time, we decided to develop new types of cross-coupling methodologies with these reagents.

As mentioned above (Section 1.1.4), α-diazoketones can react with various transition metals to form reactive metal carbenes, which can be further applied to the cross-coupling with organoboron species. Therefore we chose α-diazoketones as a component to study the cross-coupling reactions with allylboronates and allylboronic acids.

2.1 Formation of branched allylic products with copper catalysis

We initiated our study using cinnamylboronic acid pinacol ester **42a** (readily prepared from cinnamyl alcohols[52]) and α-diazoketone **43a** as substrates. When the reaction was performed in CH_2Cl_2 without transition metal catalyst, no coupling products were observed, and both substrates remained unreacted (Table 1, entry 1). Using $Pd(PPh_3)_4$ catalyst did not change the result (Table 1, entry 2). When CuI (Table1, entry 3) and CuTC (Table 1, entry 4) were employed as the catalyst, a trace amount of product **44a** was observed in both cases. Together with the formation of **44a**, a substantial amount of compound **45** was detected. The yield of coupling product **44a** could not be improved by heating the reaction to 50 ºC or changing the solvent to toluene (Table 1, entries 5-6). These results indicated that the cinnamyl-Bpin (**42a**) is not reactive under these conditions.

Table 1. Attempted reaction of cinnamyl-Bpin **42a** with α-diazoketone **43a**.[a]

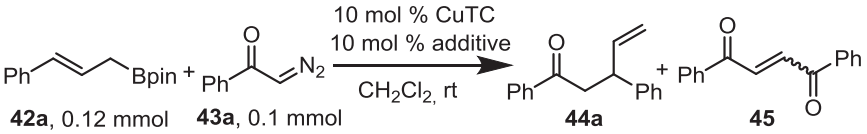


entry	solvent	catalyst	**44a** (%)[b]	**45** (%)[b]
1	CH_2Cl_2	-	0	0
2	CH_2Cl_2	$Pd(PPh_3)_4$	0	0
3	CH_2Cl_2	CuI	< 5	37
4	CH_2Cl_2	CuTC	< 5	35
5[c]	CH_2Cl_2	CuTC	< 5	32
6	toluene	CuTC	< 5	31

[a]Reaction conditions (unless otherwise stated): **43a** (0.1 mmol), **42a** (0.12 mmol), catalyst (10 mol %), CH_2Cl_2 (0.5 mL), rt, 4 h. [b]Yield was determined by ^{1}H NMR using naphthalene as an internal standard. [c]The reaction was performed at 50 °C.

Then we attempted to activate allylboronate **42a** by addition of Lewis or Brønsted acids such as $BF_3{\cdot}Et_2O$ and PhCOOH. However, the formation of the product **44a** was not improved (Table 2, entries 1-2). The use of base was not successful either, resulting in decomposition of **42a** and **43a** (Table 2, entry 3).

Table 2. The effects of $BF_3{\cdot}Et_2O$, PhCOOH, and NaOMe on the reaction of **42a** and **43a**.



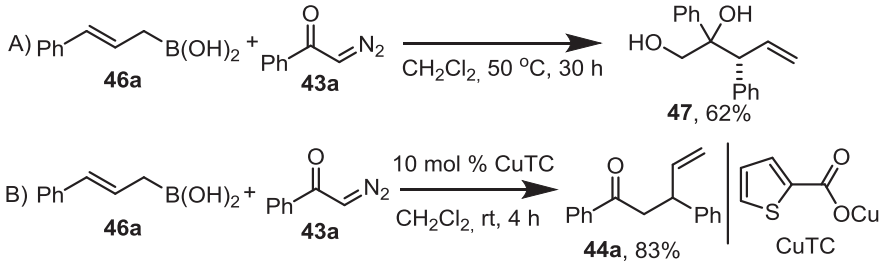
entry	additive	**44a** (%)[a]	**45** (%)[a]
1	$BF_3{\cdot}Et_2O$	< 5	24
2	PhCOOH	< 5	82
3	NaOMe	< 5	0

[a]Yield was determined by ^{1}H NMR using naphthalene as an internal standard.

Allylboronic acids are generally more reactive than their ester derivatives.[53] Moreover, it has been demonstrated that they are suitable coupling partners in transition-metal-catalyzed cross-coupling reactions (Section 1.1.1). Therefore, we continued our study by replacing cinnamyl-Bpin **42a** with cinnamylboronic acid **46a**. When the reaction of **46a** and **43a** was performed in CH_2Cl_2 at room temperature in the absence of transition metal catalysts, no reaction was observed. However, when the reaction was carried out at 50 °C, the homoallyl alcohol derivative **47** was obtained in 62% yield (Scheme 22A).

The product was likely formed via allylboration of the keto group by **46a** and then hydrolysis of the diazo intermediate. When using $Pd(PPh_3)_4$ as catalyst, several products were detected including allylbenzene, which was formed via protodeboronation of **46a**. Unfortunately, the coupling product **44a** was not observed. In contrast, when $Pd(PPh_3)_4$ was replaced with CuTC, the coupling product **44a** was obtained in good yield (83%, Scheme 22B).

The reaction is remarkably regioselective, as only the branched regioisomer was formed with the copper catalysis. In addition, a new $C(sp^3)$-$C(sp^3)$ bond was formed in this process, which is still a challenge in catalytic cross-coupling reactions. Notably, the reaction was performed without any further additives.



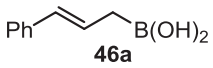
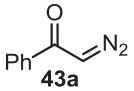
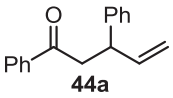
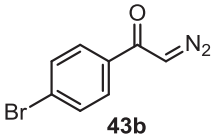
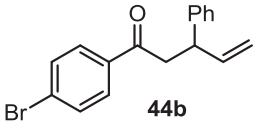
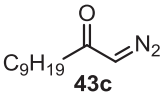
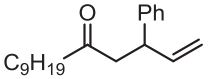
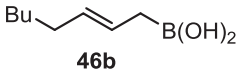
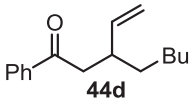
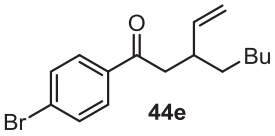
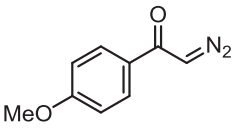
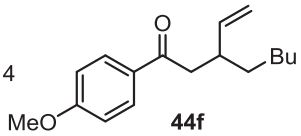
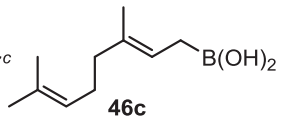
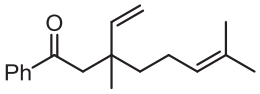
Scheme 22. Reactions of **46a** and **43a** under different conditions.

2.2 Scope of the reaction

The scope of the cross-coupling reaction was explored by employing various substituted α-diazoketones (**43a-d**) and allylboronic acids (**46a-c**). The reaction proceeded well with 4-bromophenyl α-diazoketone (Table 3, entry 2). Alkyl α-diazoketone **43c** could react with cinnamylboronic acid **46a**, giving the branched product **44c** in moderate yield. In this case, a lower temperature (- 20 °C to 0 °C) was used to reduce the side-product formation (Table 3, entry 3).

We further investigated the scope by employing 2-octenylboronic acid **46b**. The reactions of **46b** and phenyl, 4-bromophenyl, and 4-methoxyphenyl α-diazoketones **43a**, **b**, and **d** proceeded smoothly, affording the corresponding branched products **44d-f** in good yields (Table 3, entries 4-6). Geranylboronic acid **46c** could also react with **43a**, furnishing a quaternary carbon-containing product **44g**. The yield was low even with two equivalents of **46c**, probably because of the steric effect of the substituent on the γ-carbon (Table 3, entry 7).

Table 3. Substrate scope for the cross-coupling of acyclic allylboronic acids and α-diazoketones.[a]

entry	boronic acid	α-diazoketone	time (h)	product	yield (%)
1	 **46a**	 **43a**	4	 **44a**	83
2	**46a**	 **43b**	4	 **44b**	86
3[b]	**46a**	 **43c**	1	 **44c**	57
4	 **46b**	**43a**	6	 **44d**	87
5	**46b**	**43b**	4	 **44e**	83
6	**46b**	 **43d**	4	 **44f**	81
7[c]	 **46c**	**43a**	6	 **44g**	34

[a]Unless otherwise stated, a mixture of **46a-c** (0.12 mmol), **43a-d** (0.1 mmol) and CuTC (10 mol %) in CH_2Cl_2 (0.5 mL) were stirred at rt. [b]The reaction mixture of **46a** (0.2 mmol), **43c** (0.1 mmol) and CuTC (20 mol %) were stirred at -20 °C for 3 h and then at 0 °C for 1 h. [c]**46c** (0.2 mmol), **43a** (0.1 mmol) and CuTC (10 mol %) were used.

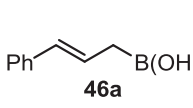
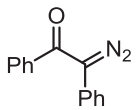
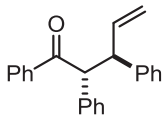
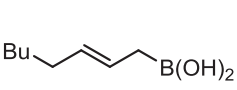
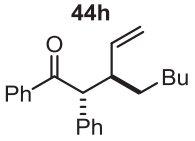
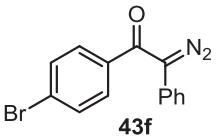
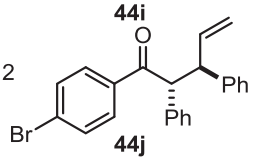
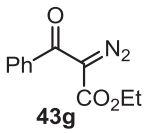
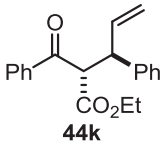
We attempted to use diazo ethylacetate as the substrate, which is available from commercial sources. However, the reaction of this diazo reagent and allylboronic acid **46a** did not give any desired product. The reactivity of disubstituted α-diazoketones and stereodefined cyclic allylboronic acids has also been examined. The stereoselectivity and regioselectivity of this process, which provided two adjacent stereogenic carbon centers, is presented in Section 2.3 below.

2.3 Stereochemistry of the Cu-catalyzed allylation of diazoketones

2.3.1 Using disubstituted α-diazoketones as substrates

To study the stereochemistry of the copper-catalyzed cross-coupling reaction of α-diazoketones and allylboronic acids, we prepared disubstituted α-diazoketones **43e-g** and used them as substrates (Table 4). Cinnamylboronic acid **46a** could react with diphenyl-substituted α-diazoketone **43e** to form the product **44h** with high diastereoselectivity (Table 4, entry 1). The major diastereomer was identified by comparison with published ^{1}H NMR data.[54] The result showed a *trans* stereoselectivity for this cross-coupling reaction.

Table 4. Stereoselective cross-coupling of acyclic allylboronic acids and disubstituted α-diazoketones.[a]

entry	boronic acid	α-diazoketone	time (h)	product	yield (%)	d.r.[b]
1[c]	 **46a**	 **43e**	2	 **44h**	77	9.1:1
2[c,d]	 **46b**	**43e**	6.5	 **44i**	65	3:1
3[c]	**46a**	 **43f**	2	 **44j**	81	4:1
4[e]	**46a**	 **43g**	12	 **44k**	78	1.2:1

[a]Unless otherwise stated, a mixture of **46a-b** (0.12 mmol), **43e-g** (0.1 mmol) and CuTC (10 mol%) in CH_2Cl_2 (0.5 mL) were stirred at rt. [b]The ratio of the diastereomers was determined from the crude product by ^{1}H NMR. [c]The reaction was performed at 0 °C. [d]**46b** (0.05 mmol), **43e** (0.1 mmol) and CuTC (10 mol %) were used. [e]The reaction was performed at 45 °C.

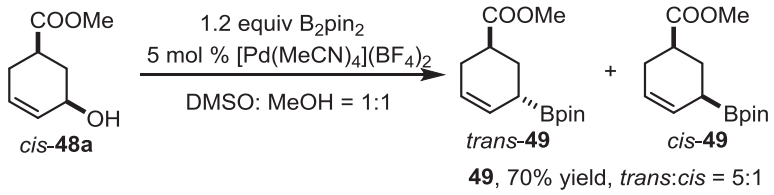
When 2-octenylboronic acid **46b** was used instead of cinnamylboronic acid **46a**, the diastereoselectivity of the reaction decreased to 3:1 (Table 4, entry 2), indicating that the pentyl moiety has a weaker stereoinductive effect on the reaction. In the case of employing 4-bromophenyl α-diazoketone **43f** as the substrate (Table 4, entry 3), the reactivity was almost the same as for **43e** (entry 1). However, the diastereoselectivity of the reaction was somewhat lower.

We also examined the stereoselectivity of the coupling of ester-substituted diazoketone **43g** (Table 4, entry 4). The reaction proceeded slowly at 0 °C and room temperature. When the reaction temperature was increased to 45 °C, a good yield of **44k** was obtained (78%). However, the stereoselectivity was low (1.2:1) under such conditions.

2.3.2 Using stereodefined allylboronic acids as substrates

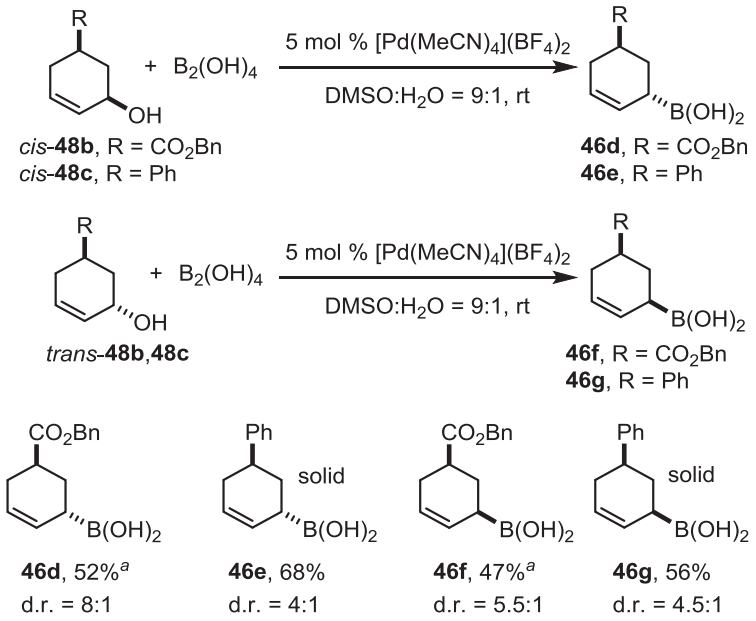
2.3.2.1 Synthesis of stereodefined allylboronic acids

To further study the stereochemistry of the cross-coupling process, we considered employing stereodefined allylboronic acids as substrates. However, methods to access stereodefined allylboronic acids were not available in the literature. The primary reason is due to the air sensitivity of these species, which leads to difficulties for their isolation and purification. In contrast, stereodefined allyl-Bpin derivatives **49** are relatively stable compounds, which can be isolated by silica gel chromatography. Our group reported a protocol for the synthesis of stereodefined cyclic allyl-Bpin **49** from the corresponding allylic alcohol *cis*-**48a** (Scheme 23).[55]



Scheme 23. Synthesis of stereodefined cyclic allyl-Bpin **49** from cyclic *cis*-allylic alcohol *cis*-**48a**.

Based on this work, we decided to develop a practical method for the synthesis of stereodefined cyclic allylboronic acids. When the reaction of cyclic allylic alcohols **48b-c** and $B_2(OH)_4$ was carried out in the presence of $[Pd(MeCN)_4](BF_4)_2$, cyclic allylboronic acids **46d-g** were formed with moderate to good diastereoselectivity (Scheme 24). As the allylboronic acids are air-sensitive, all the purification procedures were carried out under argon. Notably, **46d** and **46f** were extracted from the crude reaction mixture and stored in CH_2Cl_2 solution, while **46e** and **46g** were precipitated as white solid by degassed aqueous NaCl solution.



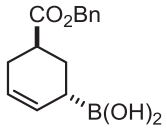
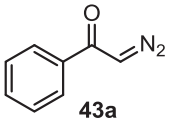
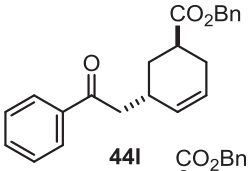
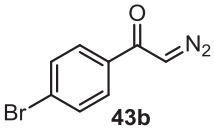
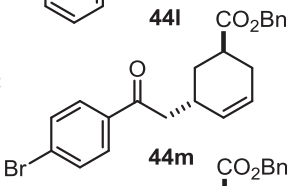
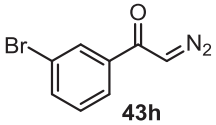
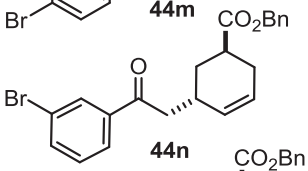
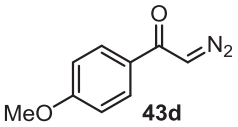
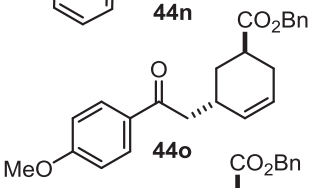
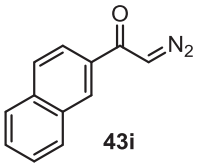
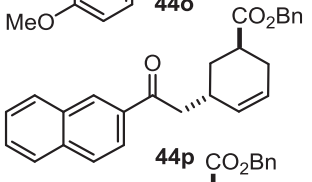
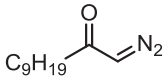
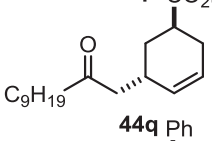
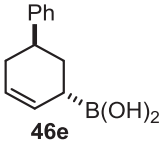
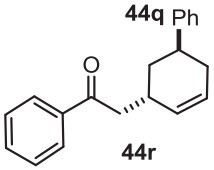
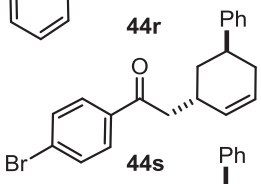
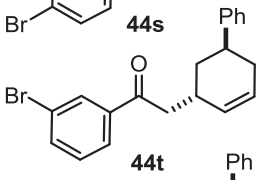
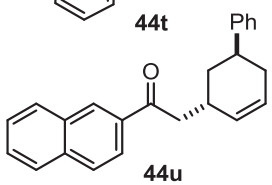
Scheme 24. Synthesis of stereodefined cyclic allylboronic acids **46d-g**. [a]NMR yield.

2.3.2.2 Reactions of the stereodefined allylboronic acids and α-diazoketones

With the stereodefined allylboronic acids **46d-g** in hand, we started the investigation of the stereoselectivity of the cross-coupling process (Table 5).

When the reaction of α-diazoacetophenone **43a** and cyclic allylboronic acid **46d** was carried out under the same conditions as with cinnamylboronic acid **46a** (Table 3, entry 1), significant protodeboronation of **46d** was observed. To our delight, this side reaction was suppressed by dilution of the reaction mixture and increase of the catalyst loading. Under the optimized conditions, the reaction of **46d** and **43a** gave the coupling product **44l** with good yield (82%) and high diastereoselectivity (d.r. = 19:1) (Table 5, entry 1). A *trans* relative configuration for the product **44l** was determined based on the ^{1}H NMR coupling constants (see Section 2.3.2.3 below). The relative configuration of **44l** indicated that the cross-coupling reaction proceeds with stereoretention. Notably, the diastereomeric ratio of the product is higher than that of the substrate, suggesting that the two stereoisomers of **46d** have different reactivity.

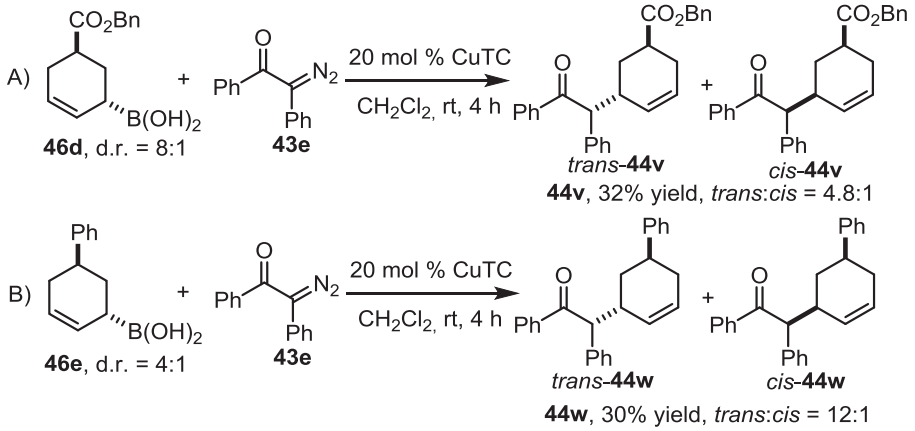
Table 5. Stereoselective cross-coupling of cyclic *trans*-allylboronic acids **46d-e** and α-diazoketones.[a]

entry	boronic acid	α-diazoketone	product	yield	d.r.[b]
1	 **46d** d.r. = 8:1	 **43a**	 **44l**	82%	19:1
2	**46d** d.r. = 8:1	 **43b**	 **44m**	73%	12:1
3	**46d** d.r. = 8:1	 **43h**	 **44n**	78%	12:1
4	**46d** d.r. = 8:1	 **43d**	 **44o**	67%	15:1
5	**46d** d.r. = 8:1	 **43i**	 **44p**	70%	15:1
6	**46d** d.r. = 8:1	 **43c**	 **44q**	67%	11:1
7	 **46e** d.r. = 4:1	**43a**	 **44r**	79%	>20:1
8	**46e** d.r. = 4:1	**43b**	 **44s**	68%	15:1
9	**46e** d.r. = 4:1	**43h**	 **44t**	72%	14:1
10	**46e** d.r. = 4:1	**43i**	 **44u**	65%	10:1

[a]A mixture of **46** (0.12 mmol), **43** (0.10 mmol), and CuTC (20 mol %) in CH_2Cl_2 (5 mL) was stirred at rt for 4 h. [b]The diastereomeric ratio (d.r.) values of product **44** were determined by ^1H NMR analysis of the crude reaction mixture.

We further examined the reaction of **46d** with a variety of α-diazoketones under the optimal conditions. α-Diazoketones with either electron withdrawing (**43b**, **43h**) or electron-donating (**43d**) substituents on the aromatic ring could react with ester-substituted allylboronic acid **46d** (Table 5, entries 2-4). All the products have the retentive *trans* relative configuration, though the diastereoselectivity is lower than that of the product **44l** from the reaction between **46d** and **43a**. Naphthyl α-diazoketone **43i** was also employed in the coupling reaction, affording *trans*-product **44p** with an acceptable diastereomeric ratio (15:1) (Table 5, entry 5). Aliphatic α-diazoketone can also be used as a coupling partner. For example, the reaction between the α-diazo methyl nonyl ketone **43c** and **46d** gave 67% yield of the product **44q** in d.r.11:1 (Table 5, entry 6). To examine the substituent effects in the 5-position of the cyclic allylboronic acids on the reactivity and diastereoselectivity of the coupling reaction, we replaced **46d** with **46e**. It was found that **46d** and **46e** react with α-diazoketones **43a-b**, **43h**, and **43i** in similar yields (Table 5, entries 7-10).

We further investigated the coupling reaction of disubstituted α-diazoketone **43e** with both cyclic boronic acids **46d** and **46e** (Scheme 25). In these cases, the yields were decreased substantially. Nevertheless, the phenyl-substituted cyclic allylboronic acid **46e** provided the product **44w** in a higher diastereomeric ratio (12:1, Scheme 25B) than that for ester-substituted cyclic allylboronic acid **46d** (4.8:1, Scheme 25A).

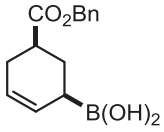
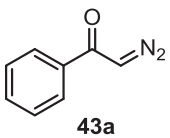
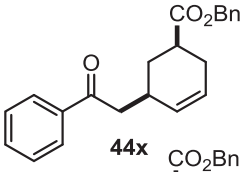
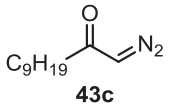
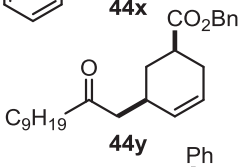
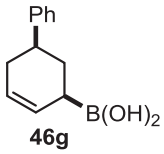
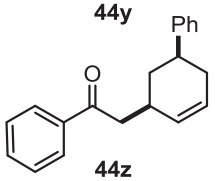


Scheme 25. Diastereoselective cross-coupling reactions of stereodefined cyclic allylboronic acids **46d** and **46e** with disubstituted α-diazoketone **43e**.

Cyclic *cis*-allylboronic acids **46f** and **46g** could also react with α-diazoketones in the presence of CuTC. All the reactions provided the products with retention of the relative configuration. However, the yields and diastereoselectivities are lower than those for the corresponding *trans*-diastereomers **46d-e**. For example, cyclic *trans*-allylboronic acid **46d** reacted with α-diazoketone **43a** to give the product **44l** in 82% yield and 19:1 d.r. (Table 5, entry 1), while the reaction of *cis*-substrate **46f** and **43a** provided **44x** in 41% yield and 5:1

d.r. (Table 6, entry 1) under the same conditions. The reaction of aliphatic diazoketone **43c** with **46f** also proceeded slower than with **46d** (Table 6, entry 2). Only 45% yield was obtained even though an excess of **46f** was used to minimize the side reactions. When 5-phenyl cyclic *cis*-allylboronic acid **46g** was employed, the reaction gave the *cis*-product **44z** with d.r. 3:1. For this process, extended time (overnight) was needed to get an acceptable yield (Table 6, entry 3).

Table 6. Stereoselective cross-coupling of cyclic *cis*-allylboronic acids and α-diazoketones.[a]

entry	boronic acid	α-diazoketone	product	yield	d.r.[b]
1	 **46f** d.r. = 4:1	 **43a**	 **44x**	41%	5:1
2[c]	**46f** d.r. = 5.5:1	 **43c**	 **44y**	45%	4:1
3[d]	 **46g** d.r. = 4.5:1	**43a**	 **44z**	69%	3:1

[a]Unless otherwise stated a mixture of **46** (0.12 mmol), **43** (0.10 mmol), and CuTC (20 mol %) in CH_2Cl_2 (5 mL) was stirred at rt for 4 h. [b]The diastereomeric ratio (d.r.) values of **44** were determined by ^1H NMR analysis of the crude reaction mixture. [c]0.1 mmol of **43c** and 0.2 mmol of **46f** were used. [d]The reaction was stirred overnight.

2.3.2.3 Assignment of the stereochemistry of **44l** and **44x**

The structures of compounds **44l** and **44x** were confirmed by ^1H, ^{13}C, COSY, HSQC NMR spectroscopy, and HRMS. The stereochemistry of the two compounds (Figure 1) was determined by analysis of their ^1H NMR spectra. In compound **44x**, the coupling pattern of Hb (δ 1.38) is (td, $J_{Hb\text{-}Hc} = J_{Hb\text{-}Ha} =$ 12.6 Hz, $J_{Hb\text{-}Hd} = 10.8$ Hz). This suggests a pseudoaxial position of both Ha and Hd. Thus the two functional groups COOBn and CH_2COPh are in pseudo-equatorial positions. This means that the relative configuration of these two groups is *cis*. On the other hand, in compound **44l**, the coupling pattern of Hb (δ 1.96) is (ddd, $J_{Hb'\text{-}Hc'} = 13.3$ Hz, $J_{Hb'\text{-}Ha'} = 10.3$ Hz, $J_{Hb'\text{-}Hd'} = 5.8$ Hz), and Hc (δ 1.84) is (ddd, $J_{Hb'\text{-}Hc'} = 13.3$ Hz, $J_{Hb'\text{-}Ha'(\text{or Hd'})} = 4.2$ Hz, $J_{Hb'\text{-}Hd'(\text{or Ha'})} = 3.4$ Hz). This indicates that Ha' is in pseudoaxial position and Hd is in pseudoequatorial position. Therefore the relative configuration of the two functional groups COOBn and CH_2COPh is *trans*.

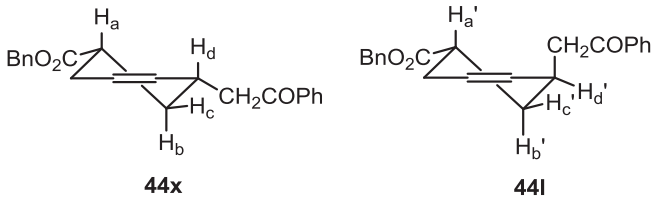
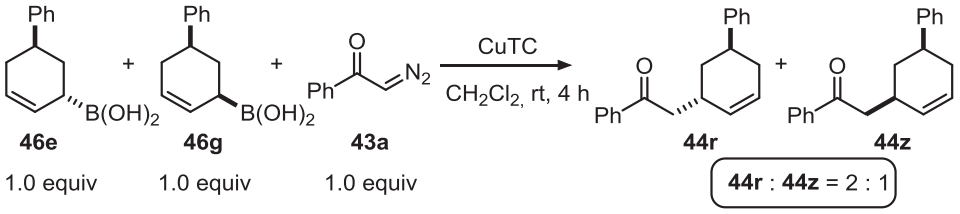


Figure 1. Stereochemistry of **44l** and **44x**.

2.3.3 Experimental mechanistic studies

2.3.3.1 Effects of the substituents in the cyclic allylboronic acids

The cross-coupling reactions of both cyclic *trans*- and *cis*-allylboronic acids afforded products with retention of the relative configuration. However, the reactivities and selectivities are different. To investigate the difference between the two substrates, a competitive reaction using a 1:1:1 ratio of cyclic *cis*-, *trans*-allylboronic acids (**46e**, **46g**), and α-diazoketone **43a** was conducted (Scheme 26). Twice as much of **44r** was obtained as of **44z**, indicating that the t*rans*-substrate **46e** gives the corresponding *trans*-product **44r** more preferably than the *cis*-substrate **46g** giving **44z**. Apparently, the relative configuration of the 5-substituent has a considerable effect on the reactivity. This also explains our finding that diastereomeric ratio of products is higher than the substrate in the reaction of cyclic *trans*-allylboronic acids.

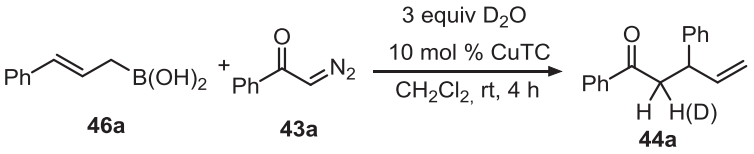


Scheme 26. Competitive reaction of cyclic *cis*-, and *trans*-allylboronic acids with α-diazoketone **43a.**

2.3.3.2 The proton source of the cross-coupling

Probably in the last reaction step (see section 2.4 below), an external hydrogen was introduced into the coupling product. To explore the origin of this hydrogen atom, we carried out deuterium labeling experiments (Scheme 27). The reaction was performed under usual conditions with addition of 3 equiv D_2O. From the ^1H NMR analysis, we found 20% deuterium uptake at the $COCH_2$ group of **44a**. This indicates that a protonation step is involved in the cross-coupling reactions. Solvent (CH_2Cl_2) as the proton source was excluded by performing the reaction in CD_2Cl_2, which gave no deuterium-containing product. Another possible proton source is the $B(OH)_2$ group. It is well

documented that cinnamylboronic acid **46a** can form boroxine under dry conditions by releasing water.[51] Thus a possible proton source is the water generated in situ from the formation of boroxine.



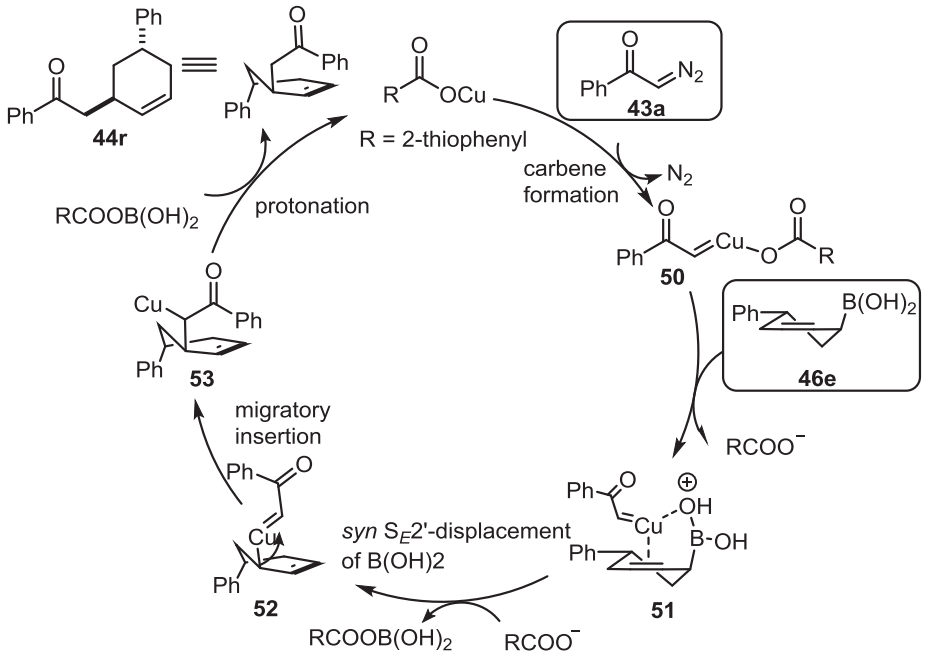
46a **43a** **44a**

Scheme 27. Deuterium labeling experiment using 3 equiv of D_2O**.**

2.4 Proposed mechanism of the Cu-catalyzed cross-coupling

The Cu-catalyzed cross-coupling reaction proceeds with high γ-regioselectivity. When stereodefined cyclic allylboronic acids were used, the relative configuration of the cyclic structure was retained after the reaction, indicating that the reaction proceeds via a *syn* displacement of the $B(OH)_2$ group. Based on these results, together with the finding from the deuterium isotope labeling experiment, we propose the mechanism for the copper-catalyzed cross-coupling reaction of allylboronic acids and α-diazoketones. The reaction of substrates **43a** and **46e** is used as a model reaction to illustrate the reaction pathway (Scheme 28). The reaction most probably initiates with the formation of a Cu-carbene species from the reaction of CuTC and α-diazoketone **43a**. Lacour and coworkers[56] have shown that CuTC is a particularly useful source of copper for decomposition of diazo reagents. In the next reaction step transmetalation of the Cu-carbene species **50** with allylboronic acid **46e** takes place. The transmetallation step is probably promoted by coordination of one of the hydroxy groups of the $B(OH)_2$ group to copper (as in **51**). In a recent mechanistic study of the Suzuki-Miyaura coupling, Denmark and coworkers have pointed out the importance of the M-O-B(OH)n (M = metal) linkage formation between the boronic acid and metal complex.[11c] This step follows a *syn*-S_E2' mechanism, which determines the regioselectivity and the stereoselectivity of the process. A plausible explanation for the lower reactivity of the 5-substituted cyclic *cis*-allylboronic acids (such as **46f** and **46g**) is that the steric hindrance of the *cis* substituent at the 5-carbon does not favor the *syn* transmetalation. A similar mechanism has been suggested for the palladium-catalyzed cross-coupling of allylboronates and electrophiles by Crudden,[21] Aggarwal,[21] and Morken[22] (Section 1.1.1). The transmetalation is probably followed by migratory insertion of the Cu-carbene species **52** to form intermediate **53**. As mentioned in Section 1.1.4, this migratory insertion process is quite general with many organic moieties including allyl group.[30a] In

the last step, the intermediate **53** undergoes proto-decupration and affords the final product **44r**.



Scheme 28. Proposed mechanism for the copper-catalyzed cross-coupling of cyclic *trans*-allylboronic acid **46e** with α-diazoketone **43a**.

2.5 Summary of the Cu-catalyzed cross-coupling reaction

We have presented a new cross-coupling reaction of diazoketones with allylboronic acids catalyzed by Cu. The reaction was performed under mild conditions without any oxidant, giving branched products with clean γ-regioselectivity. The scope of this reaction is broad on both substrates. When stereodefined cyclic allylboronic acids were used, the reactions proceeded with retention of the relative configuration. This is probably due to *syn*-S_E2' transmetalation of the allylboronic acids with the Cu-carbene complex. This highly regioselective and stereoselective reaction extends the synthesis applications of the allylboron species. It also provides a complementary method to the synthesis of functionalized alkenes by cross-coupling reaction with C(sp^3)-C(sp^3) bond formation.

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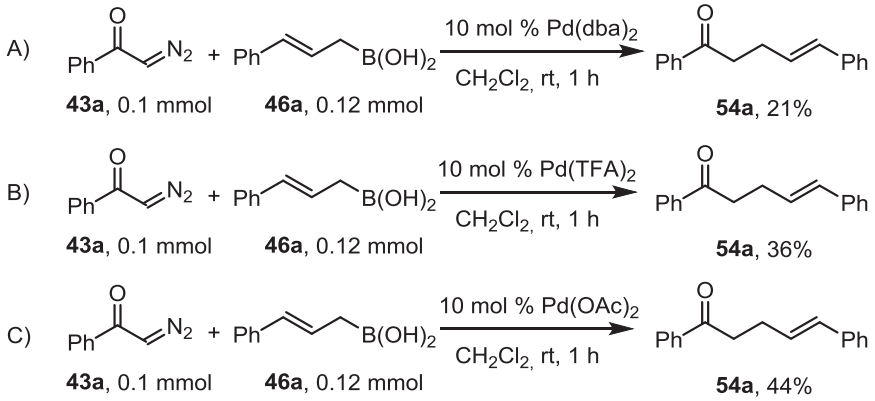
3. Palladium-catalyzed cross-coupling of α-diazoketones and allylboronic acids (Paper III)

As we have shown that copper-catalyzed reactions can be used for the cross-coupling of allylboronic acids and α-diazoketones to afford branched allylic products (Chapter 2). In this chapter, we focus on the palladium-catalyzed version of this reaction. Palladium is an efficient catalyst for the cross-coupling reactions between diazo compounds and coupling components such as aryl/vinyl/allyl halides, terminal alkenes, and alkynes (Section 1.1.4).[30a, 37a, c] Wang and coworkers reported palladium-catalyzed coupling of aryl- and alkenylboronic acids with diazo compounds (Section 1.1.4).[37b, f, 38] As far as we know, allylboron species have never been used be as organoboron reagent in palladium-catalyzed reactions with diazo compound substrates.

3.1 Development of the Pd-catalyzed cross-coupling reaction and its regioselectivity



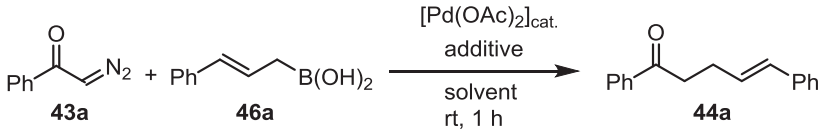
Scheme 29. Catalyst screening for the α-regioselective cross-coupling of allylboronic acids and α-diazoketones.

As mentioned above (Section 2.1), when the reaction of allylboronic acids **46a** and α-diazoketones **43a** was performed in the presence of $Pd(PPh_3)_4$, no coupling products were observed. Then we changed the catalyst to $Pd(dba)_2$ and found that a linear product **54a** was formed in 21% (Scheme 29A) yield. Pd

(II) species such as $Pd(TFA)_2$ and $Pd(OAc)_2$ can also catalyze the process and gave promising yields (Scheme 29B and C). $Pd(OAc)_2$ was the most efficient one. These results encouraged us to optimize the reaction conditions further.

Using excess of α-diazoketone led to an increase of the yield of **44a** (Table 7, entry 1). Therefore, we applied this condition in the further investigations. We tried the reactions in different solvents, such as toluene and CH_3CN (Table 7, entries 2-3). The yields of the product **44a** were sharply dropped in both cases, showing these two solvents are not suitable for the cross-coupling reaction.

Table 7. Optimization of conditions for the cross-coupling reaction of allylboronic acid **46a** and α-diazoketone **43a** using $Pd(OAc)_2$ as the catalyst.[a]

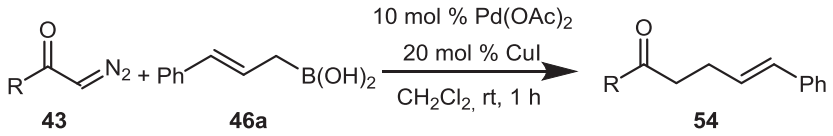


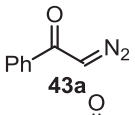
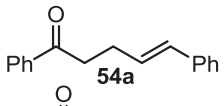
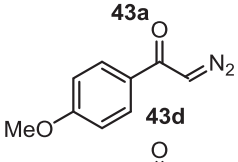
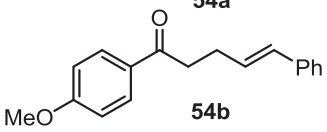
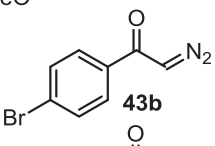
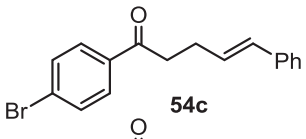
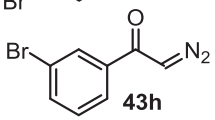
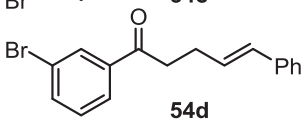
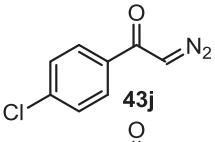
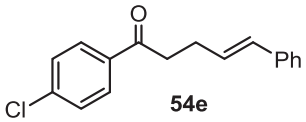
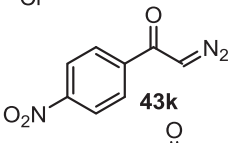
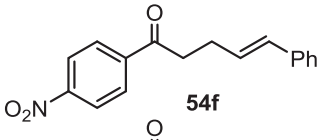
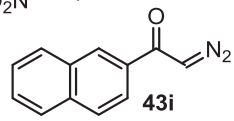
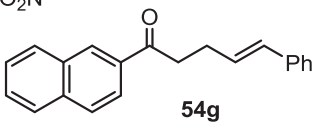
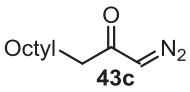
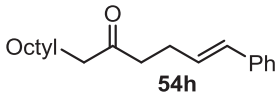
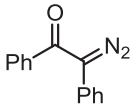
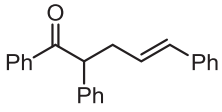
entry	solvent	additive	yield (%)
1	CH_2Cl_2	-	51
2	toluene	-	18
3	CH_3CN	-	6
4	CH_2Cl_2	CuI	60
5	CH_2Cl_2	$CuI{\cdot}Me_2S$	0
6	CH_2Cl_2	CuOAc	0
7	CH_2Cl_2	CuBr	50
8	CH_2Cl_2	CuCl	41
9[b]	CH_2Cl_2	CuI	70

[a]Unless otherwise stated a mixture of **43a** (0.12 mmol), **46a** (0.10 mmol), $Pd(OAc)_2$ catalyst (10 mol %) and the additive (20 mol %) in CH_2Cl_2 (0.5 mL) was stirred at rt for 1 h. [b]**43a** was added in two portions.

Then, we found that the yield can be improved by the addition of 20 mol % of CuI (Table 7, entry 4). Other Cu salts such as CuBr and CuCl were not as efficient as CuI, while $CuI{\cdot}SMe_2$ and CuOAc completely suppressed the formation of the coupling product **44a** (Table 7, entries 5-8). When α-diazoketone **43a** was added in two portions, the increased yield of product was achieved (Table 7, entry 9). We studied the ligand effect by using PPh_3, dppe, and 1,10-phenanthroline, but all reactions proceeded with a lower yield. Based on these results, we decided to use the conditions for the reaction of entry 9 to continue our study.

Table 8. Palladium-catalyzed cross-coupling of allylboronic acid **46a** with various α-diazoketones.[a]



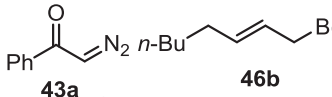
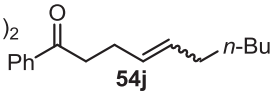
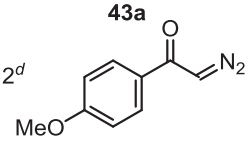
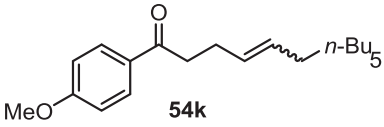
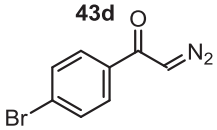
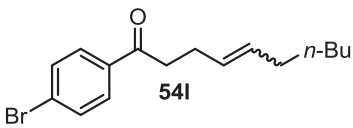
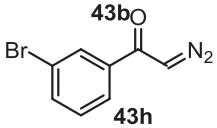
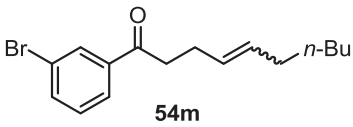
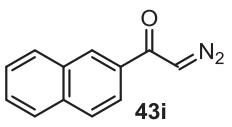
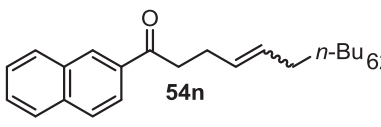
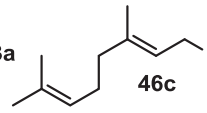
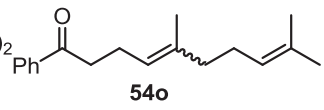
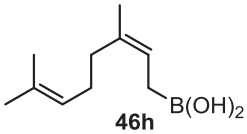
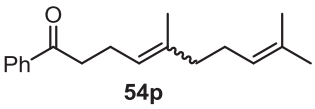
entry	α-diazoketone	product	yield (%)
1	 **43a**	 **54a**	70
2[b]	 **43d**	 **54b**	52
3	 **43b**	 **54c**	60
4	 **43h**	 **54d**	60
5	 **43j**	 **54e**	51
6[c]	 **43k**	 **54f**	53
7	 **43i**	 **54g**	64
8[c,d]	 **43c**	 **54h**	47
9[b,e]	 **43e**	 **54i**	54

[a]Unless otherwise stated a mixture of **43** (0.12 mmol, added in two portions), **46a** (0.10 mmol), $Pd(OAc)_2$ (10 mol %) and CuI (20 mol %) in CH_2Cl_2 (0.5 mL) was stirred at rt for 1 h. [b]The reaction was performed with 0.15 mmol of **43**. [c]The reaction was performed with 0.20 mmol of **43**. [d]The reaction was performed without CuI, and 1 mL of CH_2Cl_2 was used. [e]2 mL of CH_2Cl_2 was used.

Various α-diazoketones and several allylboronic acids were prepared according to the literature and then employed in cross-coupling reactions. Aro-

matic substituted α-diazoketones bearing either electron withdrawing or donating substituents could react with cinnamylboronic acid **46a** in the presence of $Pd(OAc)_2$ (Table 8, entries 2-7). In some cases, for example, when *p*-methoxyphenyl (**43d**) and *p*-nitrophenyl (**43k**) α-diazoketones were used, an excess of the diazoketone substrate had to be employed to get acceptable yields (Table 8, entries 2 and 6). Aliphatic α-diazoketone **43c** is also a suitable coupling partner under modified conditions (Table 8, entry 8). Even disubstituted α-diazoketone **43e** was able to react with cinnamylboronic acid **46a** giving the coupling product **54i** with an acceptable yield of 54% (Table 8, entry 9). All the above-described reactions provided linear products with *E* configuration for the alkene moiety.

Table 9. Palladium-catalyzed cross-coupling of allylboronic acid **46b-c** and **46h** with various α-diazoketones.[a]

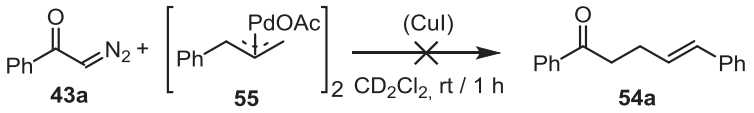
entry	α-diazoketone	boronic acid	product	yield (%)[b]	*E/Z* ratio[c]
1	 **43a**	**46b**	 **54j**	71	6.3:1
2[d]	 **43d**	 **46b**	 **54k**	51	7.1:1
3	 **43b**	 **46b**	 **54l**	68	6.0:1
4	 **43h**	 **46b**	 **54m**	64	9.1:1
5	 **43i**	 **46b**	 **54n**	62	7.0:1
6[e]	**43a**	 **46c**	 **54o**	43	1.6:1
7[e]	**43a**	 **46h**	 **54p**	57	0.9:1

[a]Unless otherwise stated a mixture of **43** (0.12 mmol), **46** (0.10 mmol), $Pd(OAc)_2$ (10 mol %) and CuI (20 mol %) in CH_2Cl_2 (0.5 mL) was stirred at rt for 1 h. [b]The product contains less than 5% of the branched product. [c]The *E/Z* ratio of **54** was determined by ^1H NMR analysis of the crude reaction mixture. [d]The reaction was performed with 0.15 mmol of **43d**. [e]The reaction was performed without CuI, and 1 mL of CH_2Cl_2 was used.

Not only cinnamylboronic acid **46a** but also alkyl-substituted allylboronic acids **46b-c** and **46h** could be used in the cross-coupling process. The reactions of octenylboronic acid **46b** and various of α-diazoketones **43a**, **b**, **d**, **h**, and **i** proceeded smoothly, providing the linear products **54j-n** as the major product. In these reactions, formation of traces (< 5%) of the branched product was observed (Table 9, entries 1-5). Moreover, both products are a mixture of *E/Z* isomers with the ratio from 6:1 to 9:1. When geranyl- (**46c**) and nerylboronic acids (**46h**) were used, the *E/Z* isomeric ratio dropped to 1.6:1 and 0.9:1 respectively, indicating a substantial isomerization of the C-C double bond occurs during the reaction. All the attempts to improve *E/Z* isomeric ratio including lowering the temperature and diluting the reaction did not work.

3.2 Mechanism of the Pd-catalyzed cross-coupling affording linear allylic products

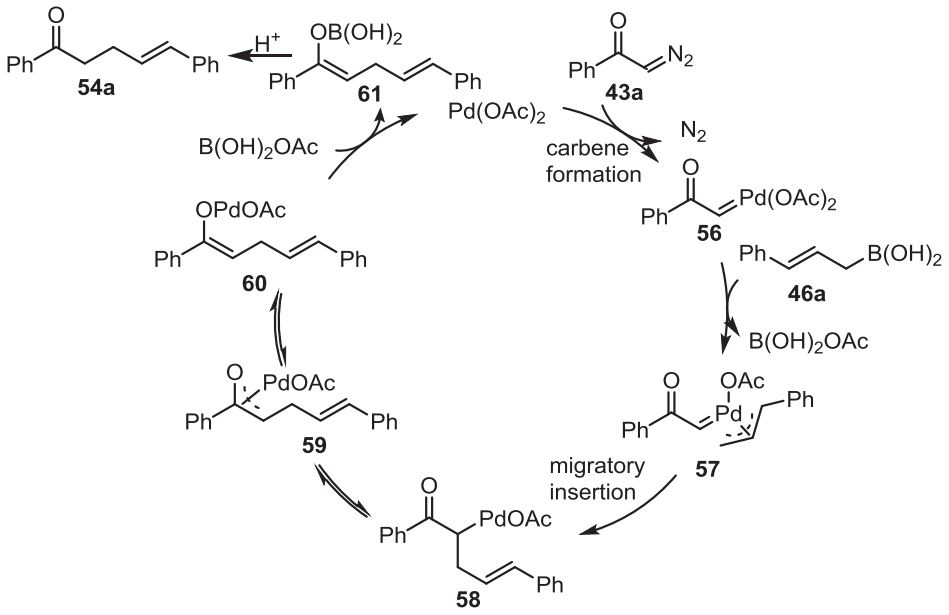
We have shown that both Cu and Pd can catalyze the cross-coupling reaction of allylboronic acids with α-diazoketones. The difference between Pd catalysis and Cu catalysis is the opposite regioselectivity. The Pd-catalyzed reactions gives linear products with high α-regioselectivity, while the Cu-catalyzed reactions proceed with γ-regioselectivity (Section 2.2). When aliphatic allylboronic acids were used in the Pd-catalyzed cross-coupling, a variation of the *E/Z* isomeric ratio of the linear allylic products was observed (Table 9). This suggests that a (η^3-allyl)palladium complex forms and undergoes η^3-η^1-η^3 isomerization.[57] Formation of traces of branched allylic product is further support for the formation of the (η^3-allyl)palladium intermediates.



Scheme 30. The reaction of (π-allyl)palladium complex **55** with α-diazoketone **43a**.

The Wang[37a] and the Gong[58] groups have shown that a (η^3-allyl)palladium intermediate is involved in the reactions of diazo compounds with allylic chlorides and other allylic species. According to our studies, the reaction of (η^3-allyl)palladium complex **55** and α-diazoketone **43a** did not provide the coupling product **54a** under the Pd-catalyzed cross-coupling conditions (Scheme 30). This finding indicates that complex **55** is not a kinetically competent intermediate in the palladium-catalyzed coupling of **43a** with **46a**. This suggests

that in the catalytic coupling reaction an (η^3-allyl)palladium carbene complex is generated from Pd-carbene and allylboronic acids.



Scheme 31. Proposed mechanism for the Pd-catalyzed cross-coupling of allylboronic acid **46a** and α-diazoketone **43a.**

Combining the above results and literature data, we propose the mechanism in Scheme 31. The catalytic cycle begins with the formation of Pd-carbene **56** from $Pd(OAc)_2$ and α-diazoketone **43a**. Pd-carbene species have been suggested in many related Pd-catalyzed transformations of diazo compounds.[30a, 59] The following step is the transmetallation of the Pd-carbene and allylboronic acid **46a** to form the (η^3-allyl)Pd-carbene intermediate **57**. Formation of similar (η^3-allyl)Pd-carbene species is also suggested in the reactions of diazo compounds with allylic substrates by Wang[37a] and Gong[58]. As the transmetallation step can be facilitated by Cu co-catalysts,[60] the addition of CuI improves the yields. The allylic Pd-carbene complex may undergo η^3-η^1-η^3 isomerization, forming various allylpalladium intermediates.[57, 61] This isomerization may explain the variation of the *E/Z* ratio of the alkene product. The η^3-η^1-η^3 isomerization and the resulted *E/Z* ratio is influenced by the steric effects of the substituents at the γ-carbon on the allylic moiety.[61-62] For example, when cinnamylboronic acid **46a** (with bulky phenyl substituent) is used, the reactions provide the *E*-products exclusively. After formation of allylPd complex **57**, migratory insertion occurs, giving intermediate **58**. This step determines the regioselectivity of the cross-coupling reaction. It is well established that the substitution of (η^3-allyl)Pd complexes preferentially occurs at the less substituted allylic terminus.[57] This terminal attack leads to formation of a linear allylic product instead of a branched one. Then, rapid

tautomerization of **58** and palladium enolate **60** via oxa-η^3-intermediate **59** occurs,[63] thus the β-hydride elimination in **58** can be avoided. Finally, the product is released, and the Pd (II) catalyst are regenerated by hydrolysis of the Pd enolate **60**. The possible proton source could be water which is generated in situ by the formation of boroxine from the dehydration of B(OH)n (n = 2, 3) species. Since the reaction does not require an external oxidant, the coupling reaction occurs without redox reactions of palladium involving only Pd (II) species.

3.3 Summary of the Pd-catalyzed cross-coupling reaction

We have developed a new method for the Pd-catalyzed cross-coupling reaction of diazoketones and allylboronic acids. The reaction gives the linear allylic product. This is the opposite to the regioselectivity of the Cu-catalyzed cross-coupling reaction described in Chapter 2. The reaction was performed under mild conditions without using oxidant, indicating that the Pd catalyst does not undergo redox processes. Pd-catalyzed cross-coupling of diazoketones and allylboronic acids method will broaden the synthetic applications of the allylboron species in transition-metal-catalyzed cross-coupling reactions, which is suitable for constructing $C(sp^3)$-$C(sp^3)$ bonds.

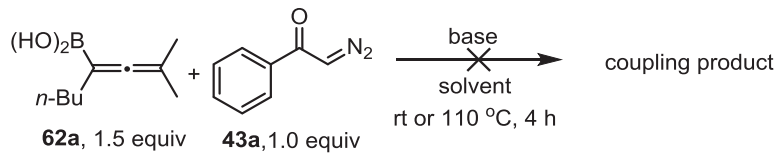
4. Transition-metal-free coupling of allenylboronic acids with in situ generated diazo compounds (Paper IV)

Allenylboron reagents have broad use in allenylation/propargylation of carbonyl compounds and imines.[28, 64] Application of these reagents in the Suzuki-Miyaura cross-coupling has also been reported (Section 1.1.3).[29] In this chapter, we present a novel cross-coupling reaction of allenylboronic acids and tosylhydrazones under transition-metal-free conditions. Although, the coupling reactions of aryl-, alkenyl-, alkylboron compounds with tosylhydrazones have been reported in the literature,[45-46, 48] cross-coupling reaction of allenylboronic acids with tosylhydrazones has not been described so far.

4.1 Development of the reductive coupling reactions involving allenylboronic acids

Diazo compounds are widely used in transition-metal-free coupling reactions with organoboron compounds (Section 1.2).[42] In many reactions, the diazo compounds are generated from bench-stable tosylhydrazone in situ.[45-46, 48] In these reactions, the tosylhydrazone precursors are heated in the presence of base (Bamford–Stevens reaction).[65]

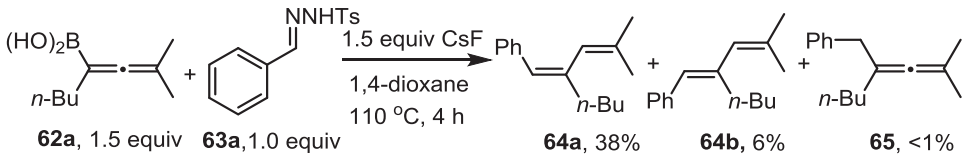
Initially, we attempted to use α-diazoketones **43a** as the coupling partner to allenylboronic acids **62a**. However, in this reaction, we did not observe formation of C-C coupling product (Scheme 32).



Scheme 32. The reaction of allenylboronic acid **62a** and α-diazoketone **43a.**

Subsequently we carried out the reaction with a reactive diazo compound, which was generated in situ from tosylhydrazone **63a** (Scheme 33) in the presence of CsF (1.5 equiv CsF at 110 °C, Scheme 33).[66] This reaction of **63a**, CsF and allenylboronic acid **62a** afforded conjugated diene **64a** as the major

product (Scheme 33). In addition, **64b** (6%) and trace amount of allene **65** was also detected by GC-MS.



Scheme 33. The reaction of allenylboronic acid and tosylhydrazone in the presence of CsF. GC-MS yields using benzyl acetate as the internal standard.

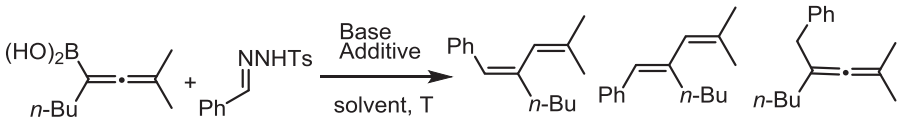
4.1.1 Optimization of the reaction conditions

Initially, we studied the effect of the applied base on the outcome of the reaction (Table 10, entries 2-9). When Bu_4NF was used instead of CsF, the yield of **64a** was unchanged, while the formation of isomeric diene product **64b** was dramatically decreased and increased amount of allene **65** (6%) was observed. Organic bases, such as Et_3N and DBU, could also be used to for the coupling reaction of allenylboronic acid **62a** and **63a** (Table 10, entries 3-4). However, the use of Et_3N led to formation of **64a** in low yield (19%) and selectivity. The use of DBU led to an increased yield, albeit with the formation of a considerable amount of the allene product **65**. Stronger inorganic bases such as NaOMe and KOH were not suitable to improve the yield of products (Table 10, entries 5-6). One of the reasons is the faster protodeboronation of compound **62a** under strongly basic conditions. Indeed we observed an increased formation of side-products arising from **62a** in the case of using strong bases. When Na_2CO_3 was used, we did not detect any formation of **64a** (Table 10, entry 7). However, application of Cs_2CO_3 (Table 10, entry 8) and K_2CO_3 (Table 10, entry 9) improved the yield and selectivity of the reaction. We attempted to decrease the reaction temperature from 110 to 80 °C. A significant decrease of the yield of **64a** was observed, indicating the importance of high temperature for the efficiency of this reaction (Table 10, entry 10). Replacing the solvent of 1,4-dioxane with toluene did not alter the reaction outcome (Table 10, compare entries 9 and 11).

When the K_2CO_3 loading was increased to 3 equiv, the yield of **64a** was improved to 55% (Table 10, entry 12). The use of a small amount of H_2O (10 equiv) further improved the yield of **64a** to 64% (Table 10, entry 13). This is probably due to increased solubility of K_2CO_3 in dioxane. Notably, only a trace amounts of byproducts **64b** and **65** were detected under these conditions (Table 10, entry 13). The use of CsF, together with K_2CO_3 (suggested by Valdés and coworkers[46b]) led to a similar result (Table 10, compare entries 12, 13 and 14). A further improvement of the yield of **64a** could be achieved by using a combination of CsF, K_2CO_3, and a small amount of water (Table 10, compare entries 14 and entry 15). Moreover, the reaction could be furnished in

half an hour with the formation of a single diastereomer of **64a** in 88% together with a small amount of the allene product **65** (Table 10, entry 16).

Table 10. Screening of the conditions for the transition-metal-free cross-coupling reaction of allenylboronic acid **62a** and α-diazoketone **63a**.



62a **63a** **64a** **64b** **65**

entry	base	solvent	additive	temp (°C)	**64a**[b]	**64b**[b]	**65**[b]
1	CsF	1,4-dioxane	-	110	38	6	<1
2	Bu_4NF	1,4-dioxane	-	110	37	<1	6
3	Et_3N	1,4-dioxane	-	110	19	6	<1
4	DBU	1,4-dioxane	-	110	67	3	13
5	NaOMe	1,4-dioxane	-	110	18	4	2
6	KOH	1,4-dioxane	-	110	20	<1	1
7	Na_2CO_3	1,4-dioxane	-	110	<1	nd	nd
8	Cs_2CO_3	1,4-dioxane	-	110	45	2	2
9	K_2CO_3	1,4-dioxane	-	110	49	7	<1
10	K_2CO_3	1,4-dioxane	-	80	16	<1	<1
11	K_2CO_3	toluene	-	110	48	4	<1
12[c]	K_2CO_3	1,4-dioxane	-	110	55	4	2
13[c]	K_2CO_3	1,4-dioxane	10 equiv H_2O	110	64	1	2
14[c]	K_2CO_3	1,4-dioxane	1.5 equiv CsF	110	68	3	<1
15[c]	K_2CO_3	1,4-dioxane	1.5 equiv CsF 10 equiv H_2O	110	84	2	3
16[c,d]	K_2CO_3	1,4-dioxane	1.5 equiv CsF 10 equiv H_2O	110	88	<1	5

[a]In a typical reaction 0.1 mmol tosylhydrazone **63a**, 0.15 mmol allenylboronic acid **62a**, 1.5 equiv of base, 0.5 mL solvent, 4 h. [b]The yield was determined by GC-MS using benzyl acetate as an internal standard. [c]The reactions were performed with 3.0 equiv of K_2CO_3. [d]The reaction time was 0.5 h. (nd = not detected).

4.1.2 Assignment of the double bond geometry of the major product

Compound **64a** was isolated from the crude reaction mixture by column chromatography as a colorless oil. The connectivity of **64a** (Figure 2) was determined by its ^1H, ^{13}C, and COSY NMR spectra. The NOEDIFF technique

was used to determine the double bond (C1=C2) geometry. As illustrated in Figure 2A, when proton H_a at 6.23 ppm was irradiated, 7% NOE was generated at the H_b protons (at 2.20 ppm). This indicates *Z* configuration of H_a and the butyl group (with H_b protons) over the C1=C2 double bond. Furthermore, in another NOEDIFF experiment (Figure 2B), irradiation of the H_c proton (at 5.75 ppm) was performed and subsequently 3% NOE was generated at the ortho protons of the aromatic ring (H_d). This indicates that the phenyl group (with H_d ortho protons) and the alkenyl group (with H_c) are also in *Z* configuration over the C1=C2 double bond. Therefore the double bond geometry was determined as *Z*. Considering the spectral similarities in the diene products, the stereochemistry of dienes **64c-k** and **64m-o** were also assigned as *Z*.

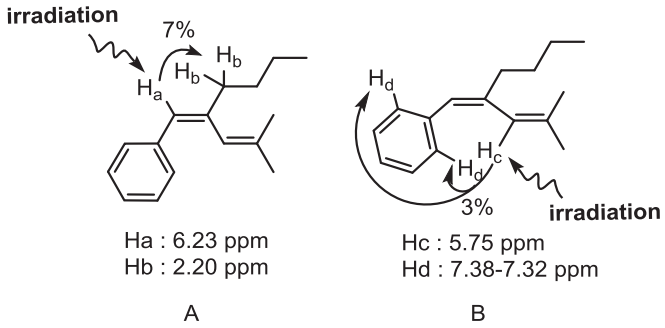
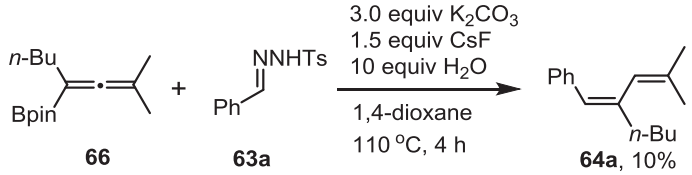


Figure 2. Stereochemistry of **64a** determined by NOEDIFF experiments.

4.1.3 Reaction with allenylboronic pinacol ester (allenyl-Bpin)

To compare the reactivity of allenylboronic acids, such as **62a** with their ester derivatives **66**, the reaction of allenyl-Bpin **66** and tosylhydrazone **63a** was performed under the optimal conditions described in Section 4.1.1 (Scheme 34). After reaction and purification, product **64a** was isolated in 10% yield. This indicates that allenyl-Bpin **66** was less reactive than the corresponding allenylboronic acid **62a** (in 80% yield) under the metal-free conditions. These results are also in accordance with the findings reported by Wang and coworkers for analog reactions.[44] These authors found that phenyl-Bpin was much less efficient than phenylboronic acid (or boroxine) in the cross-coupling reactions with diazo compounds. The reasons for the different reactivity of allenylboronic acids and their Bpin esters are given below in the mechanistic part (Section 4.2).

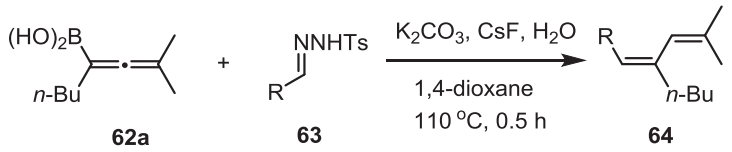


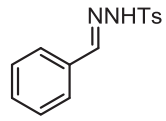
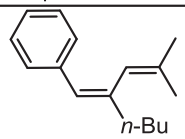
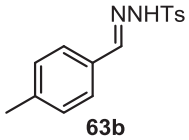
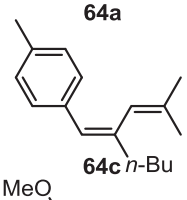
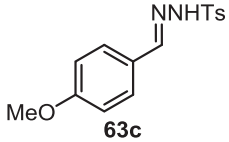
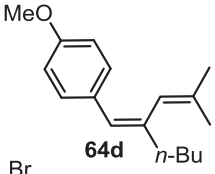
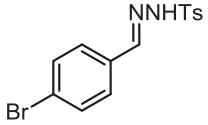
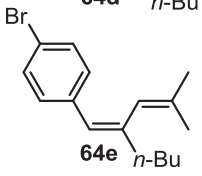
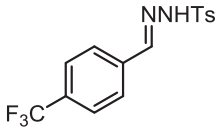
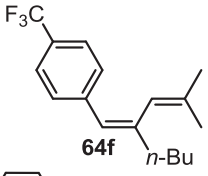
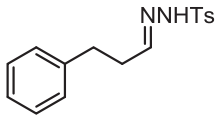
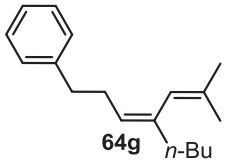
Scheme 34. The reactions of allenyl-Bpin **66** and tosylhydrazone **63a**.

4.1.4 Scope of the coupling of allenylboronic acids

Initially, we performed the reactions with allenylboronic acid **62a** and various tosylhydrazones **63a-f** under the above-optimized conditions (Table 11, entries 1-6). The reaction of **62a** and **63a** gave *Z*-1,3-diene **64a** in 80% isolated yield after purification by chromatography (Table 11, entry 1). When the

Table 11. Substrate scope of the aldimine-type tosylhydrazones.



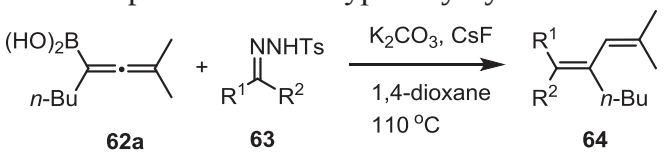
entry	tosylhydrazones	products	yield (%)
1	 **63a**	 **64a**	80 (65[b])
2	 **63b**	 **64c**	70
3	 **63c**	 **64d**	56
4	 **63d**	 **64e**	77
5	 **63e**	 **64f**	68
6[c]	 **63f**	 **64g**	55

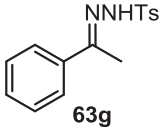
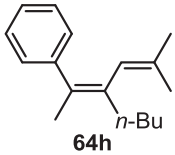
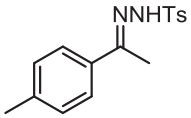
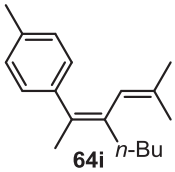
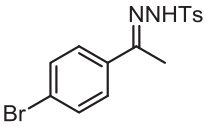
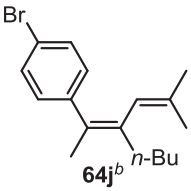
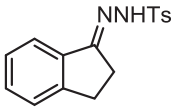
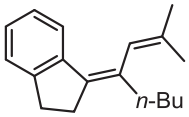
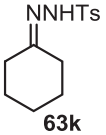
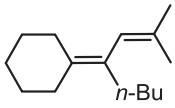
[a]Unless otherwise stated, 0.1 mmol tosylhydrazone **63**, 0.15 mmol boronic acid **62a**, 0.3 mmol K_2CO_3, 0.15 mmol CsF, 1 mmol H_2O and 0.5 mL 1,4-dioxane, 110 °C were used for the reaction; all the reactions gave *E*-product and allene product with an overall yield less than 10% and these minor products were separated from the crude product by silica gel chromatography. [b]Performed at 1 mmol reaction scale. [c]Performed at 100 °C; 13% of the *E* diastereomer was separated.

tosylhydrazone substrate **63b-c** with electron donating substituent was used, the coupling reaction gave lower yield than with **63a**. For example, the reaction of tosylhydrazone substrate **63b** bearing a tolyl group afforded the diene product **64c** in 70% yield. Replacing the tolyl with an anisyl group (**63c**) in the tosylhydrazone led to a further decrease of the yield of (56%) **64d**. In contrast, the reactions of tosylhydrazones bearing electron withdrawing groups (**63d-e**) proceeded with improved yields (Table 11, entries 4-5). Not only aromatic but even aliphatic aldehyde-based tosylhydrazones could be reacted with allenylboronic acids. For example, when **63f** was used as the substrate, the reaction afforded *Z*-diene **64g** in 55% yield (Table 11, entry 6).

Subsequently, we investigated the reaction of ketone-based tosylhydrazones **63g-k** with allenylboronic acid **62a** (Table 12). When **63g** was used as the substrate, the reaction time was extended to 2 h to get full conversion of the starting materials. We found that the use of water had a deleterious effect on the reaction. Therefore, we conducted the coupling reaction of **62a** and **63g** in the absence of water (Table 12, entry 1). The reactions of ketimine-type substrates **63h-k** and allenylboronic acid **62a** were conducted under similar conditions with different reaction times. Most of the reactions could furnish the corresponding *Z*-1,3-dienes in good yield (up to 70%; Table 12, entries 2-4). In the case of product **64j**, a small amount of *E*-diastereomer (7%) was also formed, which could not be removed by column chromatography. Notably, aromatic cyclic ketimine-type **63j** was also a suitable substrate for this reaction, affording pentasubstituted diene **64k** in good yield (63%, Table 12, entry 4). The aliphatic cyclic ketimine-type substrate **63k** showed a lower reactivity in this coupling reaction. The best result for formation of **64l** (35%) was obtained by reacting **63k** with 3 equivalents of **62a** for 2 hours (Table 12, entry 5).

Table 12. Substrate scope of ketimine-type tosylhydrazones.



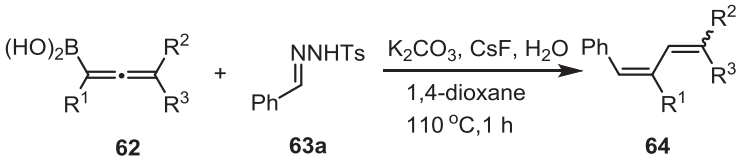
entry	tosylhydrazones	products	time (h)	yield (%)
1	 **63g**	 **64h**	2	64
2	 **63h**	 **64i**	1	65
3	 **63i**	 **64j**[b]	1	70
4	 **63j**	 **64k**	1	63
5[c]	 **63k**	 **64l**	2	35

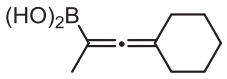
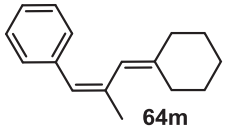
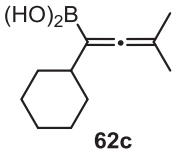
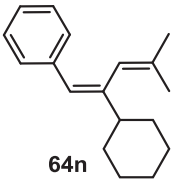
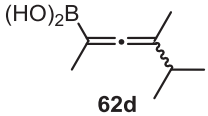
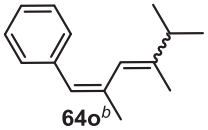
[a]Unless otherwise stated, 0.1 mmol tosylhydrazone **63**, 0.15 mmol boronic acid **62a**, 0.3 mmol K_2CO_3, 0.15 mmol CsF and 0.5 mL 1,4-dioxane, 110 °C were used for the reaction; all the reactions gave *E*-product and allene product with an overall yield less than 10% and these minor products were separated from the crude product by silica gel chromatography. [b]The product was contaminated with 7% of the *E* diastereomer. [c]Performed with 10 equiv of H_2O and 3 equiv of boronic acid.

Next, we examined the reactivity of several allenylboronic acids (**62b-d**) with tosylhydrazone **63a** (Table 13). When cyclohexane-containing allenylboronic acids **62b** and **62c** were used as the substrates, both reactions proceeded smoothly, furnishing the corresponding *Z*-1,3-dienes in up to 69% yield (Table 13, entries 2-3). The reaction of racemic allenylboronic acid **62d** and tosylhydrazone **63a** was also studied. After purification, we obtained the product **64o** as an (inseparable) mixture of isomeric dienes in 59% yield (Table 13, entries 3).

The reaction could also be scaled-up using 1 mmol of **63a** and 1.5 mmol of **62a** giving the product **64a** in 65% yield. (Table 11, entry 1).

Table 13. Substrate scope of allenylboronic acids.

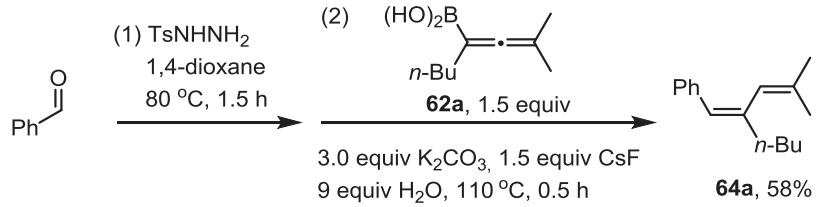


entry	allenylboronic acid	products	yield (%)
1	 **62b**	 **64m**	52
2	 **62c**	 **64n**	69
3	 **62d**	 **64o**[b]	59

[a]Unless otherwise stated, 0.1 mmol tosylhydrazone **63a**, 0.15 mmol boronic acid **62**, 0.3 mmol K_2CO_3, 0.15 mmol CsF, 1 mmol H_2O and 0.5 mL 1,4-dioxane, 110 °C were used for the reaction; all the reactions gave *E*-product and allene product with an overall yield less than 10% and these minor products were separated from the crude product by silica gel chromatography. [b] The product is a mixture of *Z/E* diastereomers (C3-C4) in a 1:1 ratio.

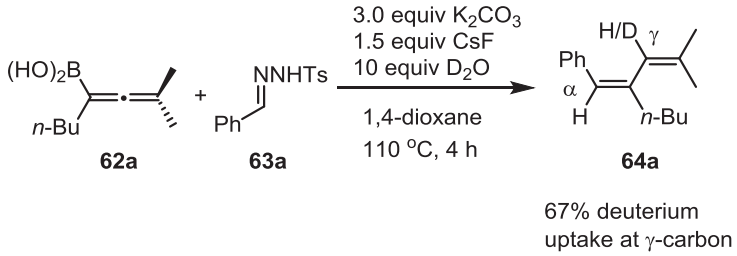
4.1.5 One-pot approach

A one-pot version of the coupling of carbonyl compounds and arylboronic acids in the presence of tosyl-hydrazine were reported by Barluenga and Valdés.[45] In the reaction, the requisite tosylhydrazone is generated in situ from the reaction of the tosyl-hydrazine and the carbonyl compound. Similarly, we tried the one-pot reductive coupling of allenylboronic acid **62a** with benzaldehyde in the presence of tosyl-hydrazine (Scheme 35). This reaction afforded 1,3-diene **64a** in 58% yield.



Scheme 35. One-pot reductive coupling of allenylboronic acid and benzaldehyde.

4.1.6 Deuterium labeling experiment



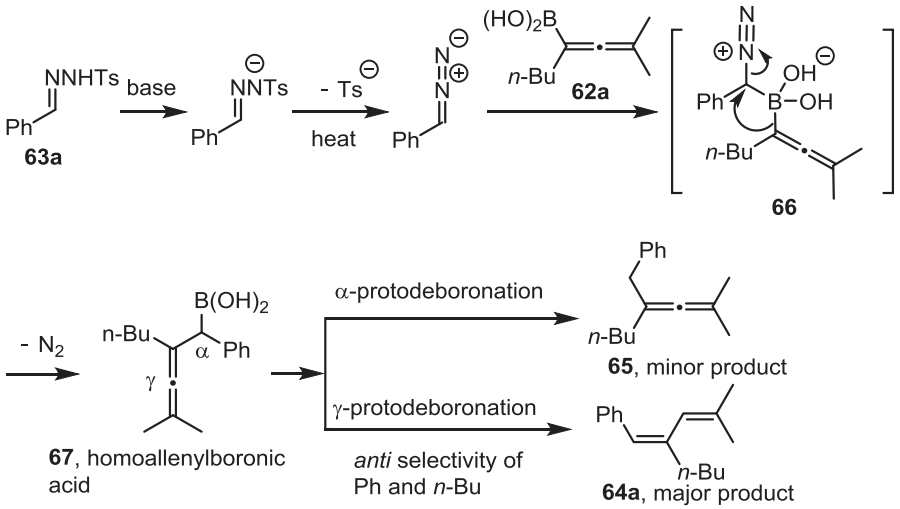
Scheme 36. Deuterium labeling experiment using D_2O**.**

To gain more insight into the reaction mechanism, a deuterium labeling experiment was performed with **62a** and **63a** in the presence of D_2O under the optimal condition of the coupling reaction (Scheme 36). Based on the analysis of the ^1H NMR spectrum a deuterium uptake of 67% at the γ position of **64a** was found. The deuterium uptake indicates that a γ-protonation step is involved in the cross-coupling reaction (see Section 4.2 below).

4.2 Proposed mechanism

Based on our results and related reductive coupling processes of tosylhydrazones and aryl, alkenylboronic acids, we propose a mechanism for the reaction of allenylboronic acids and tosylhydrazones in Scheme 37. For sake of clarity the reaction of **62a** and **63a** was selected to describe the mechanistic aspects. The first step is formation of the diazo compound from its precursor, tosylhydrazone **63a**, in the presence of base with heating. The diazo compound and **62a** form an "ate" complex **66.** The next step is 1,2-shift of the allenyl group to the geminal carbon and simultaneous extrusion of the dinitrogen. According to the DFT studies for related substrates by Valdés and coworkers, this asynchronous concerted process may proceed via a cyclic transition state. By this 1,2-shift of the allenyl group, homoallenylboronic acid

67 is generated. Ley[67] and Pastre[68] reported an analog reaction based on coupling of diazo compound, TMS-CHN_2 with vinylboronic acids. This reaction resulted in allylboronic acids, which were intercepted with aldehydes and indoles affording homoallyl alcohols and amines. We have also attempted to trap **67** by adding various electrophiles (i.e., benzaldehyde and indole) in situ to the reaction mixture but formation of addition products were not observed. According to the deuterium experiments (Scheme 36 in Section 4.1.5), a protonation step was involved in the coupling reaction. Based on the above results (Section 4.1.3 and Scheme 36), we propose γ-protodeboronation of **67** to give the final product **64a**. Formation of the allene byproduct **65** can be explained by the less favoured α-protodeboronation of **67**.



Scheme 37. The proposed mechanism of the reductive coupling reaction of allenylboronic acid **62a** and tosylhydrazone **63a**.

4.3 Summary

In summary, we have described a general method for the selective synthesis of the densely substituted 1,3-conjugated dienes with high *Z* selectivity. The reaction represents the first transition-metal-free reductive coupling of allenylboronic acids and tosylhydrazones. The reaction can be conducted via an operationally simple procedure using readily available starting materials. The key step of the coupling process probably involves the 1,2-shift of the allenyl group from boron to the diazocarbon atom.

5. Allylation of quinones with allylboronates (Paper V)

Quinones are prevalent and essential compounds in nature, particularly in living organisms, and in several fields of science and technology.[69] For example, ubiquinone, also known as Coenzyme Q10, plays a critical role in aerobic cellular respiration (Figure 3).

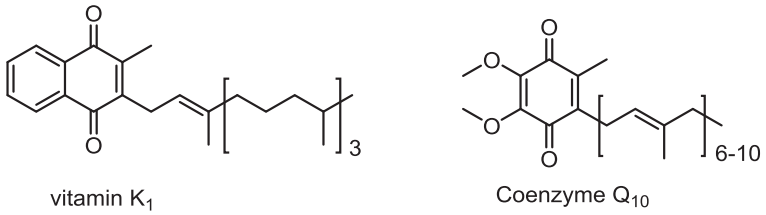


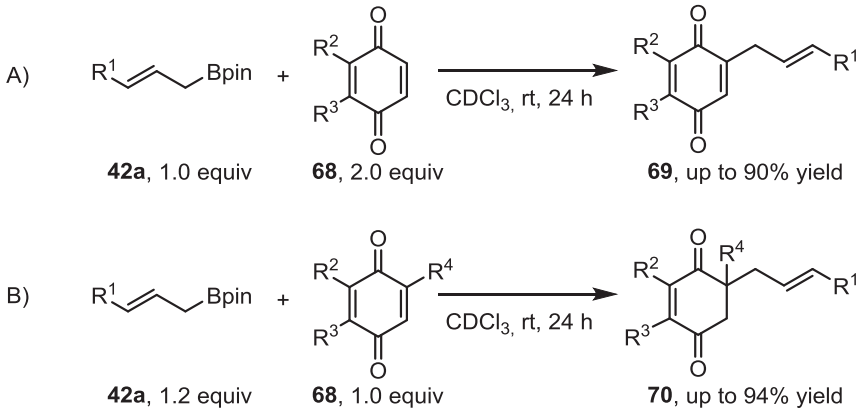
Figure 3. Examples of important quinones.

Despite the importance of quinone derivatives, methods to access these molecules are limited. Direct functionalization of quinones is an important methodology for the synthesis of densely substituted derivatives. Among those methods, direct allylation of quinones using allylating reagents such as allylstannane,[70] allylnickel,[71] allyltrifluorosilane,[72] and allylindium[73] have been studied. The allylation reactions usually suffer from drawbacks such as low selectivity and the use of toxic instable allylmetal reagents. Allylboronates have been widely used in stereocontrolled carbon-carbon bond formation reactions (Section 1.1).[74] However, there are few reports on the allylation of quinones using allylboronates regents, except a single example of using farnesyl-Bpin, in which transformation of this allyl-Bpin to farnesyl-BF_3K before the reaction is necessary.[75]

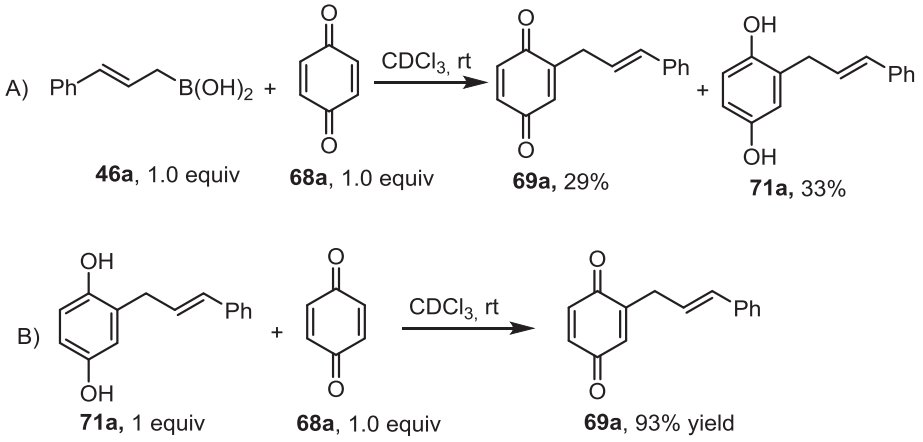
5.1 Scope of the allylation of quinones

Allyl-Bpin compounds were readily prepared from commercially available allylic alcohols[24e] which were then employed to study the allylation reaction of quinones using allylboron reagents.

The reactions of allyl-Bpin **42** and quinone derivatives **68** could be performed under mild conditions at rt. The outcome of the reaction was dependent on the substituent pattern of the quinone and the ratio of the quinone and allyl-Bpin reactants. When two equivalents of BQ, monosubstituted BQ, and naphthoquinone were employed, the reactions gave the C-H allylation products **69** (Scheme 38A). However, using certain substituted BQs, and naphthoquinones as the substrates with about equimolar amounts of allyl-Bpin compounds, the reactions provided addition products **70** (Scheme 38B).



Scheme 38. The different outcome for the reaction of allylboronates and quinone derivatives.

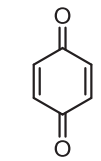
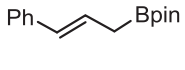
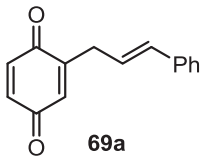
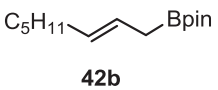
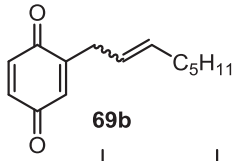
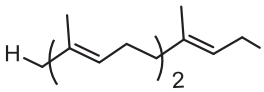
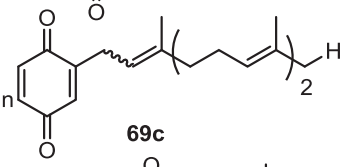
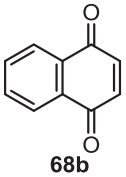
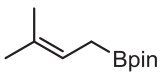
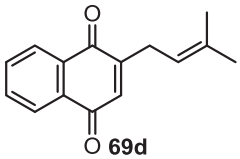
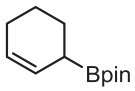
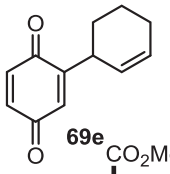
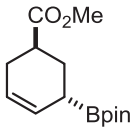
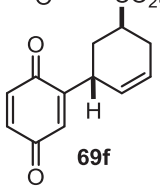
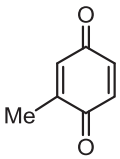
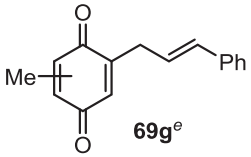


Scheme 39. A) Reaction of equimolar amounts of allyl-Bpin **46a** and BQ **68a**. B) Oxidation of hydroquinone **71a** by BQ **68a**.

The reaction of two equivalents of BQ (**68a**) and one equivalent of cinnamyl-Bpin **42a** afforded linear allylic BQ **69a** in high yield and high *E/Z* stereoselectivity on the alkene moiety (Table 14, entry 1). Interestingly, when one equivalent of BQ **68a** was used under the same conditions, a mixture of allylic hydroquinone **71a** and allylic quinone product **69a** was formed

(Scheme 39A). In a subsequent reaction, the (isolated) allylic hydroquinone product **71a** was reacted with BQ to afford the allylic quinone product **69a** (Scheme 39B). This indicates that BQ is not only the substrate but also an oxidant, which oxidize the hydroquinone to the final product **69a**. This finding also explains that *two equivalents* of BQ were required for the clean C-H functionalization reaction affording allylated quinone product **69a**.

Table 14. Allylation of quinones with allylboronates.[a]

entry	quinone	allylboronate	product	yield	*E*:*Z*[b]
1	 **68a**	 **42a**	 **69a**	90%	>95:1
2[c]	**68a**	 **42b**	 **69b**	50%	5.8 :1
3	**68a**	 **42c**	 **69c**	83%	1.2 :1
4	 **68b**	 **42d**	 **69d**	53%	-
5[d]	**68a**	 **42e**	 **69e**	67%	-
6[d]	**68a**	 *trans*-**49**	 **69f**	45%	-
7	 **68c**	**42a**	 **69g**[e]	69%	-

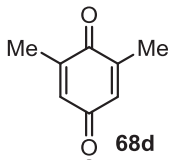
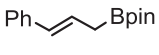
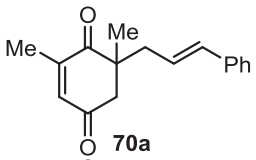
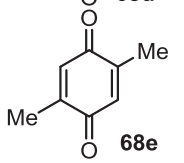
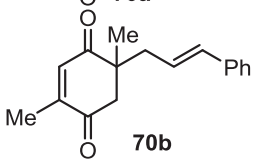
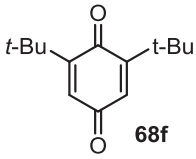
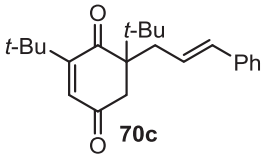
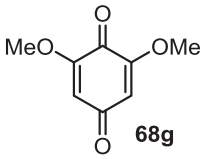
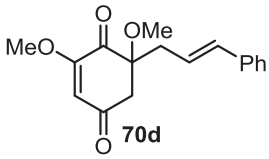
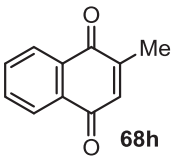
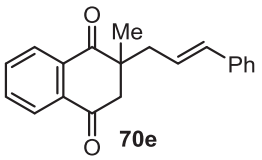
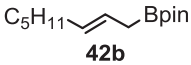
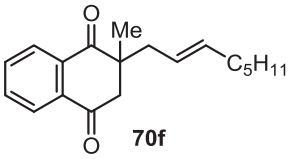
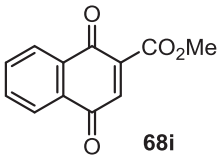
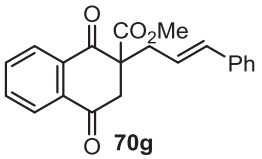
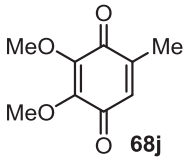
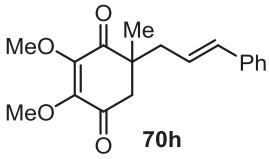
[a]The reactions were carried out with **68** (0.2 mmol) and **42** (0.1 mmol) in $CDCl_3$ (0.5 mL) at room temperature for 24 h. [b]The *E/Z* ratio of **69** was determined by ^1H NMR analysis of the crude reaction mixture. [c]CF_3COOH (0.05 mmol) was used as an additive. [d]Diphenylphosphinic acid (0.05 mmol) was used as an additive. [e]The 6- and 5-Me-substituted regioisomers were formed in 2.5:1 ratio.

Alkyl allyl-Bpin **42b** can also be used in the allylation reactions to form the linear allylic product, but the reaction was slower than with cinnamyl-Bpin **42a** (Table 14, entry 2). The addition of a CF_3COOH additive can improve the yield to 50%, but the *E/Z* ratio is still relatively poor (5.8:1).

Farnesyl-Bpin **42c** reacted with BQ easily under the same conditions to cinnamyl-Bpin, providing farnesyl-BQ **69c** in high yield (83%) (Table 14, entry 3). This is interesting since Baran and coworkers claimed that farnesyl-Bpin has a sluggish reactivity.[75] These authors employed the farnesyl-BF_3K salt and reacted it with BQ in the presence of $AgNO_3$ and $K_2S_2O_8$. The reaction gave farnesyl-BQ in moderate yield (58%) and similar *E/Z* selectivity as our reaction. Isoprenyl-Bpin **42d** can be used in the allylation of naphthoquinone as well, affording isoprenyl quinone derivative **69d** in 53% yield. Not only acyclic allyl-Bpin but also more sterically strained cyclic allyl-Bpin, such as **42c** and *trans*-**49**, reacted with BQ **68a** (Table 14, entries 5 and 6). The reactions proceeded slower than with cinnamyl-Bpin **42a**. The addition of a catalytic amount of diphenylphosphinic acid facilitated the reaction, providing an acceptable yield of the products **69e** and **69f** (67% and 45% respectively). Notably, when stereodefined cyclic allyl-Bpin *trans*-**49** was used, the reaction gave a single diastereomer with retention of the stereochemistry. To the best of our knowledge, this is the first example of the stereochemistry study for the allylation of quinone derivatives. Monosubstituted BQ **68c** reacted with **42a**, giving the linear *E*-products in good yield. However, the regioselectivity was poor as 2,6- and 2,5-disubstituted products were obtained in 2.5:1 ratio (Table 14, entry 7).

When 2,6-disubstituted BQ **68d** reacted with cinnamyl-Bpin **42a**, addition product **70a** was formed with high yield using an equimolar ratio of **68d** and **42a** (Table 15, entry 1). The product cannot be further oxidized by BQ derivatives due to the presence of the 6-methyl group, indicating the reaction does not involve an oxidation step. Similar addition product was formed in the reaction of 2,5-disubstituted BQ **68e** and **42a** with good yield (79%, Table 15, entry 2). Quinone derivative **68f** with a bulkier *t*-Bu group can also be used in the reaction, affording the addition product **70c** in 68% yield (Table 15, entry 3). 2,6-Dimethoxy substituted BQ **68g** reacted with **42a** slower than its methyl analog **68d** (Table 15, entry 4). However, a good yield of 63% can be obtained by using an excess of **68g**. Monosubstituted naphthoquinone **68h** can also be easily allylated with cinnamyl-Bpin **42a** and isoprenyl-Bpin **42b**, except that when **42b** was used, the addition of CF_3COOH additive was required in order to obtain an acceptable yield of 67% (Table 15, entries 5-6). The reaction of ester-substituted naphthoquinone **68i** and **42a** had the same outcome with the formation of addition product **70g** in moderate yield (57%), indicating less dependence on the electronic property of the substituent (Table 15, entry 7). In the case of trisubstituted BQ, such as **68j**, the addition reaction also worked well, providing product **70h** in 87% yield (Table 15, entry 8).

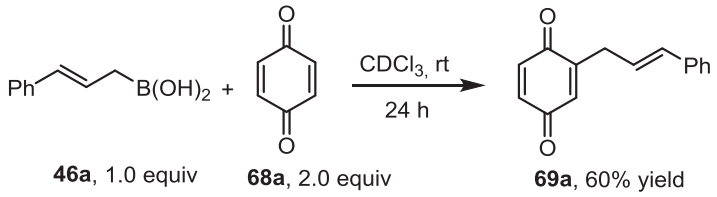
Table 15. Addition reaction of allylboronates with quinones.[a]

entry	quinone	allylboronate	product	yield	*E*:*Z*[b]
1	 **68d**	 **42a**	 **70a**	94%	>95:1
2	 **68e**	**42a**	 **70b**	79%	>95:1
3	 **68f**	**42a**	 **70c**	68%	>95:1
4[c]	 **68g**	**42a**	 **70d**	63%	>95:1
5	 **68h**	**42a**	 **70e**	90%	>95:1
6[d]	**68h**	 **42b**	 **70f**	67%	>95:1
7	 **68i**	**42b**	 **70g**	57%	>95:1
8	 **68j**	**42b**	 **70h**	87%	>95:1

[a]The reactions were carried out with **68** (0.1 mmol) and **42** (0.12 mmol) in $CDCl_3$ (0.5 mL) for 24 h. [b]The *E*/*Z* ratio of **70** was determined by ^1H NMR analysis of the crude reaction mixture. [c]**68g** (0.15 mmol) was used. [d]CF_3COOH (0.1 mmol) was used as an additive.

5.2 Reactivity of allylboronic acids

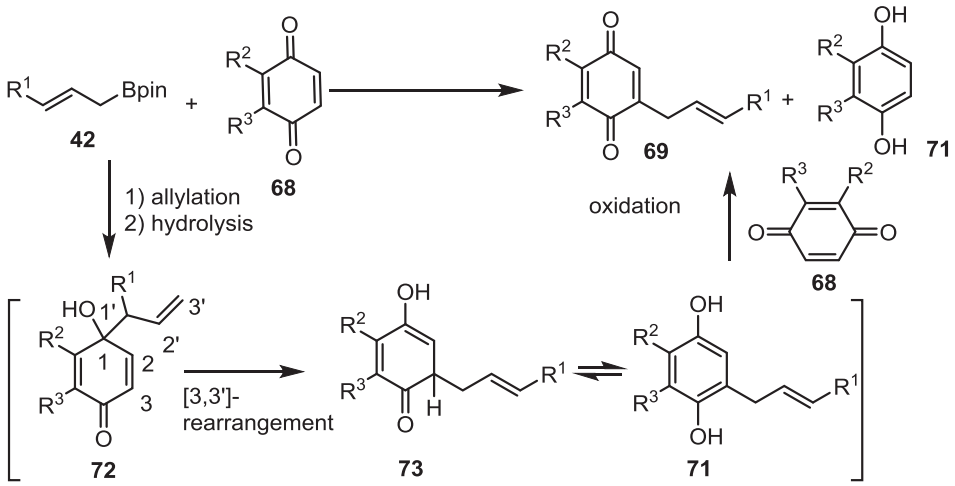
The application of allylboronic acid in the C-H allylation of BQ was also examined. We used cinnamylboronic acid **56a** as the allylating reagent (Scheme 40). The reaction furnished the linear allylic BQ **69a** in 60% yield. As demonstrated above, the reaction of allyl-Bpin and BQ gave **69a** in 90% yield in the same conditions (Table 14, entry 1). Thus, using allylboronic acid **56a** is less efficient as using its ester derivative **52a** in the allylation reactions. This is probably due to the relative instability of **56a** compared to **52a**.



Scheme 40. Allylation of BQ with allylboronic acid **56a**.

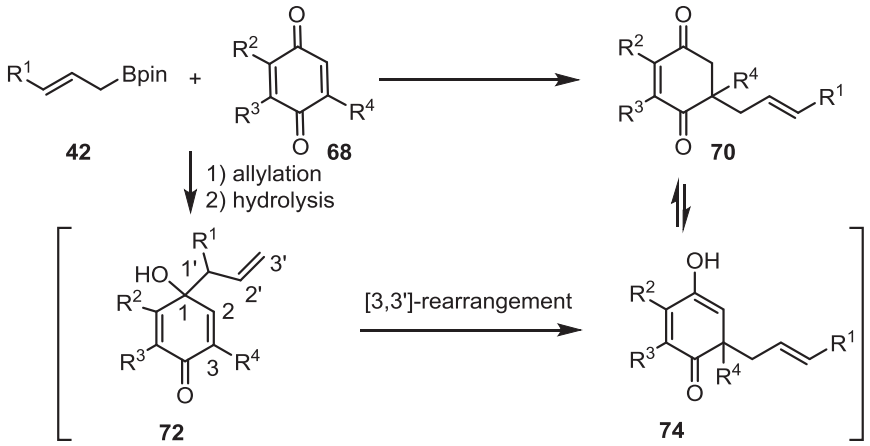
5.3 Proposed mechanism for the allylation of quinones

According to the above results, we propose a mechanism involving three steps for the reaction of nonsubstituted benzoquinone, monosubstituted benzoquinone, and naphthoquinone (**68a-c**): allylation of the carbonyl group, [3,3']-rearrangement, and oxidation (Scheme 41). The first step is the addition of allyl-Bpin to the carbonyl group of the quinones. The reaction probably proceeds via a six-membered ring transition state,[76] affording the branched allylic intermediate **72**. This mechanism is quite common and reliable in the reactions of allylboronates with carbonyl compounds.[74] The quinoid structure probably activates the carbonyl group for the reaction. Intermediate **72** is a highly reactive species,[73] which undergoes fast Cope-type [3,3']-rearrangement to form **73**. Similar rearrangements have been reported for the allylation of quinones using allylindium, allylnickel and allylsilane.[71-73] Intermediate **73** can be transformed into hydroquinone derivative **71** via tautomerization. Then **71** is readily oxidized to the benzoquinone derivative **69** by another quinone molecule **68**. Thus quinone **68** acts as both substrate and oxidant, which can explain that two equivalents of quinone are required for the clean C-H allylation reaction. In some case, an acid was used to improve the yield. This is because using acid as additive probably accelerates both the addition step[77] and oxidation step[78].



Scheme 41. Proposed reaction pathway for the C-H allylation of BQ derivatives **68** with allyl-Bpin **42**.

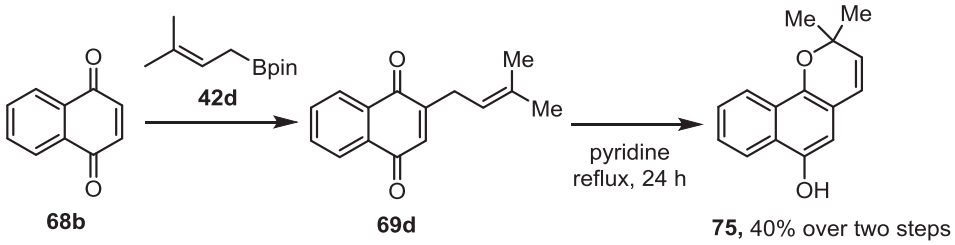
When quinone derivative **68** ($R^4 \neq H$) was employed (Scheme 42), the first step is γ-selective allylation of the allyl-Bpin to the sterically less hindered carbonyl group of the quinone substrate. Then a similar [3,3']-rearrangement occurs, transforming the intermediate **72** to **74**. After tautomerization, compound **70** is formed, which cannot be further oxidized by the quinone derivative.



Scheme 42. Proposed reaction pathway for the addition reaction of allyl-Bpin **42** and BQ derivatives **68**.

5.4 Synthesis of hemi-tectol

The allylation of naphthoquinones **68b** can be used for the synthesis of hemi-tectol **75** (Scheme 43), which is a substructure of the natural product, Tecomaquinone I. The reaction was carried out in two steps from **68b** and **42d**, with an overall yield of 40%.



Scheme 43. Synthesis of hemi-tectol from **68b**.

5.5 Summary of the allylation of quinones

We have developed a useful method for the direct C-H functionalization of BQ and naphthoquinone derivatives using allyl-Bpin reagents. The reaction can be performed under mild conditions, in some cases, with acid catalysis. The reactions are regio- and stereoselective. When stereodefined cyclic allyl-Bpin is employed, the allylation reaction gives the allylic product with clean retention of the stereochemistry. In the case of 2,5- and 2,6- disubstituted benzoquinone and monosubstituted naphthoquinones, addition products are obtained in high selectivity, which further extends the synthetic utilization of the allylboronates in the preparation of quinone-based structures. In addition, the reaction of quinones and allylboronates will be an essential consideration in the reactions of allylboronates under oxidative conditions using BQ as an oxidant.

6. Closing remarks

The studies in this thesis are focused on development of new methods for carbon-carbon bond formations using allyl- and allenylboronic acids and their ester derivatives. The main efforts have been made on the coupling reactions of these reagents with diazo compounds, tosylhydrazones, and quinones.

Allylboronic acids and diazoketones undergo $C(sp^3)$-$C(sp^3)$ coupling reactions in the presence of copper or palladium catalysts. In the presence of a copper catalyst, the reaction proceeds with *syn* stereochemistry affording the branched allylic product. Using palladium catalyst under similar conditions, the coupling reaction shows the opposite regioselectivity, resulting in the linear allylic product.

Allenylboronic acids can be coupled with diazo compounds, which are generated in situ from tosylhydrazones and a base. This coupling reaction does not require the application of transition metal catalyst. The process probably involves 1,2-shift of the allenyl moiety from the boron to the diazocarbon atom.

In the last part, allylation of quinones with allyl-Bpin reagents is presented. The outcome of the reaction is dependent on the substitution pattern of the quinone and the applied ratio of the quinone and allyl-Bpin components. Thus, with 1,4-benzoquinone, 1,4-naphthoquinone and monosubstituted 1,4-benzoquinone as the substrate, direct allylation of the quinones occurred. When 2,4- and 2,6-disubstituted quinones are used, the addition of the allylboronate to the double bond happened.

7. Summary in Swedish

Denna avhandling fokuserar på utvecklingen av nya metoder för att bilda kol-kol bindningar med hjälp av övergångsmetallkatalyserade och övergångsmetallfria reaktioner där substraten består av allyl-, allenylborsyror och deras esterderivat.

Vi har utvecklat kopparkatalyserade korskopplingsreaktioner av allylborsyror och α-diazoketoner. Reaktionen fortskrider med hög regioselektivitet, vilket ger grenade allylprodukter. Vid användning av stereodefinierade cykliska allylborsyror som substrat, uppvisade reaktionen en hög diastereoselektivitet, vilket resulterade i stereodefinierade cyklohexenprodukter med samma relativa konfiguration som utgångsmaterial. Vidare etablerades en palladiumkatalyserad korskoppling av allylborsyrorna och α-diazoketoner. Reaktionen visades ha en motsatt regioselektivi tet vid jämförelse med den kopparkatalyserade och istället resulterade palladiumkatalysatorn i linjära produkter med hög regioselektivitet.

En ny övergångsmetallfri kol-kol bildning av allenylborsyror och tosylhydrazoner är även beskriven. Reaktionen genomfördes i närvaro av bas och genererade nya C = C dubbelbindningar. Genom att använda denna metod uppnåddes olika tätt funktionaliserade konjugerande diener.

Slutligen presenterar vi en allylering av kinoner genom att använda allylboronreagens. Reaktionerna kan fortskrida utan extra tillsats reagens. Vid användning av 1,4-bensokinon, 1,4-naftokinon samt monosubstituerad 1,4-bensokinon som substrat, skedde direkt allylering av kinonerna. Vid användning av 2,4- och 2,6-disubstituerade kinoner adderades allylboronatet till dubbelbindningen.

Appendix A: Reprint permissions

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III. Belhomme, M.-C.; Wang, D.; Szabó, K. J. *Org. Lett.* **2016**, *18*, 2503-2506.

IV. Wang, D.; de Wit, M. J. M.; Szabó, K. J. *J. Org. Chem.* **2018**, *ASAP*, DOI: 10.1021/acs.joc.8b01104.

V. Deng, H.-P.; Wang, D.; Szabó, K. J. *J. Org. Chem.* **2015**, *80*, 3343-3348.

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